The impact of antiretroviral use in resource-poor settings: insights from mathematical models

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DECLARATION

The work presented in this thesis is the result of original research carried out by the author, Rebecca Baggaley, unless otherwise stated below or in the text. No part of this thesis has been submitted for a degree elsewhere.

Supervision

The research was carried out under the supervision of Professor Geoff Garnett and Professor Neil Ferguson at the Department of Infectious Disease Epidemiology, Imperial College London, and Dr Jamie Robinson at GlaxoSmithKline.

Publications

Publications arising from this thesis or from work related to this thesis are included in Appendix A. Where work included in this thesis has been published in joint names, the role of each author is outlined below, as directed by the University of London regulations.

Chapter 2

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Rebecca Baggaley was the primary author. Neil Ferguson and Geoff Garnett supervised the work.

Chapter 3

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Chapters 4 and 5

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Signed.....RFBaggaley..... **Date**...28/7/06...

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ABSTRACT

This thesis focuses on formulating mathematical models describing antiretroviral use, and in particular, on their potential effect in resource-poor settings. Over recent years, many steps have been taken towards rolling out antiretroviral therapy (ART) access on a large scale throughout sub-Saharan Africa, the progress of which is evaluated.

The models aim to describe the impact of antiretroviral use in a more realistic way than has been achieved previously by incorporating factors that are important in ART use, such as stages of HIV infection. The thorough literature review for parameterising the ART models has led to a systematic review and meta-analysis of transmission probabilities for sexual HIV transmission, including heterosexual and homosexual per act and per partnership transmission probabilities.

The population-level effect of ART is investigated, showing that even with high coverage levels and timely treatment initiation, ART cannot be used as a control measure in the absence of prevention initiatives. Key issues regarding treatment delivery in ART programmes are investigated, examining the impact of treatment initiation by infection stage (at AIDS or before) and by availability of laboratory facilities. This is investigated within the context of a limited capacity programme where demand for treatment exceeds supply and leads to a discussion of the ethical stances that various possible treatment strategies would implicitly represent. An extended model incorporating use of a second line regimen is used to illustrate the epidemiological consequences of providing further, more expensive treatment to those failing the original regimen, which again provokes debate as to the right strategy for distribution of limited resources.

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TABLE OF CONTENTS

DECLARATION 2

ABSTRACT 3

ACKNOWLEDGEMENTS 4

TABLE OF CONTENTS 5

TABLE OF FIGURES 9

TABLE OF TABLES 12

ABBREVIATIONS AND ACRONYMS 14

CHAPTER 1 INTRODUCTION 16

1.1 Background 16

1.2 Stages of HIV infection and when to initiate treatment 18

1.3 Treatment failure 20
1.3.1 Adherence 21
1.3.2 Evolution of drug resistance (secondary resistance) 24
1.3.3 Transmission of drug resistance (primary resistance) 26
1.3.4 Toxicity and immune reconstitution 29

1.4 Use of ART in resource-poor settings 30
1.4.1 Priority setting 33
1.4.2 Existing ART programmes 34
1.4.3 ART use outside official programmes and "antiretroviral anarchy" 36
1.4.4 Monitoring, laboratory facilities and official guidelines 38
1.4.5 Second line therapy and cessation of treatment 42
1.4.6 Treatment of opportunistic infections 42
1.4.7 Sexual behaviour change 43

1.5 Key research questions 44

1.6 Discussion 48

CHAPTER 2 ART USE AND MATHEMATICAL MODELS 49

2.1 Background: Models in infectious disease epidemiology 49

2.2 Some key statistics in infectious disease modelling 50
2.2.1 The basic reproductive number R_0 50
2.2.2 The exponential growth rate r and the generation time T_g 51

2.3 Compartmental models in epidemiology - the SIR model 52

2.4 Models of sexually transmitted infections 54

2.5 ART Models 59

2.6 Defining the basic reproductive number R_0 60

2.6.1 ART Model 1 description 60

2.6.2 Calculating R_0 62

2.7 ART Model 2 description 63
2.7.1 State variables 66
2.7.2 Transmission equations 66
2.8 Multistage model – ART Model 3 69
2.8.1 Model description 69
2.8.2 Patterns of infectiousness and epidemic growth 70
2.9 Calculation of R_0 for heterogeneous sexual mixing 73
2.10 The range of ART models 76
2.11 Dynamic model structures 77
2.12 Behaviour change in ART models 80
2.13 Stage of HIV infection 81
2.14 Emergence of ART drug resistance 85
2.15 Parameterisation 88
2.16 Discussion 88

CHAPTER 3 SEXUAL HIV TRANSMISSION PROBABILITIES 93
3.1 Abbreviations and acronyms 94
3.2 Background 95
3.3 Methods 96
3.4 Summary of search 98
3.5 Heterosexual transmission 100
3.5.1 Per partner transmission 101
3.5.2 Per contact transmission 125
3.6 Anal intercourse 135
3.7 Relationship between per contact and per partnership risk 139
3.7.1 Sexual activity with stage of infection 141
3.7.2 Transmission probability estimates used in the ART models 143
3.8 Discussion 146

CHAPTER 4 MODEL DEFINITION AND PARAMETER ASSIGNMENT 147
4.1 Model description 147
4.1.2 Other terms 152
4.1.3 Transmission equations 153
4.1.4 Mixing matrix definition 155
4.1.5 Treatment 156
4.1.6 Pessimistic sexual behaviour assumptions 157
4.2 Parameter assignment 157
4.3 Infectiousness 161
4.4 Effect of ART on infectiousness 161
4.5 Sexual activity 162
4.5.1 Sexual activity of AIDS patients 165
4.5.2 Changes in sexual activity in the ART era 165
4.6 Entry and exit rates 167

4.7 Survival times of AIDS patients and duration of HIV infection 167
4.7.1 Duration of primary infection 167
4.7.2 Duration of HIV infection and incubation 167
4.7.3 Duration of pre-AIDS 168
4.7.4 Survival times of AIDS patients 169
4.8 Effect of ART on survival 170
4.9 Effect of ART in resource-poor settings 171
4.10 Effect of ART by stage of infection upon treatment initiation 175
4.11 Effect of treatment failure on survival and disease progression 177
4.12 ART resistance and treatment failure 177
4.12.1 Treatment failure by stage of infection 180
4.12.2 Replicative fitness and transmission of drug resistance 181
4.12.3 Other treatment failure and drop-out 183
4.13 Monitoring and evaluation 183
4.14 Discussion 185
CHAPTER 5 IMPACT OF ART – RESULTS AND TREATMENT STRATEGIES 186
5.1 Background 187
5.2 Treatment scenarios 188
5.2.1 Effect of ART on different HIV epidemics 188
5.2.2 Impact of ART – levels of coverage 189
5.2.3 Impact of ART – treatment strategies 189
5.2.4 Parameter assignment 190
5.3 Results 192
5.3.1 Effect of ART on different HIV epidemics 192
5.3.2 Impact of ART – levels of coverage 195
5.3.3 Impact of ART – availability of laboratory facilities 198
5.3.4 Sensitivity of results to partner change rate estimates 200
5.4 Discussion 201
CHAPTER 6 SECOND-LINE THERAPY 203
6.1 Background 203
6.2 Methods 204
6.2.1 State variables 206
6.2.2 Other values 206
6.2.3 Transmission equations 206
6.2.4 Treatment scenarios 212
6.3 Results 218
6.3.1 Switching regimen and withdrawing treatment: scenarios 1 to 4 218
6.3.2 Timing of switching regimens: scenarios A to F 222
6.4 Discussion 224
CHAPTER 7 DISCUSSION 226
7.1 Introduction 226
7.2 Overview 227
7.3 The ethics of distribution of ART in resource-poor settings 234

7.4 Future directions 238
7.5 Conclusions 239

GLOSSARY 241

APPENDIX A 249

APPENDIX B 288

APPENDIX C – MODEL DESCRIPTIONS 290
C.1 ART Model 3 – staged HIV progression 290
C.2 ART Model 4 – heterogeneous sexual activity 294

BIBLIOGRAPHY 297

TABLE OF FIGURES

Figure 1.1 Natural history of plasma viral load and CD4 count with HIV infection 18
Figure 1.2 Summary of key studies of HIV-1 primary drug resistance in Western Europe and the US for a) primary mutations and b) phenotypic resistance. 28
Figure 2.1 Flow diagram illustrating the classic SIR model 52
Figure 2.2 Structure of ART Model 1, a one-stage model of HIV transmission and ART. 62
Figure 2.3 Schematic illustration of the structure of ART Model 2, a one-stage model of HIV transmission and ART 65
Figure 2.4 Schematic illustration of the structure of the stages of HIV infection for the four-stage model, ART Model 3 69
Figure 2.5 Comparison of modelled HIV epidemics with different patterns of infectiousness with stage of infection but equal values for R_0 73
Figure 2.6 Comparison of R_0 calculation methods. 75
Figure 2.7 Model predictions of the effect of ART on a mature epidemic, under various assumptions 79
Figure 2.8 Model predictions of the effect of ART on a mature epidemic using more realistic timing of initiation of ART 83
Figure 2.9 Predictions of the impact of ART by stage of infection at which treatment is initiated. 84
Figure 2.10 Model predictions of transmission of ART drug resistance by relative fitness of strains and model structure. 87
Figure 3.1 Breakdown of search results for articles describing HIV transmission probabilities based on publication type. 99
Figure 3.2 Summary of studies estimating HIV transmission probability per heterosexual partnership for combined M→F and F→M transmission, with 95% confidence intervals ... 119
Figure 3.3 Summary of studies estimating HIV transmission probability per heterosexual partnership for M→F transmission, with 95% confidence intervals 120
Figure 3.4 Summary of studies estimating HIV transmission probability per heterosexual partnership for F→M transmission, with 95% confidence intervals 121
Figure 3.5 Summary of studies estimating HIV transmission probability per heterosexual partnership, stratified by risk categories, with 95% confidence intervals 122
Figure 3.6 Summary of studies estimating HIV transmission probability per heterosexual contact – logarithmic scale 134

Figure 3.7 Average number of sexual contacts per partnership for each per partnership study, calculated using per sexual partnership and per sexual contact HIV transmission probability data. 140
Figure 3.8 Average number of sexual contacts per partnership calculated using per sexual partnership and per sexual contact HIV transmission probability data, stratified by stage of infection of the index partner. 142
Figure 3.9 Per partnership transmission probability estimates by stage of infection of index case (asymptomatic or symptomatic) – comparison with ART model parameters..... 145
Figure 4.1 Schematic illustration of the structure of the HIV transmission model..... 148
Figure 4.2 Schematic illustration of the structure of the treatment stages of the HIV transmission model 151
Figure 4.3 Comparison of the projected epidemic using baseline parameter values, with UNAIDS prevalence estimates from antenatal clinics in Malawi..... 164
Figure 5.1 Total number of HIV infections through time for different HIV epidemics and under different assumptions regarding behaviour change of treated patients 193
Figure 5.2 Total number of HIV infections averted per person year of treatment for various HIV epidemics and under different assumptions regarding behaviour change of treated patients 194
Figure 5.3 Effect of programme capacity. 196
Figure 5.4 Comparison of life years gained per person year of treatment over time for AIDS only and AIDS and pre-AIDS treatment strategies 197
Figure 5.5 Description of potential treatment strategies for ART programmes in resource-poor settings..... 199
Figure 5.6 Comparison of predicted effect of ART using different partner change rate estimates 200
Figure 6.1 Flow diagram of patient management for an ART model incorporating second-line therapy, without drug resistance 205
Figure 6.2 Salvage regimen model, stratified by stages of infection and sexual mixing, modelling treatment failure but not drug resistance. 209
Figure 6.3 Schematic of ART model illustrating transitions between treatment compartments (stages $j=1$ to $j=9$) upon initiation of treatment. 210
Figure 6.4 Key model outcomes for scenarios investigating switching regimen and withdrawing treatment. 220
Figure 6.5 Cost per person year of treatment by relative cost of the second-line regimen and average duration of viral suppression with regimen A 221
Figure 6.6 Change in programme cost and cost per life year gained with increased cost of regimen B relative to regimen A, when treatment failure rates for regimens are equal 222

Figure 6.7 Key model outcomes for scenarios investigating the timing of switching regimens 223

Figure 7.1 Increasing number of publications by year for antiretroviral (Title) AND Africa (Any field) in MEDLINE 227

TABLE OF TABLES

Table 1.1 Most common side effects of ART 29
Table 1.2 Cost of triple ART regimens in Uganda, 1998 to 2002 31
Table 1.3 Revised WHO clinical staging of HIV/AIDS for adults and adolescents 40
Table 1.4 WHO recommendations for initiating ART in adults and adolescents with documented HIV infection 41
Table 1.5 Scaling up ART: examples of research questions at different levels 47
Table 2.1 Model parameters and values used for analytical analysis 61
Table 2.2 Baseline parameter values used in ART Model 2 67
Table 2.3 Summary of parameter values used for Scenarios 1 to 4, investigating the impact of varying patterns of HIV infectiousness on the timing of epidemics. 72
Table 2.4 Summary of existing ART models, by date of publication. 89
Table 3.1 Number of identified studies of HIV transmission probabilities for heterosexual transmission and anal intercourse 100
Table 3.2 Transmission probabilities per partner for heterosexual intercourse – combined M→F and F→M transmission 107
Table 3.3 Transmission probabilities per partner for heterosexual intercourse – M→F transmission 110
Table 3.4 Transmission probabilities per partner for heterosexual intercourse – F→M transmission 114
Table 3.5 Transmission probabilities per partner for heterosexual intercourse – stratified by risk categories 116
Table 3.6 Transmission probabilities for heterosexual intercourse – excluded studies 118
Table 3.7 Per partner HIV transmission probabilities: meta-analysis results 123
Table 3.8 Difference in per partner transmission probabilities by stage of infection and research setting: meta-regression results 124
Table 3.9 Transmission probabilities per contact for heterosexual intercourse – combined M→F and F→M transmission 129
Table 3.10 Transmission probabilities per contact for heterosexual intercourse – M→F transmission 130
Table 3.11 Transmission probabilities per contact for heterosexual intercourse – F→M transmission 132
Table 3.12 Transmission probabilities per contact for heterosexual intercourse – stratified by risk categories 133
Table 3.13 Transmission probabilities per partner for anal intercourse. 137
Table 3.14 Transmission probabilities per contact for anal intercourse 137
Table 3.15 Transmission probabilities for anal intercourse – excluded studies 138

Table 3.16 Per contact transmission probability for M→F HIV transmission derived using data from Seidlin et al 1993 [266]. 141
Table 3.17 Summary of studies providing per partnership and per contact transmission probability estimates stratified by stage of HIV infection (combined M→F and F→M transmission only) 142
Table 4.1 Summary of parameters used in the ART model 158
Table 4.2 Input values for curve fit to Malawi prevalence data 163
Table 4.3 Selection of studies estimating AIDS survival time in resource-poor settings 170
Table 4.4 Summary of a selection of studies reporting performance of ART in resource-poor settings 173
Table 4.5 Selection of studies reporting survival by CD4 count 176
Table 5.1 Summary of treatment scenarios – effect of ART on various epidemics, changes in size and maturity of HIV epidemic. 188
Table 5.2 Summary of treatment scenarios – effect of ART on various epidemics, changes in ART patients' risk behaviours. 189
Table 5.3 Summary of treatment scenarios – availability of laboratory facilities 191
Table 6.1 Descriptions and baseline values of model parameters for the salvage regimen model, with sources. 211
Table 6.2 Summary of treatment scenarios 1 to 4 – switching regimens and withdrawal of failing treatment. 215
Table 6.3 Summary of treatment scenarios A to F – timing of switching regimens 216

ABBREVIATIONS AND ACRONYMS

ADC	AIDS-defining condition
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ASSA	Actuarial Society of South Africa
AZT	Azidothymidine (zidovudine)
CD4	Plasma CD4 (cluster of differentiation antigen 4) cell count
CI	Confidence Interval
CSW	Commercial sex work(er)
DAI	UNAIDS Drug Access Initiative
DOT	Directly Observed Therapy
EPP	Epidemic Projection Package
FDA	Food and Drug Administration (US)
HAART	Highly Active Antiretroviral Therapy
HCW	Health care worker
HIV	Human Immunodeficiency Virus
IDU	Injecting/intravenous drug use(r)
IRIS	Immune restoration/reconstitution inflammation syndrome
LHS	Latin Hypercube Sampling
MDR	Multidrug resistant/resistance
MSF	Médecins Sans Frontières
MSM	Men who have sex with men
NNRTI	Nonnucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic infection
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission
pVL	Plasma viral load
RNA	Ribonucleic acid
STI	Sexually transmitted infection
TB	Tuberculosis
TLC	Total lymphocyte count
UN	United Nations
UNAIDS	United Nations Joint Cosponsored Programme on HIV/AIDS

VCT	Voluntary counselling and testing
WHO	World Health Organisation
ZDV	Zidovudine

Chapter 1 Introduction

Summary

This chapter provides a brief introduction to antiretroviral therapy (ART) and its impact in industrialised and resource-poor countries. Its effects in terms of extending life expectancy, decreasing infectiousness and its potential influence on risk behaviours of populations are considered. Attention is given to the following areas which will be further explored in this thesis: the role of mathematical modelling in predicting and explaining the impact of treatment (Chapter 2), the importance of evidence-based parameterisation of models (Chapters 3 and 4), the impact of therapy in resource-poor settings, exploring different approaches to treatment programme design (Chapter 5), including prioritisation of therapy by stage of infection, availability of laboratory facilities, and provision of salvage regimens (Chapter 6). The current status of scale-up of ART is described.

1.1 Background

ART has greatly reduced HIV/AIDS-related mortality and morbidity in industrialised countries [1, 2]. It has reduced mortality, hospitalisation, incidence of opportunistic infections (OIs), and the use of home-care services, skilled nursing facilities and hospices. In 1996 triple therapy (highly active antiretroviral therapy or "HAART", from now on referred to as ART) was introduced, generally consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). A full list of US Federal Drug Administration (FDA)-approved anti-HIV medications is provided in Appendix B Table B1. These drugs have been shown to dramatically reduce HIV replication in vivo [3]. The suppression of viral replication results in an increase in plasma CD4 cell count (CD4 count) and improved immune function, thus delaying clinical progression and prolonging survival. Simultaneous therapy with three drugs, typically working on at least two different viral target sites has meant that the evolution of antiretroviral (ARV) drug resistance can be delayed by many more years than with mono- or dual therapy.

ART is not without problems. Despite the advance of triple therapy, there is still significant risk of evolution of resistant virus strains which can render ART ineffective, particularly if there is poor adherence. Patients must follow demanding regimens and treatment is associated with many side effects. Toxicity includes insulin intolerance, elevation of cholesterol, redistribution of body fat, hepatotoxic effects and a number of poorly understood metabolic derangements. Maintaining adherence, which is difficult for all medications, is further challenged by such problems. Side effects may be so severe that patients withdraw from therapy completely, and there can be other types of

treatment failure such as bioavailability problems or interactions with other drugs [4]. In resource-rich countries, some patients have now exhausted all therapeutic options through a combination of resistance evolution and problems with tolerability [5].

Successful ART decreases plasma [6] and seminal viral load [7] and is thought thereby to reduce HIV infectiousness. However, despite decreased plasma viral loads (pVLs) there is still some potential for transmission, with a substantial residual viral replication predicted by models, even with good adherence and drug penetration [8]. The principal function of ART is to increase the life expectancy of infected individuals [9], and over time this causes the pool of potential transmitters of infection to grow. These two factors – decreased infectiousness but increased duration of infectiousness – have opposing effects on HIV incidence. Higher HIV prevalence, due to increased life expectancy [10] and possible increases in risk behaviour due to new optimism regarding HIV diagnosis and risk of HIV transmission [11, 12], may be contributing to increased HIV incidence among certain groups. Therefore a key research question is: how will introduction of ART impact on an HIV epidemic?

In resource-poor countries, the introduction of ART may additionally decrease HIV transmission by increasing willingness of individuals to undergo voluntary counselling and testing (VCT) and disclose HIV status in order to procure treatment. This would lead to an increased knowledge of individuals' serostatus and thus a potential reduction in risk behaviour of those who test positive, whether they are currently on ART or not (this will depend on the extent to which an individual has autonomy over his or her sexual behaviour). It may also help to relieve some of the stigma associated with HIV/AIDS [13], which in turn could have an effect on transmission, such as reducing prejudice associated with negotiating condom use. For example, Farmer et al believe that, "access to effective therapy has lessened AIDS related stigma" in a poor community in rural Haiti [14].

As the political will for scale-up of ART coverage in resource-poor settings has now been achieved, the impacts of the introduction of therapy, including the competing effects of treatment on transmission and the emergence of drug resistance, shall be explored. The aim of this thesis is to demonstrate how predictions as to the effects of ART scale-up in resource-poor regions with high HIV prevalence can aid strategies for drug delivery and programme design. Key research questions that are addressed include the predicted impact of ART on such epidemics, with different levels of coverage and with different approaches to drug delivery. Different approaches include the timing of initiating ART, at different stages of infection, the availability of monitoring facilities such as CD4 count testing, and the availability of salvage, second-line regimens. Such practical questions regarding the design and operation of ART programmes need to be answered, using predictions from mathematical models, as used here, and by empirical evidence, in order to produce the most appropriate and effective ART delivery systems for these settings.

1.2 Stages of HIV infection and when to initiate treatment

The progress of HIV infection to AIDS can broadly be divided into four stages: primary infection, incubation, the period preceding AIDS ("pre-AIDS") and AIDS. The chances of transmission are highest during primary infection and AIDS, when pVL is at its highest. Figure 1.1 is an illustration of a "typical" HIV infection (although in reality, pVL can rapidly fluctuate by an order of magnitude within each infection stage, and there is considerable heterogeneity between individuals). It shows the early peak in pVL and transient dip in CD4 count, followed by a long and gradual decrease in CD4 count, and eventually an increase in pVL at an advanced stage of infection.

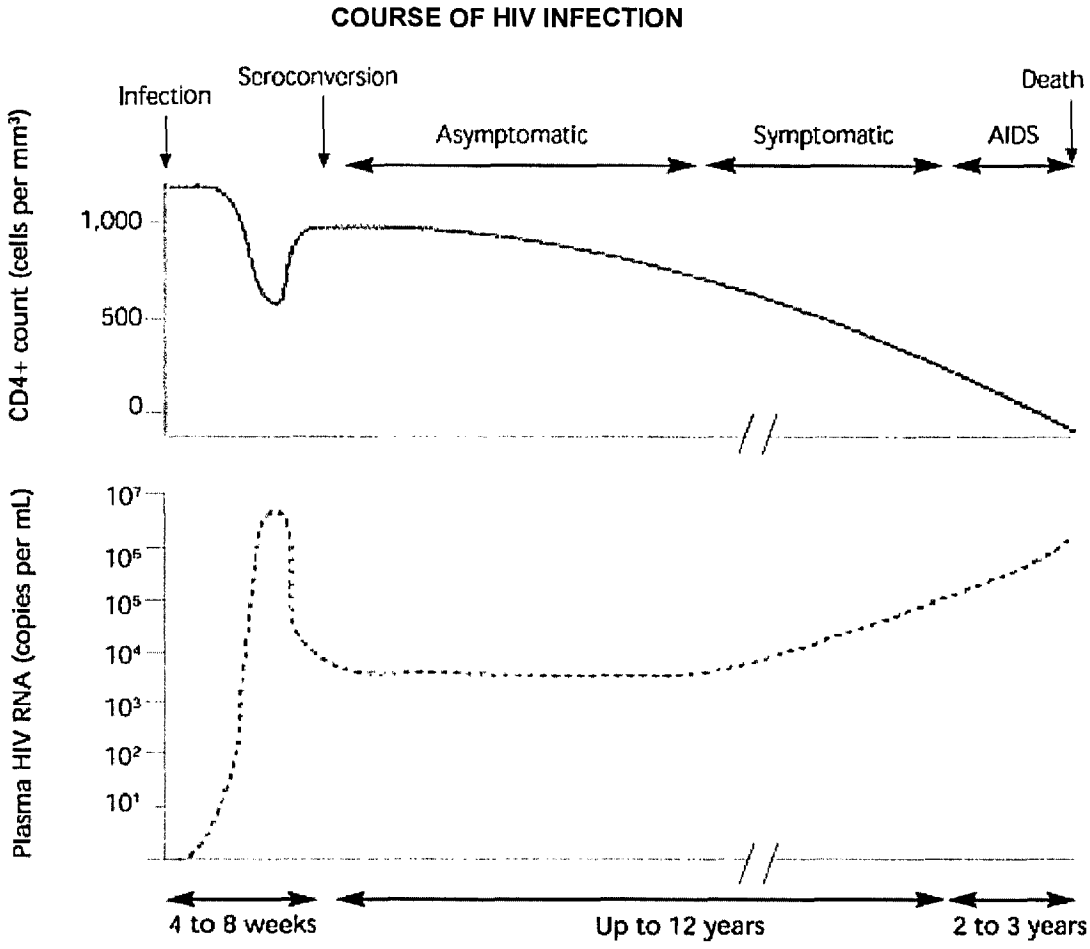


Figure 1.1 Natural history of plasma viral load and CD4 count with HIV infection.
From Sande MA, Volberding P. The medical management of AIDS. 4th ed. Philadelphia: Saunders, 1995:40.

ART can only be initiated upon HIV diagnosis and so will have no effect on transmission from individuals undergoing primary infection, when risk of transmission is high. Some experts believe that primary infection carries the highest risk of transmission, because it is associated with elevated HIV ribonucleic acid (RNA) levels and continued sexual activity [15, 16]. Furthermore, in populations with

high frequencies of concurrency (partnerships that overlap in time), the introduction of one infected individual can lead to rapid spread of HIV through the sexual network during this early stage of infection [17]. By the time an individual has developed AIDS, their sexual activity is likely to have decreased and so they will not contribute as much to HIV transmission as the duration of this phase would suggest. In view of this, Garnett et al [18] state that, "if ART is to be viewed as a public health tool to reduce the spread of HIV, it will have to be implemented differently than has been proposed; patients without clinical symptoms of HIV infection will need to be identified and immediately administered ARVs". Evidently, there are not enough resources for this kind of action, or to conduct the mass screening required to identify infected individuals. More importantly, such early treatment is unwarranted clinically and could cause more harm to patients through side effects. Therefore, optimistic predictions of ART being used to control HIV epidemics are not realistic [19]. The epidemiological impact of treatment at different infection stages is discussed further in Chapter 2.

Bos et al [20] state that in most cases in industrialised countries, HIV is not detected until the patient visits the hospital with HIV-related illness. Detection of asymptomatic infection would enable an individual to change their risk behaviour, thus reducing the number of secondary infections. Although VCT initiatives have met with some success in resource-poor settings [21], the lack of any effective treatment being offered following a positive result, plus the stigma associated with such a diagnosis, make screening less attractive. Moreover, in resource-poor countries suffering a high prevalence of HIV, candidates for ART may be more readily identified from the large number of easily-identifiable patients suffering full-blown AIDS, and so an earlier diagnosis may not translate into earlier treatment options.

The point at which treatment is initiated is very important because early treatment decisions can irrevocably alter a patient's response to future therapy. There has been a shift in opinion toward deferring ART initiation until CD4 counts fall below 350 cells/mm^3 rather than the previously recommended 500 cells/mm^3 in industrialised countries [22, 23]. The beneficial effect of immune restoration must be balanced against the risk of drug-related toxicities and development of drug resistance [24] and, more relevant for resource-poor settings, the wasting of already scarce resources. Any delay in treatment below a CD4 count of 200 cells/mm^3 leads to a significantly worse prognosis [25, 26], greater risk of treatment failure or incomplete viral suppression [27], and increased frequency of side effects and immune reconstitution diseases [28]. Therefore current recommendations are to start treatment at or below 350 cells/mm^3 in order to ensure individuals initiate therapy before their CD4 count drops below 200 cells/mm^3 [29].

Considerations of when to initiate treatment by CD4 count may remain an unrealistic luxury for many resource-poor countries for the foreseeable future, where drug rationing means that only those in gravest need can qualify for therapy, and diagnosis typically only occurs very late in infection [30, 31]. Considerable immune reconstitution is still possible, even in patients starting ART at very low CD4 counts [32]. A more detailed review of the literature on these effects, used to parameterise the

models described in this thesis, is provided in Chapter 4. Unfortunately, in the absence of laboratory testing, it can be difficult to determine which patients are closest to death and should be prioritised for treatment.

Therefore a key research question relates to timing of initiation of treatment. An investigation of the effect of initiating ART at the earliest stage of symptomatic infection, pre-AIDS, versus delay until progression to AIDS, is presented in Chapter 5.

1.3 Treatment failure

ARV drugs work in various ways to inhibit virus replication, but all interfere with stages in the viral replication cycle [33]. This means that the drugs are only able to attack virus that is actively replicating. During infection some virus will always remain quiescent within latently infected CD4 lymphocytes and other cells, having integrated into the host genome. Many of these cells can survive for years and are not a focus for attack by ARV agents. Thus, ART cannot entirely eliminate HIV infection because there will always be latent virus present which is liable to re-emerge upon cessation of therapy [34].

HIV does not possess a genetic proofreading mechanism. Therefore any errors introduced during the replication process cannot be corrected and are incorporated into the viral genome. Estimates place the error incorporation rate during viral replication at approximately one mutation for each new genome of 9200 nucleotides [35]. As HIV has such a massive replicative turnover, genomes with each possible mutation as well as many with double mutations will be generated daily. This is to the advantage of the pathogen, as certain mutations may confer superior qualities for survival and replication – for example, mutations conferring resistance to antiviral drugs. When AZT (zidovudine, ZDV) was first introduced, HIV pVL was seen to decrease to undetectable levels in treated patients, but then recover within six months. Since then it has been discovered that combining therapies vastly decreases the rate of mutant strains arising, hence the introduction of triple therapy. Factors affecting the rate of ART resistance include poor drug absorption, drug-drug interactions, variable drug metabolism, and poor adherence. Not all treatment failure is due to viral resistance, in either previously drug-naïve [36] or heavily pre-treated patients [37]. However, for treatment failure without resistance, inadequate suppression risks emergence of resistant virus if therapy is continued [23].

There are several definitions of treatment failure: virological, immunological and clinical failure. These can occur alone or in combination, although virological failure generally precedes immunological failure which itself precedes clinical treatment failure, with each type often separated by months or years [22, 38]. Virological failure is typically defined as the persistence of detectable virus (e.g. >20-50 copies/ml within 24 weeks) or the appearance of detectable virus in a patient whose pVL was previously suppressed [39]. Immunological failure is defined by CD4 count changes

or other proxy measures such as total lymphocyte count (TLC). Clinical failure relies on the appearance of clinical symptoms or markers such as body mass index.

The definition of virological failure may be influenced by several factors such as the sensitivity of the HIV RNA assay, the clinical status of the individual, in particular whether or not they have had prior ART, and the pVL at initiation of treatment. However, the dominant paradigm that treatment failure is virological failure has been challenged by some on the grounds that patients tend to remain free of symptoms despite detectable pVLs for extended periods [40].

Although therapy is beneficial as long as the pVL is maintained below baseline, Gallant [39] believes that it is important to change therapy as soon as possible once virus is suppressed but detectable, in order to maintain durability and prevent cross-resistance, which can seriously limit the number of viable treatment options that are available. When treatment fails, the timing and choice of subsequent therapy may be critical in determining the magnitude and durability of the response. When a regimen is changed, the patient should be treated with at least three (and preferably all) new drugs, to which no resistance is anticipated.

Longitudinal studies have found that durable viral suppression occurs in only a minority of patients starting ART [41-44] (although higher rates of viral suppression have been reported in some cohorts [27, 45]), with the risk of clinical disease progression or death similar in patients who achieve durable HIV suppression and those in whom initial viral suppression is followed by rebound [27, 46, 47]. However, these cohorts have typically followed patients for two years or less; Lucas et al [41] found that the survival trajectories of patients with durable suppression were similar to patients with rebound over two years, but they became significantly different over prolonged follow-up. Therefore, when future treatment options are limited, it may not be in the best interest of the patient to change regimen immediately, but to delay for one or two years, before mortality rates diverge.

While a change of regimen may be recommended on clinical or laboratory grounds, switching to a more expensive second-line regimen may not be affordable, despite the risks of disease progression and drug resistance evolution. It has been recommended by the World Health Organisation (WHO) that patients who experience treatment failure with their initial regimen are to be given second-line salvage therapies [29]. However, these later regimens have substantially lower success rates than initial therapy, partly because of cross resistance [2]. This is investigated further in Chapter 6, where the one triple ART regimen assumed in all other chapters of this thesis is replaced by first-line regimen A and second-line salvage regimen B.

1.3.1 Adherence

Intermittent therapy and poor adherence are probably the most common reason for treatment failure [48, 49]. Failure rates increase sharply with decreasing levels of adherence [50]. Adherence is crucially important in limiting treatment failure and the evolution of ART-resistant variants. ART regimens are designed so that the minimum concentrations of the drugs are never sufficient to allow

appreciable virus replication. The longer a dose is delayed, the lower the concentration falls and the more virus replication occurs. If ART is interrupted, there is likely to be an increased number of target cells compared to the number in an untreated person, because new target cells have been produced during therapy which have escaped infection due to the decrease in pVL. Therefore theoretically there is an opportunity for the virions to replicate at a faster rate than they would normally in the absence of therapy, until the excess of uninfected target cells have all become infected, and the rate of viral replication within the host returns to the steady-state level (this is assuming that a reconstituted immune system is not suppressing viral replication). There is a higher risk of resistance developing immediately after cessation of therapy and before the pVL returns to its pre-therapy level and the prevalence of both wild type and mutant strains may increase during this period. If there is continual short-term cessation followed by resumption of therapy, the overall replicative capacity for resistance-carrying strains may increase. Phillips et al predicted that the risk of resistant virus evolving was far higher for frequent short-term treatment cessations (therapy taken every other day or two out of every three days i.e. simulating poor adherence) than for longer term drug 'holidays' of 50 days or more because the "riskiest" time for resistance emergence, immediately after stopping ART, is repeated many times [51].

Missing doses is particularly important during the period immediately after initiation of ART. This is because viral replication and therefore viral mutation rate are proportional to pVL, which is high at the start of therapy. A break in treatment at this point could lead to suboptimal drug levels in the presence of a high replication rate, leading to the rapid accumulation of viral mutations. However, those on therapy are continually challenged in maintaining adherence by complicated drug regimens and side effects.

The relationship between adherence and the risk of ART resistance emerging is postulated to be a bell-shaped curve, with a resistance peak at a moderate level of adherence [52]. This is based on the assumption that the presence of ART during viral replication creates a selective advantage for drug resistant virus, and that levels of adherence high enough to completely halt viral replication will prevent the development of drug resistance. A model by Bangsberg et al, based on empirical estimates of adherence, viral suppression and the rate of accumulation of PI mutations, predicted that the maximal rate of PI resistance occurs at 87% adherence, but declines only modestly at 100% adherence [48]. Therefore even with perfect levels of adherence, resistance evolution seems inevitable. It appears that very high ART adherence levels, perhaps 90-95%, are required in order to achieve lasting health benefits and to prevent emergence of drug resistance in the short-term [53], yet maintaining this level of adherence is difficult. Imperfect adherence is common and surveys indicate that one-third of patients miss doses within three days of survey [54]. Prior to the advent of triple ART, studies among HIV-infected patients suggested that levels of adherence to ARV regimens (mainly ZDV monotherapy) were similar to those observed in patients taking general medications, and were usually lower than 80% [55]. The complexity of ART regimens does raise concerns about the capacity

of most patients to reach higher levels of adherence and to maintain adherent behaviour for a long time.

Studies of other chronic conditions such as diabetes, coronary artery disease and tuberculosis (TB) have shown that: 1) adherence is poor across all populations and disease types; 2) clinicians cannot predict who will or will not be adherent; and 3) care providers consistently overestimate the proportion of patients who will be adherent [56]. In terms of patient characteristics, adherence cannot be predicted solely on the basis of demographic factors such as age, race, gender or educational status. Patient characteristics that can predict adherence include patient-clinician relationship, regimen complexity, degree of lifestyle alteration required to take medication as prescribed, forgetfulness, drug toxicity, being too ill, patient education and knowledge and beliefs about disease and medication, social support, and comorbid conditions such as substance abuse, cognitive impairment, depression and other mental illness [57]. Unfortunately, current ART regimens fair badly on almost all these points. However, no characteristics are fully predictive in individual patients, and all patients may be amenable to interventions. Better counselling facilities to stress the importance of adherence and more convenient regimens will help.

Adherence was seen as a significant barrier to the delivery of ART in sub-Saharan Africa [58, 59], despite little having been known about rates of adherence or predictors of adherence in this region or in other resource-poor settings [60]. Now that reports from pilot ART programmes in resource-poor settings are starting to be published, there are numerous examples of reported adherence rates as high as those in industrialised countries [61, 62]. Results are difficult to compare because different studies have different definitions of good adherence; Wood et al defined adherence as ≥75% [63], yet rates of at least 90% are desirable for long-term benefit from ART. Rates of adherence comparable to those from industrialised countries are ascribed to the simplicity and tolerability of regimens, free and uninterrupted supplies, and close medico-social support in the programmes, conditions that probably will not be enjoyed as programmes expand [30, 64]. Many reports are from the first year or two of a programme, when adherence and motivation are at their highest [65]. There are also several reports of ART resistance emerging in Africa in programmes where the above, ideal conditions for ART distribution are not met [66, 67]. Unfortunately, even adherence rates comparable to those from industrialised countries may not be sufficient to allow patients to substantially benefit from ART, if choices of salvage regimen are limited. Popp and Fisher argued in 2002 that adherence rates from wealthier nations would be "wholly inadequate" in a developing country context [58].

The most common reasons for failures in adherence to ART in resource-poor settings have been financial constraints, forgetfulness, stigma, transportation and/or migration issues, and tolerability, reasons which vary region by region. In Botswana, gaps in treatment (29%) were reported more frequently than day-to-day nonadherence (17%) [60]. The most common reasons cited for gaps in treatment were inadequate insurance coverage for expensive medication regimens (69%), frequent

travel and migration (16%) and lack of access to alternative regimens when side effects proved intolerable (22%). In Senegal, the main stated reasons for non-adherence were forgetfulness (35.2%) and financial difficulties (18.5%) [30].

Patients must be made aware of the importance of adherence before ART is initiated. For example, a study by Holmes and Pace found that patients with more optimism regarding their prognosis were significantly more likely to report both medication and safe sex nonadherence [12]. These authors recommended that a better understanding of seropositive patients' prognostic beliefs and the factors determining them is warranted. Carefully designed counselling and support services are required, because knowledge does not necessarily translate into behaviour change.

Gallant suggested that before starting therapy, a patient must understand the potential consequences of nonadherence, and that clinicians must monitor and reinforce adherence and work with their patients to design realistic regimens that are convenient and tolerable [39]. Counselling should be given to discourage risk behaviour, as well as to promote drug adherence. However, these provisions will inevitably raise the cost of an ART programme. Community health officers and volunteers may be in a better position to spend time with patients to counsel them about adherence.

The search continues for new drugs, not only with different modes of action, but drugs from existing classes with better bioavailability (and therefore smaller pill burden) or a longer half life (permitting once daily dosage) or with increased potency, less toxicity or a different resistance profile. Despite the good levels of adherence for pilot ART programmes, patients in resource-poor areas face other challenges to maintaining adherence, including disruptions to drug supply and, even where ARV drugs are provided free of charge, out of pocket expenses such as transportation costs and time away from work. Generic fixed dose combinations are widely regarded as crucial for scaling-up AIDS treatment in resource-poor settings because they improve adherence by requiring fewer daily doses, although this form of compounding also presents clinical and pharmacologic quality assurance issues [68]. Several of these combinations have been pre-qualified by WHO [69] and the FDA approved a generic version of a combination ARV drug for use by the President's Emergency Plan for AIDS Relief (PEPFAR) in January 2005. Médecins Sans Frontières (MSF) found that the WHO-recommended, fixed-dose combination of stavudine, lamivudine and nevirapine was affordable and easy to use (one pill twice a day) and could also be used to treat pregnant women [70].

1.3.2 Evolution of drug resistance (secondary resistance)

Currently the vast majority of resistance is secondary, meaning that it has evolved within that individual rather than having been transmitted to them as an ART-resistant HIV variant (primary resistance) [71]. Secondary resistance is extremely common in industrialised countries [71]. Multi-drug resistant (MDR) HIV strains due to single mutations or insertions are now emerging [72-74]. These strains are of particular concern because they can limit future treatment options. A study by

Gallego et al reported that 78.5% of individuals who had experienced drug failure harboured HIV strains which showed resistance to two or more drug classes [75].

In resource-poor settings there is restricted access to high quality facilities and experienced physicians. There are potential problems of drug sharing, black market dealing and inappropriate prescribing of mono- and dual therapy outside of official ART programmes [59]. The differences between ART programmes in industrialised and developing countries may be so marked that predicting programme impact and patterns of drug resistance from those in the West, as has been attempted [71], may not be particularly informative.

Rates of resistance evolution will depend on the choice of drug regimen. High-level resistance to certain drugs such as indinavir takes six months to two years to emerge, whereas for other drugs such as nevirapine and lamivudine it can develop in as short a time as one month after monotherapy treatment initiation [76]. High-level resistance to some drugs is conferred by single substitutions and for other drugs by a relatively large number of mutations which accumulate sequentially under therapeutic conditions [77]. Therefore, the constituent drugs of a triple combination therapy regime should be chosen to be as therapeutically effective (maximum viral suppression with minimal toxicity), cost effective and resilient to treatment interruption as possible. Interactions with other drugs and diet affect the efficacy of such regimens, and so an ART programme must involve education on lifestyle and support, perhaps dietary supplements and management of OIs, in order to fulfil their objectives, to minimise resistance emergence and maximise effectiveness of treatment. Wide scale prevention of mother to child transmission (PMTCT) of HIV using nevirapine monotherapy may be of concern in the future if resistance evolves over the long half-life of this drug. This is especially true where nevirapine is also included in standardised triple regimens for therapy.

There can also be treatment failure without resistance evolution, where there is viral rebound to detectable levels (although usually not as high as baseline) with wild type virus. Thus, it is not clear whether acquired resistance causes treatment failure or whether failure precipitates drug resistance [78-80], although biologically it seems likely that increases in viral replication facilitate the generation of mutant strains. The models used in this thesis assume that viral rebound precedes evolution of drug resistance.

The degree to which ART resistance will affect HIV epidemics is unclear. An optimistic estimate of 10% of treated cases developing ART-resistant strains per annum is used in some mathematical models [19]; this represents the optimal performance of ART in clinical trials. However, rates of emergence of up to 60% per annum have been generated from clinical- and community-level studies of ART resistance [81]. The high mutation rate of HIV implies that incompletely suppressed viral replication, on a scale sufficient to facilitate viral mutation in the presence of selective pressure from the drug, drives the evolution and fixation of drug-resistant virus at an alarming rate. Continued replication in the presence of the drug selects for even greater levels of resistance to each

administered drug, progressive cross-resistance to drugs of the same class [82] and potentially further compensatory mutations improving viral fitness.

1.3.3 Transmission of drug resistance (primary resistance)

Transmission of resistant strains is of crucial importance because it could render current drugs ineffective within a very short period of time. ART-resistant variants are generally not as fit in terms of replication turnover as wild type [83, 84], and so are not as easily transmitted. However, there is considerable concern that the widespread use of ART may result in increased transmission of drug resistant virus if ART is introduced to high prevalence resource-poor nations such as those in sub-Saharan Africa on a large scale [59]. Such transmission may jeopardise the success of currently potent regimens; consequently wide-scale surveillance of the prevalence of ART resistance is recommended [85]. Because individuals infected with resistant HIV strains may have predominantly wild type virus in the absence of treatment pressure, it is important to monitor the acquisition of treatment-resistant strains by focusing on patients with evidence of recent infection [86]. However, it is difficult to ensure adequate representativeness of samples, because it is hard to recruit recently infected persons. Nevertheless, several studies have reported ART resistance in newly infected individuals in Europe and the US.

Figure 1.2 summarises the findings of key studies of HIV primary drug resistance from Western Europe and the US, for primary mutations and phenotypic resistance. The evidence for increasing ARV resistance over time is weak and there are a number of outliers, but there remains a positive correlation. A recent review has reported that in urban areas of the US, there has been a dramatic increase in the proportion of individuals infected with HIV strains with high phenotypic resistance, and that a parallel increase has been recorded for the transmission of MDR strains [87]. Data from Europe are more heterogeneous, with increases in transmitted resistance reported for some countries, but not others.

A recent editorial on ART resistance concluded that, "for the next decade, large-scale surveillance for detecting transmitted resistance in Africa is unnecessary," and as an alternative, patients should be closely monitored for acquired resistance, and sentinel surveillance (in a few urban centres) should be used as an alternative monitoring system [71]. However, de Felici points out that individual therapy monitoring in such circumstances is unlikely, which may amplify the emergence of resistance. De Felici asserts that, "as we scale up to reach millions of people in developing countries, early identification of HIV resistance to ARV drugs and its causes will be critical to policy makers and programme managers," [87]. High rates of resistance emergence have already been reported from some small-scale studies in Africa [66, 67]. As a result, the global HIV drug resistance surveillance programme, as part of the WHO Global Strategy for Containment of Antimicrobial Resistance, has been established to provide representative data to guide national and international ART plans,

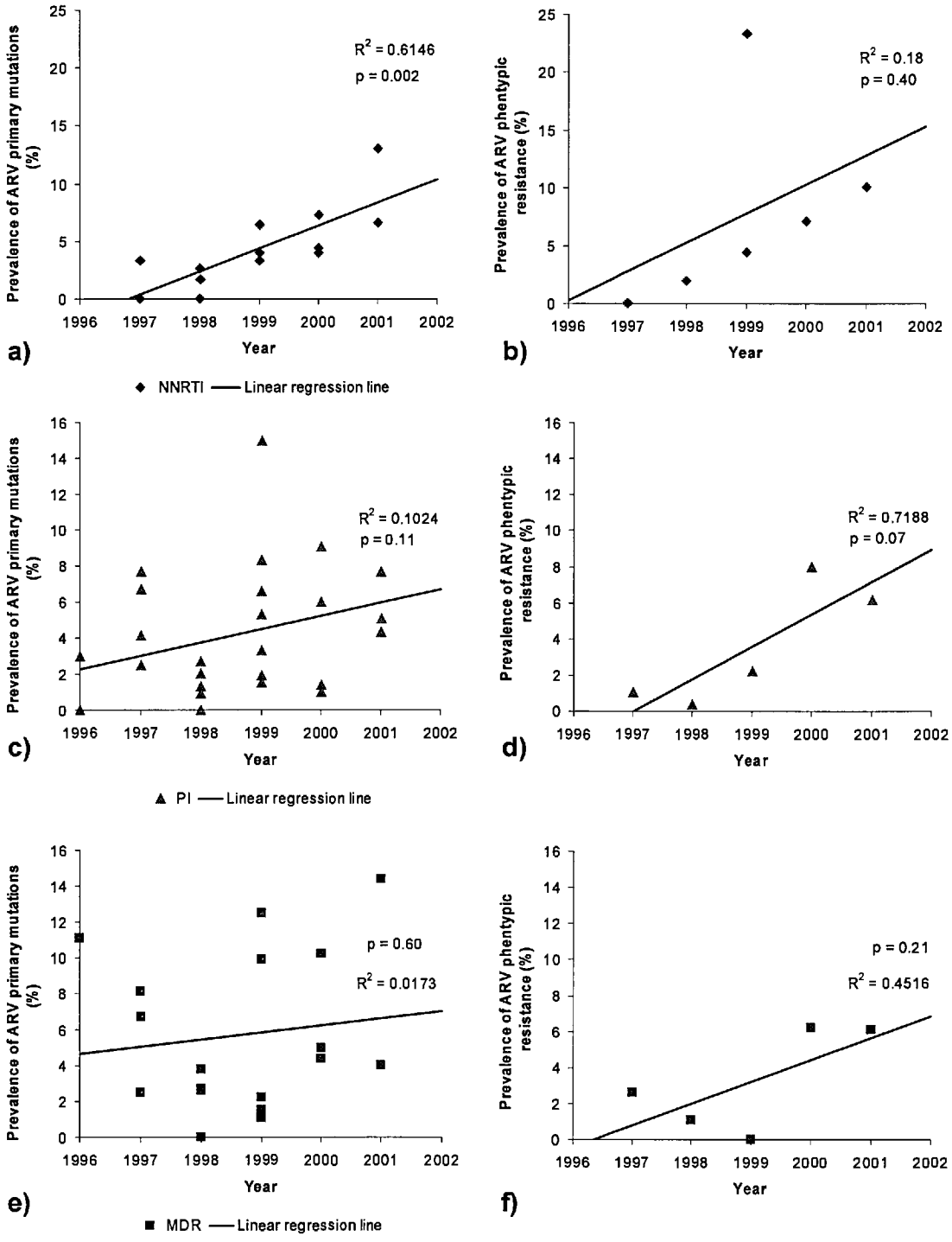
guidelines and other measures to sustain the effectiveness of ART programmes [87]. However reports on the details of this strategy are not currently available.

The rebound of pVL as a result of resistance evolution tends to be below baseline levels [42, 88] and drug-resistant HIV-1 has been demonstrated to have decreased replication capacity in vitro [89]. The low observed prevalence of transmitted MDR compared with high rates of such resistance among treated patients [71], also suggests a lower replicative fitness of mutated strains. Furthermore, Goudsmit et al [90] interpreted the rapid replacement of ZDV-resistant mutants in newly-infected individuals in their study as being a reflection of the lower fitness and therefore infectiousness of resistant mutants. Leigh Brown et al estimated that resistant virus was also only transmitted 20% as frequently as wild type virus [83]. However, Nijhuis et al found that continuous pressure in culture with a PI led to production of virus containing compensatory mutations that actually increased fitness, and predict that after an initial dip, infectivity will eventually increase in patients with ART-resistant phenotypes [91]. An individual with primary (transmitted) resistance may have a high risk of passing on the resistant viral phenotype during their period of primary, acute infection, but over time these resistant strains, which have a relatively poor replicative capacity, will not persist in the absence of treatment pressure. Therefore, at a later stage of infection, the individual is more likely to transmit an ART-sensitive viral variant. However, resistant phenotypes are archived as provirus in long-lived memory T-cells and will be rapidly selected when therapy is initiated.

Unless a drug resistant strain evolves which is more fit than wild type, superinfection is probably only likely in the successfully treated individual, where suppression of pVL allows the target cell population to recover, hence increasing the chance of successful replication and establishment of a new strain. In the untreated individual, it is unlikely that low frequency resistant virus, even with the same replicative capacity, would be able to compete against the established viral population sufficiently successfully to allow long-term persistence of the invading strain.

If ART use were common among individuals from core groups, the possibility of superinfection of those on ART means resistance could spread with the same pattern as the original HIV epidemic. HIV co-infection with different wild-type viruses [92], and by wild-type strains re-infecting patients harbouring drug-resistant viruses after a short period of treatment interruption [93], have both been documented. Chakraborty et al postulate that it is possible for patients infected with wild type HIV isolates and under successful ART to become exposed to drug-resistant strains that would have significant selective advantage, leading them to out-compete the original wild-type strain and instigate treatment failure [94]. They concede that the probability of an individual undergoing successful treatment of a wild-type strain being exposed to a drug-resistant strain is low, but the large-scale roll-out of ART in high prevalence, resource-poor settings may increase this probability substantially.

Figure 1.2 Summary of key studies of HIV-1 primary drug resistance in Western Europe and the US for a) primary mutations and b) phenotypic resistance.



NNRTI – non-nucleoside reverse transcriptase inhibitor
PI – protease inhibitor
MDR – multi-drug resistance (defined here as primary mutations to ≥2 classes of ARV drug
Linear regression performed using S-Plus version 6.0
Based on a review by Blower et al 2005 [71]

1.3.4 Toxicity and immune reconstitution

A summary of the most common side effects associated with ART is shown in Table 1.1. ART toxicities can be divided into early- (within the first days to weeks), medium- (within the first months) and late-term (typically in the second and subsequent years of ART) side effects. There is considerable overlap within these groupings and many side effects can occur at any time during therapy. Drug interactions also complicate ART, increasing toxicity or the risk of treatment failure. The wide range of conditions indicates the high level of clinical expertise required to manage these symptoms.

Table 1.1 Most common side effects of ART

Early-term

- Skin rash
- Central nervous system effects: drowsiness, insomnia, dizziness, confusion, vivid dreams
- Hepatotoxicity: elevation of liver enzymes and symptoms of hepatitis
- Teratogenicity: disturbance of foetal development, birth defects (efavirenz and ddI+d4T)
- Anaemia
- Gastrointestinal toxicity: nausea, vomiting, diarrhoea

Medium-term

- Lactic acidosis: unexpected clinical deterioration characterised by weakness, weight loss, abdominal pain and distension, anorexia, nausea, vomiting and diarrhoea
- Peripheral neuropathy: numbness, hyperaesthesia (abnormal or pathological increase in sensitivity to sensory stimuli) or dysaesthesia (impairment of any of the senses) and episodic shooting pain
- Pancreatitis

Long-term

- Dyslipidemia: elevation of serum cholesterol and triglyceride levels
- Lipodystrophy: abnormal fat distribution
- Cardiovascular disease: increased risk of myocardial infarction
- Hyperglycaemia and insulin resistance (diabetes)

Adapted from WHO biannual HIV/AIDS Antiretroviral Newsletter Issue No. 10 December 2003 (http://www.wpro.who.int/NR/rdonlyres/E4C44DA7-33FD-4AB6-99AF-86CE1AB621E8/0/ART_Newsletter_Issue_10.pdf accessed 3rd October 2005)

In addition to side effects directly attributable to drug toxicity, suppression of HIV replication by ART and the resultant increase in CD4 cells can be associated with inflammation in tissues infected by opportunistic pathogens, known as immune restoration or reconstitution syndrome (IRIS). Patients initiating ART with low CD4 counts are prone to develop these symptoms of OIs within the first few months after starting treatment [95], which can result in death [31]. Disease related to sub-

clinical or pre-existing infections with *Mycobacterium avium* complex, *M. tuberculosis*, Bacille Calmette-Guerin, cytomegalovirus, hepatitis B and C, *Cryptococcus neoformans* and others have been reported in patients who have experienced beneficial virological and immunological effects of ART [96]. Such manifestations of immune recovery require expert medical care.

Data on ART tolerability in Africa are limited, although many pilot studies from resource-poor settings have reported that side effects did not pose a large barrier to adherence [30, 60, 64, 97]. However, reports claiming that they are not a problem have still indicated high incidences of side effects. In Senegal, Landman et al reported that permanent treatment discontinuation was never necessary for serious adverse effects [64], yet in Botswana, Weiser et al [60] reported that 51% of patients noted some side effects associated with the use of ART and nearly 10% of patients reported side effects as a significant barrier to treatment. In a cohort in South India, 26% of patients developed side-effects and 10% discontinued treatment as a result [97]. Generally these pilot projects enjoy expert medical care, so side effects may be better managed than in rolled-out ART programmes, where laboratory facilities, medications and expert care may not be available. Standardised regimens or fixed dose combination pills employed by large-scale programmes would not have the flexibility to substitute one or two drugs within a regimen due to side effects.

1.4 Use of ART in resource-poor settings

> "The fact that countries with the highest HIV seroprevalences tended to have the lower total health expenditure, had fewer nurses and doctors, and provided more limited access to essential medications highlights the challenges in providing ART to HIV-infected patients in developing countries."
>
> *Drain et al 2004* [98]

The main barrier to introducing ART in resource-poor settings has been cost. This includes the much-publicised expense of treatment regimens, but also the costs of diagnosis, distribution and monitoring requirements for an ART programme. However the extra cost of ART is partially offset by savings through reduced rates of hospitalisation and OIs. Once the indirect costs (productivity losses associated with morbidity in HIV-infected individuals) are taken into account, ART has been shown to reduce overall costs in industrialised countries [99]. This is now also the case among many population groups in resource-poor settings, as shown by the increasing number of private companies in Africa that provide ARVs or subsidise their costs for their employees [100]. While the cost of programme infrastructure remains high, at least the costs of ARV drugs have fallen over the years. Table 1.2 shows the example of decreases in drug costs in Uganda.

Table 1.2 Cost of triple ART regimens in Uganda, 1998 to 2002[1].

Date	Cost (US dollars)		
	Brand name[2] NNRTI-based ART[3]	Non-brand name[4] NNRTI-based ART[3]	Brand name[2] PI-based ART[3]
August 1998	NA	NA	479-556
February 2000	440-533	NA	531-650
December 2000	113-411	185-190	163-540
June 2001	69-188	50-60	107-529
August 2002	69-121	35-50	76-379

[1] Prices are in US dollars for a 30-day supply of some typical combinations of ARV drugs available in Uganda. Prices reflect the cost for typical three-drug ART combinations available in Uganda at the time periods noted.
[2] Brand name drugs are those available from the large multinational pharmaceutical companies who were the innovators of the drugs.
[3] ART considered to be two NRTIs with one NNRTI or with one PI for this analysis.
[4] Non-brand name drugs refer to products produced by pharmaceutical companies that produce multisource products. Most non-brand name drugs available in Uganda are those from companies in India. During the time period of this analysis, St. Francis Hospital stocked only brand name drugs, but patients could purchase non-brand name drugs from other nearby centres.
NA – not available
From: Kabugo et al 2005 [101]

In 2001, the United Nations (UN) convened a 'special session' on AIDS: plans were made to strengthen HIV prevention and risk reduction, and to stave off death among those already infected. In September 2003, the leaders of the WHO, the UN Joint Cosponsored Programme on HIV/AIDS (UNAIDS), and the Global Fund to Fight AIDS, TB and Malaria joined together to declare the lack of access to ARV medications a "global health emergency". This prompted the launch of the "Treat Three Million by 2005" initiative (otherwise known as the "3 by 5" initiative). This initiative aimed to provide ART to three million people in the developing world by the end of 2005 [102]. This corresponds to treating half of those in need worldwide. While it is agreed that this target will not be met, the WHO asserts that "3 by 5" has helped to show how targets can shift debates, helping policy makers move from "if" ART can be provided, to "when", and now "how" it can be done effectively [103]. A detailed report providing in-depth data and analysis on the progress made at country level is due to be published at the end of 2005.

Notable donors include the Global Fund, PEPFAR and other bilateral donors, the World Bank, international non-governmental organisations and the private sector. PEPFAR is a US-based five year, US$15 billion, global initiative to combat the HIV/AIDS epidemic, with 55% of the budget earmarked for treatment and 15% for palliative care. While PEPFAR appears to be on target to meet their spending plan, the Global Fund has reported a funding gap that may prevent it awarding new grants to fight the pandemic [104]. Due to such initiatives, the situation regarding ART access has been completely transformed since the inception of the research described in this thesis.

The effectiveness of ART in resource-poor settings has been predicted to be less than in industrialised countries due to differences in prevalence of co-infections including TB and malaria (which may affect the natural history of HIV disease and the risk-benefit profile of ART) [105, 106], and socioeconomic differences (affecting variables such as nutritional status and access to potable water). This has already been observed in the duration of AIDS before death in the absence of ART being shorter in resource-poor settings [107], a fact that is in part due to differences in nutrition and treatment of AIDS-defining illnesses and other OIs. A substantial challenge that health care providers will face is the responsibility to ensure adequate nutritional support and treatment of OIs, not only to ART patients to maximise drug performance, but for all individuals, regardless of eligibility for an ART programme or even HIV status. Unfortunately, the provision of the support services required for ART to have maximum impact will further restrict numbers for whom treatment can be afforded. Furthermore, countries with the lowest health care indicator scores will have numerous competing needs, many of which will offer more cost-effective approaches than ART provision. ART roll-out guidelines stress that treatment delivery should not be at the expense of other health priorities [68], but in areas of chronic shortages, including those of health care personnel, it is hard to envisage how this is achievable. With the unprecedented political will to provide ART rather than more general improvements in health care, further disparities in other areas of health care provision are likely.

To aid the design of successful ART programmes in resource-poor settings, more information on the impact of ART provision is crucial, including data on tolerability, treatment failure and the possible emergence of drug resistant strains. This would inform design of cost-effective programmes producing the maximum benefit to patients at minimum risk to continuing drug effectiveness. ARV drugs must be procured at the lowest possible cost (generic versions if feasible), but not to the detriment of providing the most suitable regimen for the target population. Factors to consider when choosing appropriate regimens include drug potency, efficacy, convenience, tolerability and the implications of failure on future treatment options. Therefore, as well as sufficiently high patient adherence, the most efficacious drugs are required. They must be the most effective at inhibiting viral replication, have the longest half-life in the patient (thus being more permissive to poor adherence) and require many mutations in the viral genome to reduce significantly the drug's ability to suppress replication, given that options in the aftermath of treatment failure will be more limited in such areas. ARV drugs should be rationally sequenced in order to preserve future treatment options for as long as possible, although cost may often compromise this [22, 108].

According to the WHO, successful application of ART in resource-poor settings depends on keeping the drug regimen as simple as possible by limiting the choice of drugs for first-line treatment [29]. This will simplify the job of the physician in prescribing and monitoring patients on such complex regimens with an array of side effects. However, the simpler the programme, the less well it will fit the needs of individual patients. The regimen most tolerable to treatment interruption may not be suitable for pregnant women (in whom efavirenz and combinations of ddI with d4T are contraindicated). A

well-designed programme would also include a carefully designed support infrastructure so that issues such as consistent drug supply would be adequately addressed.

Harries et al see the situation in resource-poor settings thus: "there are few physicians skilled in the use of ARV drugs. The health infrastructure is incapable of monitoring pVL, immune status, or side-effects of the drugs. Drug procurement and distribution systems are weak, and drug interruptions are likely. Theft of drugs from health institutions for sale in markets, shops, private clinics and across national borders is a real concern. There are no monitoring systems in place to check on drug adherence or drug effectiveness," [59]. In this case, another argument for the establishment of large-scale ART programmes would be to guarantee proper ARV usage and thus minimise the extra risk of resistance transmission due to drug sharing and black market sales. Proper support systems need to be implemented for ART programmes in order to provide formal, reliable drug sources and minimise inappropriate ART practices.

It is often overlooked that it is not merely the price of ART that limits its use in resource-poor countries. It is apparent that wide-scale adoption of ART in resource-poor countries would require a marked increase in trained medical staff or a change in the role of other health care workers (HCWs), provision of counselling and outpatient care, and potentially, the installation of sophisticated laboratory equipment. ART is very complex and clinicians prescribing it require considerable expertise. Therefore, delegation of responsibilities to nurses and/or community health workers and volunteers could well compromise the effectiveness of treatment. Vergne et al add that in order to avoid the rapid emergence of resistant viruses on a large scale in the developing world, it is important that the infrastructures necessary to monitor ARV treatment are also rapidly created in these countries and that clinicians are trained in the appropriate use of ARV drugs [109]. Continuous surveillance to detect ARV drug resistant viruses must be organized to guide ARV treatment strategies and policies. In order to increase adherence through increased tolerability, the serious toxicity associated with all ARV drugs, as well as minor toxicity, must be managed properly [110]. Expert care improves survival [111] and decreases cost [112], but its scarcity is now regarded as impeding scale-up [103].

1.4.1 Priority setting

The WHO has provided ethical guidance on the issues that countries must address in order to ensure fair distribution of health resources in scaling up ART in the "3 by 5" initiative [113], yet any method of selecting patients for an ART programme would be highly political and unlikely to be random. Loewenson & McCoy believe that providing treatment on a "first come, first served" basis would not improve equality as it would favour "urban, higher educated people who are not poor" [114]. Nguyen et al believe that relying on medical criteria, such as CD4 counts, may also be inequitable, because the poor access health care later and often present with significant co-morbidity that may label them as being at a higher risk for treatment failure [115]. This assumes that a utilitarian approach is

adopted, where those with the best prognosis preferentially receive treatment, but it is at least as likely that those closest to death would get priority. The experience of MSF has been that, "putting those with the greatest risk of death first is most in keeping with the notion of fairness held by people living with HIV/AIDS," especially because those closest to death still experience considerable benefit from ART [70].

An ART programme may target certain groups of infected individuals, for instance 'socially worthy' or 'economically worthy' groups, such as nurses and school teachers. Certainly the AIDS epidemic has led to great shortages of such workers in many countries [116, 117]. Alternatively, groups contributing disproportionately to transmission, such as commercial sex workers (CSWs), could be targeted. Garnett et al stated that the cost-effectiveness of any HIV prevention programme is maximised by targeting socially and economically marginalised sections of the population, with CSWs being an obvious example [18]. However, it is now accepted that ART is unlikely to be an effective HIV prevention tool (see Chapters 2 and 5).

The consensus is that involving communities in decisions regarding patient selection would be most appropriate [114, 118], although this may allow policy makers to relinquish any responsibility for making unpalatable and often unpopular decisions and to withdraw from the process. A rationing mechanism used in resource-poor regions may have to select individuals who are able to pay at least something. One reason for this is that private patients already on medication may move into a free programme and thus deny entry to others who are more in need. However, the main resource that requires rationing is likely to be the time and expertise of the HCW, rather than the drugs themselves. Evidently, the selection of patients to enrol in an ART programme that cannot be universal would involve difficult decisions being made over who can benefit from treatment and who cannot.

1.4.2 Existing ART programmes

Since late 2003, when "3 by 5" was launched, ART coverage has more than doubled, increasing from 400,000 to approximately one million people receiving ART at the end of June 2005 [103]. This falls short of the 1.6 million target. Fourteen low- and middle-income countries have achieved ART coverage of at least 50% of those in need, consistent with the targets, but these are the exceptions. It is conceded that current data and trends indicate that providing ART to three million people by the end of 2005 will be unlikely [103]. Nevertheless, the initiative has achieved much in expanding access, making ART provision on a significant scale in these regions a realistic target. It also appears that the rate of roll-out is increasing. Unfortunately, most African countries report that demand for treatment still outstrips capacity, and stress the urgent need for increased resources and technical support in order to maintain their momentum in scaling up. Approximately 500,000 people in sub-Saharan Africa now receive ART (a three-fold increase over the preceding 12 months), meaning that roughly 50% of all treated patients are in this region. However, according to the most recent figures [119], the 25.8 million HIV infections in sub-Saharan Africa constitute approximately 64% of infections

worldwide and 77% of all adult and child deaths due to AIDS in 2005. The interim report on progress of the "3 by 5" initiative focuses on the implementation of ART provision [103]; a comprehensive report and country-specific analysis of access efforts and obstacles that remain is due to be released in early 2006.

Among the recommendations of the interim report is a shift from a physician-oriented model of ART delivery, with training of non-physician health workers using simplified and standardised ART regimens and clinical monitoring procedures. The aim is to maximise the number of people who can receive "quality HIV treatment", but follow-up reports on the performance of such programmes are urgently needed. To date, reports on outcomes of ART cohorts from resource-poor settings have not provided treatment through this type of structure [65].

Brazil and Thailand have been providing triple combination ART in the public health sector since 1996 and 2000, respectively. Brazil provides the most extensive ART coverage of any resource-poor country and has produced positive outcomes; mortality has decreased by 50% and inpatient hospital days caused by HIV by 60% [120]. Despite some limitations of public health hospitals and clinics, they perform better than the majority of resource-poor countries. A key factor in the success of this programme is the free distribution of ART. MSF pilot initiatives have been established in seven low- and middle-income countries: Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand and Guatemala. Treatment has been provided free to patients. The six month outcomes from these projects were positive, with good adherence and survival rates [121]. However these results are short-term. An informal report of survival at 24 months of 85% with 12% of patients lost to follow-up, from ten countries including Malawi, has also been encouraging [122]. Other programmes include the Drug Access Initiative (DAI), formed in 1998 by UNAIDS in collaboration with the Ministries of Health of Chile, Côte d'Ivoire, Uganda and Vietnam, aiming to set up the necessary infrastructure and systems to improve availability of ART and other AIDS drugs 'on a small but sustainable scale' [123]. Reports from the first two years of the initiatives in Côte d'Ivoire, for example, have been positive [124], with immunological and virological outcomes similar to those reported from industrialised countries. In Senegal, the government introduced its own pilot Initiative for Access to ARV Drugs (ISAARV) in 1998 [30, 125].

There are several examples of ART provision through pilot projects in resource-poor settings that are starting to provide local evidence and guidelines on which to base scaled up ART [14, 65, 126]. These sporadic and small-scale ART programmes have differed in their methods of delivery. Some have adopted the Directly Observed Therapy (DOT) approach used in TB treatment, but this will not be suitable in many settings because many patients will live a long way from treatment centres, and daily visits could reveal their HIV status and expose them to stigma. However, combined TB/HIV DOT has met with some success [127]. Appropriate management of concomitant TB and HIV infections is important because of the large numbers with dual infections (approximately two thirds of TB patients in KwaZulu Natal are co-infected with HIV [127]). Projects have also varied in their levels

of subsidies, but with time have increasingly favoured free medicines for the poorest patients. While Farmer et al have used a clinical approach to patient management in their programme in Haiti [14], the majority of reports of ART provision have included more sophisticated monitoring systems. These initiatives are in their infancy and probably do not reflect the approach to ART delivery on a wider scale. They have been able to recruit HCWs to their projects, but these individuals are in short supply. There are examples of bad approaches as well as good ones, such as the haphazard prescription and consumption practices reported from parts of India [128] and Thailand [129], and suboptimal therapy in Africa [60, 115]. More evidence of the performance of programmes adopting clinical management is urgently required to validate current guidelines for ART scale-up promoting this approach [103]. Additionally, the long-term performance with scale-up needs to be monitored. Laurent et al concede that, "the problem will be to keep the quality of care and drug availability at the same level as in this pilot study," [30]. Studies reporting successes in delivering ART in Africa have had relatively strict exclusion criteria, with participants tending to be urban with above average education and income. Therefore, they are probably not representative of most African patients requiring treatment [30, 130].

While there is increasing evidence that ART can be successful in Africa [30, 125, 131, 132], programme reviewers have conceded that there are many difficulties to overcome. Laurent et al [30] reported that in Senegal, "hindrances include the complexity of ARV drug administration, drug interactions, rapid emergence of viral resistance, the frequency of adverse effects, poor adherence, the frequency of hepatitis virus infection which can increase ARV hepatotoxicity, and inadequate knowledge of biological and clinical responses in patients infected by non-subtype B HIV-1 strains. Furthermore, most patients have advanced HIV disease by the time treatment is initiated and this could lead to higher toxicity, lower efficacy and severe immune restoration syndrome [96]".

1.4.3 ART use outside official programmes and "antiretroviral anarchy"

The last section touched upon the occurrence of unsuccessful programmes. This situation can often arise as a result of poor planning. As roll-out of ART on a meaningful scale begins ARVs will be more readily available outside established programmes. Kent et al warn that without careful implementation of ART, the distribution of drugs might be harmful not only because it could divert scarce resources, but also because future therapeutic options may be limited by the emergence of drug resistant organisms and because of community concerns about toxicity [133].

Blower et al believe that drug resistance will not be a major obstacle to ART use in resource-poor settings, and have set the case forward in influential editorials [71] and policy reports [68]. Criticisms of the assumptions made in these studies are discussed in Chapter 2. A further reason why we must not be complacent is that different clades may preferentially develop different mutations [133], which may have far reaching implications. This should not be used to delay roll-out, but population level monitoring of patterns of drug resistance will be required as ART roll-out begins.

More optimistically, ART regimens have consistently been demonstrated as safe and effective in pilot projects [65], and a study by Penzak et al reported that several generic nevirapine formulations from four developing countries contained the labelled amount of drug [134], although there have been isolated reports of counterfeit medications [135].

The simplest, most basic triple regimen recommended by WHO is ZDV, lamivudine (3TC) and either efavirenz or nevirapine. The Indian generics company Cipla sells a three-in-one pill called Triomune, to be taken twice a day, for $304/year, and the WHO have endorsed the quality of such generic drugs as those manufactured by Cipla.

Even the subsidised prices for ART are still unimaginable sums for the vast majority in resource-poor nations, where per capita income is typically less than $200/year. These people will only be able to access ART through public or privately funded programmes, or by haphazard and irregular ARV drug supplies through the black market, when money is available. This kind of therapy will almost certainly result in treatment failure and the evolution of drug resistance, and possibly its transmission. Vergne et al claim that "it is not rare to observe that patients [in resource-poor countries] receive monotherapy, or various combinations of two or three different drugs, often with unadapted daily doses and on a discontinuous basis as a result of the lack of continuous supply of the drugs or to economic constraints" [109]. For example, in Côte d'Ivoire, prior to the UNAIDS-DAI, no official policy on ART provision existed, yet 10% of HIV-infected people questioned reported having already received ARVs, mainly through provisions sent by friends or relatives in Europe or the US (equating to erratic supplies that are easily broken and risk leading to the evolution of ART resistance) [66]. Of those already receiving ARVs, 57% were found to have a primary mutation associated with ARV drug resistance, of whom 18% had MDR. Of those who could recall their regimens, 61% were on one or two NRTIs only, which would encourage resistance evolution.

Vergne et al [109] have also reported patients in Gabon with mutations to drugs other than those that they were receiving, suggesting that their treatment schedules were not constant over time, and that they had previously had therapy with several different drugs or drug classes: "it is not rare to observe that patients [in developing countries] receive monotherapy, or various combinations of two or three different drugs, often with unadapted daily doses and on a discontinuous basis as a result of a lack of continuous supply of the drugs or economic constraints". The Côte d'Ivoire DAI found that 12% of patients (n=307) had previously received ART [124]. Increasing access to ART for some (but still a minority) of those in need could increase inappropriate use by others through theft, corruption and distribution on the black market. There is an urgent need for proper support systems to minimise such inappropriate ARV treatment practices as suboptimal treatment regimens, interruption of ARV supplies and poor adherence.

1.4.4 Monitoring, laboratory facilities and official guidelines

Monitoring identifies treatment failure and allows the reassessment of the needs of the patient, in order to maintain clinical benefits of ART and minimise outgrowth of resistant virus. There are four main aspects of monitoring ART programmes: therapeutic effectiveness, drug toxicity, adherence to medication regimens, and emergence of resistant virus strains [133]. Monitoring in industrialised countries involves a suite of tests, including CD4 count, pVL and resistance testing. However, laboratory capacity and economic constraints mean that such resources will not always be available for such testing in resource-poor settings. It is generally considered that pVL monitoring is not a high priority for these settings [136]. CD4 count is cited as the best prognostic indicator in the short term [25, 124], whereas pVL monitoring is a strong predictor of clinical outcome in the mid- and long-term, but considerably increases the expense of monitoring. However, such testing can identify treatment failure at an earlier stage, and the benefits of this to the programme are investigated in Chapter 5. While CD4 testing is an important prognostic indicator, WHO recommends TLC, in combination with clinical staging, as a useful marker of prognosis and survival (but only for patients with symptomatic infection) [29]. ART can also be initiated in the absence of all laboratory tests (in many areas where ART roll-out is envisaged, particularly rural settings, any laboratory testing is unlikely to be feasible).

Farmer et al also believe that expensive pVL and CD4 count testing are unnecessary and that surrogate, clinical markers are sufficient [14]. The programme in Haiti initiates ART based on simple clinical criteria designed to identify those most likely to benefit. They claim that the most important criteria, weight loss and decreased body mass index, have been shown to predict survival and disease progression in HIV infection. However, authors also note that Brazil has introduced sophisticated pVL assays costing a small fraction of test costs in the USA, so such monitoring may be feasible in some other settings.

The interim WHO Classification System for HIV infection, summarised in Table 1.3, attempts to distinguish between patients at different stages of HIV infection in order to identify those requiring treatment, with or without information from TLC or CD4 count testing. In 2004, the WHO issued guidelines for use of ART in resource-poor settings [29], building on previous recommendations [108, 136]. The recommendations for initiating ART in adults and adolescents are based on the WHO clinical staging system and CD4 count or TLC testing, and are summarised in Table 1.4. However, early versions of the staging system for clinical management of ART have received criticism [107, 137, 138]. There is concern that the clinical guidelines result in some patients in need of treatment being missed by the criteria, while others may be over-treated. For example, in a cohort of Ethiopians followed without treatment (n=155), 41% of the adults who died never met the treatment indication as specified by the WHO simplified criteria [137]. In South Africa, the application of WHO criteria increased the treatment-eligible proportion of the target population from 44.5% to 56.7%, but did not prevent more deaths than treating symptomatic disease [139]. In Uganda, the sensitivity of the WHO criteria was low (18.4%), and only 56 of 615 deaths (9.1%) met the WHO criteria for the clinical

definition of AIDS [107]. In Rwanda, survival was similar at WHO stages III and IV [140]. A substantial problem in diagnosing AIDS patients using clinical criteria alone is the high prevalence of OIs, such as TB, among the general population. Chronic diarrhoea and 'wasting' are not striking characteristics in areas where food is scarce and hygiene is poor. It is therefore difficult to differentiate HIV-related illness from non-HIV-related illness. For example, in a study by Morgan et al in Uganda, 11 of 236 HIV-negative controls developed conditions which are classified as AIDS-defining, although none died during follow-up [141]. Studies in Uganda have found that a high proportion of HIV-positive subjects have no antecedent symptoms suggestive of terminal HIV less than a year prior to death [107, 142]. An asymptomatic patient turned away from a programme may be on the verge of a rapid deterioration in health and may not be able to return for treatment once sick. Recently the WHO clinical staging system and guidelines on when to initiate ART for the African region have been reviewed in preparation for wide-scale ART roll-out, with an interim report available [143] and a finalised version expected in the near future.

Table 1.3 Revised WHO clinical staging of HIV/AIDS for adults and adolescents

Interim African Region version for persons aged 15 years or more with positive HIV antibody test or other laboratory evidence of HIV infection. Simplified staging system that is clinically based and flexible enough to be used in different parts of the world [143].

Primary HIV infection	Asymptomatic; acute retroviral syndrome
Clinical stage 1	Asymptomatic; persistent generalised lymphadenopathy
Clinical stage 2	Moderate unexplained weight loss (<10% of presumed or measured body weight); recurrent respiratory tract infections (respiratory tract infections, sinusitis, bronchitis, otitis media, pharyngitis); herpes zoster; angular cheilitis; recurrent oral ulcerations; papular pruritic eruptions; seborrhoeic dermatitis; fungal nail infections of fingers
Clinical stage 3	***Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations*** Severe unexplained weight loss (>10% of presumed or measured body weight); unexplained chronic diarrhoea for longer than one month; unexplained persistent fever (intermittent or constant for longer than one month); oral candidiasis; oral hairy leukoplakia; pulmonary TB diagnosed in the last two years; severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia); acute necrotising ulcerative stomatitis, gingivitis or periodontitis ***Conditions where confirmatory diagnostic testing is necessary*** Unexplained anaemia and/or neutropenia and/or thrombocytopenia for more than one month
Clinical stage 4	***Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations*** HIV wasting syndrome; pneumocystis pneumonia; recurrent severe or radiological bacterial pneumonia; chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration); oesophageal candidiasis; extrapulmonary TB; Kaposi's sarcoma; Central nervous system toxoplasmosis; HIV encephalopathy ***Conditions where confirmatory diagnostic testing is necessary*** Extrapulmonary cryptococcosis including meningitis; disseminated non-tuberculous mycobacteria infection; progressive multifocal leukoencephalopathy; candida of trachea, bronchi or lungs; cryptosporidiosis; Isosporiasis; visceral herpes simplex virus infection; cytomegalovirus infection (retinitis or of an organ other than liver, spleen or lymph nodes); any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis); recurrent non-typhoid salmonella septicaemia; lymphoma (cerebral or B cell non-Hodgkin); invasive cervical carcinoma; visceral leishmaniasis

Immunological Staging of HIV Infection

CD4 levels in relation to the severity of immunosuppression:

>500/mm^3	Not significant immunosuppression
350-499/mm^3	Mild immunosuppression
200-349/mm^3	Advanced immunosuppression
<200/mm^3	Severe immunosuppression

Clinical and Immunological Criteria for Initiating ART in Adults and Adolescents

Clinical Stage	ART
4	Treat
3	Consider treatment: CD4, if available, can guide the urgency with which ART should be started.
1 or 2	Only if CD4 <200/mm^3

Table 1.4 WHO recommendations for initiating ART in adults and adolescents with documented HIV infection [29]

If CD4 testing available, it is recommended to document baseline CD4 counts and to offer to ART patients with:

- **WHO Stage IV disease, irrespective of CD4 count**
- **WHO Stage III disease** (including but not restricted to HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), **with consideration of using CD4 cell counts <350 cells/mm^3 to assist decision making**
- **WHO Stage I or II disease with CD4 counts ≤200 cells/mm^3**

If CD4 testing unavailable, it is recommended to offer ART to patients with:

- **WHO Stage IV disease, irrespective of total lymphocyte count**
- **WHO Stage III disease** (including but not restricted to HIV wasting, chronic diarrhoea of unknown aetiology, prolonged fever of unknown aetiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), **irrespective of the total lymphocyte count**
- **WHO Stage II disease with a total lymphocyte count ≤1200 cells/mm^3**

The absence of pVL and perhaps CD4 count or TLC testing from ART programmes may accelerate the evolution and spread of drug resistance. It is important to monitor treatment failure to minimise outgrowth of resistant virus, discontinuing ineffective regimens as soon as possible. Stevens et al believe that, "unless monitoring of virus load is adopted alongside the introduction of ART in developing countries, the risk of drug resistance arising and being transmitted are greatly increased," [49]. Without such monitoring facilities clinicians must rely on clinical relapse to detect treatment failure, by which point opportunities to limit cross resistance may have been lost. Where only one or at the most two regimens are available, the importance of this diminishes at the patient level because there are no alternative regimens accessible. However, at the population level it is all the more important because if widespread resistance renders first-line regimens useless, expensive second-line regimens would be required. The majority of studies that have reported on ART programmes in resource-poor settings have used pVL as well as CD4 count testing as part of their monitoring [65].

Genotypic and phenotypic resistance assays are important tools to help design more effective salvage regimens in industrialised countries [79]. However, interpreting the results of resistance tests remains a challenge, with interpretive guides rapidly becoming outdated. Tests may not be sensitive enough to detect small subpopulations of strains resistant to drugs the patient has taken in the past. Their expense means that such assays will not be used for individual patient monitoring in resource-poor settings, but may play an important role in maintaining surveillance of the extent of drug resistance, particular primary (transmitted) ARV resistance, within populations. An exception to this

may be their use in perinatal resistance testing of pregnant women who have previously received ART [144]. Weinstein et al suggested that baseline testing may be cost-effective when the prevalence of drug resistance in the relevant drug-naïve population is ≥5% [80].

The optimum frequency with which the progress of a patient receiving ART is followed up requires a trade-off between use of resources (HCWs' time, laboratory reagents and laboratory workers) and timeliness of identifying problems with treatment and addressing them. However, for ART programmes on shoe-string budgets, where no, or very few, alternative regimens are available, the usefulness of identifying treatment failure quickly is far less (with the obvious exception of minimising drug resistance evolution and transmission). The resources expended identifying failure early may be better deployed elsewhere. Therefore the relative performances of ART programmes with pVL or CD4 count testing, or neither of these, is a key research question when considering the design of treatment programmes in resource-poor settings. The relative effects in terms of benefits to the patient and emergence of drug resistance should be addressed.

1.4.5 Second line therapy and cessation of treatment

The reasons for changing an ART regimen include side effects, inconvenient regimens concerning dosing/number of pills that may compromise adherence, treatment failure, occurrence of active TB and pregnancy [136]. Future treatment options will depend on the availability of alternative, second-line regimens, which may be more expensive. The ART model described in Chapter 5 assumes that patients who suffer treatment failure are withdrawn from therapy and that drug supplies are then used to benefit another patient. Although treatment failure means that ART is less effective, there remains considerable clinical benefit [27]. Continuing ART with viral rebound will promote the emergence of drug resistance and increases the risk of accumulating additional resistance mutations conferring high levels of resistance, yet discontinuing therapy (even with ongoing viraemia) leads to a rapid increase in pVL, decreased CD4 count and increased risk of clinical progression [145] and is therefore not recommended [146]. The US Department of Health and Human Services (USDHHS) guidelines state that, "it is reasonable to observe a patient on the same regimen, rather than changing it (depending on the stage of HIV disease), if there are few or no treatment options," [22]. However, where resources are scarce and not all patients in need can even obtain first line therapy, this raises a moral dilemma, as doctors and other decision makers must decide whether to adopt a utilitarian approach and transfer therapy, or whether to respect the physician's commitment to the existing patient. Chapter 6 compares the epidemiological impacts of programmes offering first-line only versus salvage regimen provision approaches.

1.4.6 Treatment of opportunistic infections

Progression to symptomatic disease, and from AIDS to death, in Africa is rapid without ART. One of the contributing factors is that non-specific signs and symptoms associated with HIV are also

common in the general population and hence go unrecognised as symptomatic of viral infection, and also because secondary prophylaxis for AIDS-defining conditions (ADCs) is often not available [147].

An effective precaution used to delay infection with OIs as CD4 count declines is to start patients on *Mycobacterium avium* complex (MAC) prophylaxis when CD4 count is less than 75 cells/mm^3 and *Pneumocystis carinii* pneumonia (PCP) prophylaxis when CD4 count is less than 200 cells/mm^3 [46]. It is important to provide adequate treatment and prophylaxis for a range of possible OIs that may develop within ART patients [103].

1.4.7 Sexual behaviour change

The possibility of wide scale use of ART leading to changes in patterns of risk behaviour, particularly a behavioural disinhibition effect, has been of considerable concern. There are competing possible future effects. At the individual level, treated patients may increase their frequency of sexual activity due to the severity of their symptoms decreasing, but they may also receive effective prevention counselling, which could decrease their frequency of risky activities. At the population level, in areas with substantial treatment coverage and successful treatment outcomes, there may be an increase in complacency among the general population about HIV, leading to increases in risk behaviour. Despite considerable debate, this relationship has not been convincingly demonstrated in industrialised countries where ART is readily available [11, 148-151]. Boily et al have suggested that recent increases in risk-taking behaviour among men who have sex with men (MSM) may be the result of non-volitional changes at the individual level over time [10]. The depletion of the pool of high-risk individuals in the pre-ART era made it more difficult for the remaining high risk-taking individuals to find partners to engage in risky sex with, but ART has facilitated the differential replenishment of this group. Therefore individuals who previously had to reduce their levels of risky sex could resume their initial high-risk behaviours.

The behavioural effects resulting from ART use in resource-poor settings are unlikely to follow patterns of industrialised countries. A person's decision to have sex, protected or unprotected, is influenced by a different set of considerations in resource-poor settings than those common in industrialised countries. Key is the ability of an individual to negotiate their own sexual activity – as defined by fear of stigma, financial need, or the status of women within society. An individual is also less likely to be aware of their serostatus, due to lack of testing facilities and/or fears regarding a positive result. The provision of treatment may increase interest in VCT services, which may in turn lead to a decrease in frequency of risk behaviour by those knowing their infection status. In Côte d'Ivoire for example, individuals reported low sexual activity following an HIV diagnosis, and this was not increased by the offer of ART [152].

While such results may be encouraging, they are not universal. For example, only a minority of Western African women disclose a positive serostatus to their main partner and find it difficult to avoid unprotected sexual relations [153, 154]. Increases in risky behaviour at the population level

could have catastrophic consequences, with the costs of substantial ART coverage in areas of increasing HIV incidence quickly spiralling out of control.

Behavioural interventions in Africa have not always met with success, and it may be that if individuals did not substantially change their levels of risk behaviour in response to the HIV pandemic, the introduction of ART may also not have a marked effect. Until ART has been rolled out with a sufficiently high coverage and has been demonstrated to improve the lives of patients, the views of the individual regarding HIV and AIDS are unlikely to change and will presumably be reflected by a similar absence of behaviour change. However, the consequences of successful ART provision to a large proportion of those affected could instigate such changes, which are highly unpredictable. Therefore, behavioural surveillance with scale-up and models predicting best and worst case scenarios are important areas of research.

1.5 Key research questions

Egger et al highlighted key research questions regarding scaling up of ART in resource poor settings, which are summarised in Table 1.5 [155]. These questions reiterate many of the points and uncertainties in ART delivery that have been raised in this chapter. Many of these issues can be investigated using the results from appropriately designed mathematical models. In particular, issues relating to the following questions asked by Egger are addressed in this thesis:

1.1 When should treatment be started?

A discussion of the timing of initiation of ART is presented in section 1.2. The question is addressed using mathematical models in Chapter 5, which compares treatment of AIDS patients with preferential treatment of pre-AIDS patients, as well as a 'first come, first served' approach, where symptomatic HIV patients start treatment in the order in which they present to an ART clinic, rather than being differentiated by severity of disease. The question is also examined in Chapter 2 using more preliminary models. Very early treatment initiation, even during primary infection, is investigated. In both chapters, the impact of these various strategies on the epidemic is assessed. In Chapter 2, this is for unlimited treatment only, in order to look at the maximum impact that ART could have. In Chapter 5, unlimited treatment is compared to more realistic scenarios where treatment is rationed, and programme-level outcomes as well as population-level outcomes are discussed.

1.2 How can treatment be monitored if laboratory facilities are limited?

Problems relating to monitoring of ART patients in resource-constrained settings are discussed in section 1.4.4. Clinical management, where patients are assessed based on clinical criteria, saves on costs, but there are difficulties in prioritising ART to those closest to death and there is greater risk of emergence of drug resistance. Comparisons of outcomes for ART programmes using clinical-based criteria for initiating treatment and potentially also withdrawal of failing treatment, is investigated using the model presented in Chapter 5. The model in Chapter 6 investigates the implications of offering a

salvage regimen, and timing of switching to the second-line regimen, which is dependent on when treatment failure is detected, is modelled.

1.3 When should treatment be changed?

As discussed in the previous question, the model described in Chapter 6 incorporates two lines of ART and investigates switching regimens based on clinical, immunological or virological criteria. Switching based on immunological or virological criteria require the availability of CD4 count and pVL testing, respectively. The implications of different strategies in terms of benefits to the patient and costs to the ART programme are investigated.

1.4 What is the quality of life of treated patients and what toxicities and adverse events do they experience?

While the quality of life of treated patients is difficult to assess, the frequency and severity of toxicities and adverse events that they experience as a result of ART are broadly addressed in the models. The models in Chapters 5 and 6 investigate best and worst case scenarios, which relate to the quality of the ART programme. Higher rates of drop-out are experienced in the worst case scenarios, because such programmes cannot manage side effects adequately. Best case scenario programmes are assumed to provide better access to expert care, in terms of HCW time, provision of drugs to treat side effects, simple laboratory facilities to identify problems (such as liver function tests), ability to switch an ARV drug within the triple regimen, or any combination of these.

1.5 How does treatment affect patients' preventive behaviours?

The discussion in section 1.4.7 regarding sexual behaviour change highlighted the importance of behavioural surveillance to interpret how risk-taking changes with the introduction of ART. While mathematical models cannot predict how patients' risk behaviours will change as a result of ART, they can look at how different assumptions regarding risk behaviour change may impact the epidemic. Chapter 5 compares optimistic and pessimistic assumptions regarding patients' risk behaviours after starting ART and their effect on the HIV epidemic in an unlimited treatment scenario.

2.1 Is access to treatment and care equitable?

Chapters 5 and 6 look at the relationship between effectiveness of treatment for each treated patient (duration on ART) and access to treatment (total ever treated) when ART use is rationed. For a programme offering a finite number of places for patients, the more effective treatment is, the longer a patient remains in the programme, but the smaller is the overall number in need that can benefit. This is discussed in Chapter 6, but is only part of a much wider range of problems in this area. Other models have been designed to address certain aspects of inequalities in access to ART, such as spatial inequalities (urban versus rural) [156], but questions regarding prioritisation of treatment where resources are limited require substantial input from ethicists [118, 157].

5.1 How will treatment scale-up influence the course of the epidemic?

As discussed at the beginning of this chapter in section 1.1, ART use influences several parameters that affect HIV transmission, and since the demonstrated success of triple therapy in the mid-1990s,

the effect of ART on transmission within industrialised countries has been investigated. The impact of ART in resource-poor settings is investigated in Chapter 5 of this thesis, including examination of the effect by degree of coverage of those in need, by stage of infection at which ART is initiated, and by predicting degree of behavioural change of patients once treatment is started.

Table 1.5 Scaling up ART: examples of research questions at different levels

Research Question	
1	**Individual and household level**
1.1	When should treatment be started?
1.2	How can treatment be monitored if laboratory facilities are limited?
1.3	When should treatment be changed?
1.4	What is the quality of life of treated patients and what toxicities and adverse events do they experience?
1.5	How does treatment affect patients' preventive behaviours?
1.6	What is the impact of treatment on the household economy?
2	**Treatment programme**
2.1	Is access to treatment and care equitable?
2.2	How should patients be prepared for treatment to maximise adherence and reduce adverse events?
2.3	What is the place of family-based approaches to treatment?
2.4	What is the role of the private sector and of traditional medicine?
2.5	What are the main points of entry into the treatment programme?
3	**Community**
3.1	What is the role of community-based treatment support, for example, community health workers?
3.2	What are the levels of stigma and how does stigma and discrimination affect treatment programmes and outcomes?
4	**Health systems**
4.1	How can treatment programmes best be integrated with other programmes, including TB and mother and child health programmes?
4.2	What is the appropriate level of staffing of treatment programmes and what is the role of medical assistants?
4.3	How can the supply of medicines be secured and made sustainable?
5	**Country**
5.1	How will treatment scale-up influence the course of the epidemic?
5.2	What is the impact on macro-economic indicators?
6	**International**
6.1	How can the agenda of trade organisations, governments, donor agencies, and the pharmaceutical industry be influenced?

Adapted from Egger et al 2005 [155]

1.6 Discussion

This thesis presents a series of mathematical models which are designed to predict the impact that ART programmes will have in resource-poor settings, and how different strategies of ART delivery may affect epidemiological outcomes. Current data on the performance of ART programmes in such regions are limited and generally come from carefully designed studies, which may not reflect the performance of scaled-up ART programmes over time. Models can be used to inform public health efforts and predict the impact of scale-up under these less than perfect conditions.

However, public health interventions should not be based on the predictions of one model alone. The uncertainty regarding the effects of ART, including related infectiousness and risk behaviour, means that different model assumptions, with regard to structure and parameter estimates, may drastically affect the results. The review of models examining the effects of ART, together with the examination of the implications of various structural assumptions investigated in Chapter 2, highlight this fact. The model described in Chapter 5 that is used to investigate the impact of ART has been constructed in light of these issues. The model is used to predict the maximum impact of ART during epidemics of different magnitudes and stages. It also investigates the impact of different treatment strategies, including the stage of infection at which treatment is initiated (analogous to Stage III versus Stage IV treatment initiation according to the WHO criteria).

Chapter 4 presents the evidence on which the parameterisation used in Chapter 5 is based. It demonstrates the effort required to assess the available literature on HIV/AIDS adequately, and therefore suggests that there should be increased sharing, both formal and informal, of such evaluations in order to inform future HIV transmission models. Chapter 3 presents a comprehensive systematic review for just one parameter, infectiousness.

Chapter 6 investigates the impact of provision of salvage, second-line treatment. Provision of second-line treatment is recommended by WHO guidelines for ART provision in all resource-poor settings, and so this model provides a more realistic scenario than earlier models. In particular, the timing of regimen switching is considered. In Chapter 7, the findings of the thesis are reviewed and the work placed in the wider context of ART scale-up.

Chapter 2 ART use and mathematical models

Summary

This chapter summarises the work of theoretical studies attempting to assess the population impact of ART use on key outcomes such as mortality, HIV incidence and ARV drug resistance, with an emphasis on predicting outcomes in resource-poor settings. Mathematical models of disease transmission are the natural framework within which to explore the interaction between ART use and the dynamics of an HIV epidemic. The chapter begins with an introduction to mathematical modelling including some key concepts and a description of the classic SIR (Susceptible-Infected-Recovered) model, followed by a review of the state of the art of mathematical models for sexually transmitted infections (STIs). There follows a description and characterisation of some simple ART models which have been developed as part of the progression towards more complex models used in later chapters. This is followed by a review of the utilisation of mathematical models in the context of ART use in particular, with some issues illustrated with results from the simple models. In terms of investigating ART use, choice of model type and structure, the potential for risk behaviour change following widespread introduction of ART, the importance of the stage of HIV infection at which treatment is initiated, and the potential for spread of drug resistance, are all discussed. These issues are illustrated with results from models of HIV transmission. HIV transmission models predicting the impact of ART use should incorporate a realistic progression through stages of HIV infection in order to capture the effect of the timing of treatment initiation on disease spread. The uncertainty surrounding certain effects of ART, such as changes in sexual behaviour and transmission of ART-resistant strains, demands exploration of best and worst case scenarios in modelling, but this must be complemented by surveillance and behavioural surveys in order to quantify such effects in settings where ART is implemented.

2.1 Background: Models in infectious disease epidemiology

A mathematical model is an abstract model that uses mathematical language to describe the behaviour of a system. Mathematical models usually describe a system by a set of variables and a set of equations that establish relationships between the variables. The variables represent some properties of the system, such as different types of people or different types of immune cell within the body. The actual model is the set of functions that describe the relations between the different variables. Such models can be used to generate and test hypotheses of how systems work, and thus within the context of infectious disease epidemiology, can be used to try to gain a deeper understanding of the underlying processes that generate observed patterns of disease or infection.

Such models can be used as tools with which to predict changes in infection and/or disease patterns, either with time, age or space alone, or accompanied by changes in behaviour or biology, which may be associated with interventions. Results from models are useful when there is insufficient time or money for field studies or laboratory tests, or where alternative methods of research are not possible. Models can explore the relationship between an intervention and its impact during the planning phase of such an intervention. However, the limitations of model predictions must be appreciated – inappropriate assumptions, poor quality data for estimating parameters or validating outputs and uncertainty regarding parameter values will all affect the ability of a model to predict valid or precise trends.

The application of mathematics to the study of infectious disease appears to have been initiated in 1760, when Daniel Bernouilli used a mathematical method to evaluate the effectiveness of various techniques of variolation against smallpox. Hamer and Ross were the first to formulate specific theories about the transmission of infectious disease in simple but precise mathematical statements and to investigate the properties of the resulting models. Hamer (1906) postulated that the course of an epidemic depends on the rate of contact between susceptible and infectious individuals. This so-called 'mass-action' principle, in which the rate of spread of infection is assumed to be proportional to the product of the density of susceptibles times the density of infectious individuals, has become one of the most important concepts in mathematical epidemiology.

2.2 Some key statistics in infectious disease modelling

2.2.1 The basic reproductive number R_0

The epidemiology of any infectious disease is heavily influenced by the basic reproductive number R_0 of the organism, which is defined as the average number of secondary infections generated by one primary case in a totally susceptible population [158]. The value of R_0 characterises the initial growth rate of an epidemic, although more accurately, R_0 is a multiplication factor: it is dimensionless. There is a threshold value of R_0 of one, in the sense that, on average, an epidemic will result from the introduction of an infectious agent into a wholly susceptible population when $R_0 > 1$, while the number of infecteds is expected to decline after the introduction of an agent when $R_0 < 1$. If $R_0 = 1$ the infection will be endemic because each infected individual will, on average, infect one more individual while infectious, and so the number of infected individuals at any point in time will be constant. The concept of R_0 is central to any discussion of the overall population biology of an organism. For STIs, R_0 can be defined in its simplest form as the product of the average probability that the infection is transmitted per sexual partnership (or contact) (β), the average number of sexual partners (or contacts) per unit time (c), and the average duration of infectiousness

of an infected person (D). This can be expressed in the following equation, which provides the conceptual framework for the models used in this thesis:

$R_0 = \beta cD$ (2.1)

When such infections become established in a host population, the fraction remaining susceptible decreases. When the general population is not totally susceptible to infection, the "effective" reproductive number will be less than R_0 and is designated $R_{E(t)}$. Eventually an equilibrium may be attained, with the rate at which susceptible individuals become infected being balanced against the rate at which newly susceptible individuals appear (by birth, immigration or loss of immunity). At equilibrium, each infection will on average produce exactly one secondary infection, and so the effective reproductive number ($R_{E(t)}$) of the infection is given as $R_{E(t)} = 1$.

2.2.2 The exponential growth rate r and the generation time T_g

At the beginning of an epidemic, the initial, exponential growth rate r is given as $r = \beta c - \gamma$ and therefore also as $r = \gamma(R_0 - 1)$ because $R_0 = \beta c / \gamma$ if $D = 1/\gamma$ (from equation 2.1). This relationship between R_0 and r is important because it can be used to estimate the value of R_0 from epidemic data. In general, a high value of R_0 does not necessarily imply a high value of r, the rate at which an infectious disease epidemic increases. To use demography as an analogy: if people have many children, but only when they themselves are already quite old, population growth may still be slow. In terms of infectious disease, the formula for R_0 depends only on the difference in number of infections between two time points, the time of infection of the primary case, and average time of infection of secondary cases (the definition of the generation time, also known as the serial or transmission interval, T_g). In contrast, r depends on the magnitude of the difference in time between these time points. For r, the time course of infectivity matters, whereas for R_0 it does not. r is important because it determines the rapidity of infection spread in a population, which R_0 does not account for. The doubling time for the number of cases in a growing epidemic is of the order $\ln(2)T_g/(R_0 - 1)$ [159]. The effective reproductive number $R_{E(t)}$ can be defined as the factor of increase or decrease in infection incidence over a time period equal to the average generation time.

The generation time is the interval between successive infections (i.e. between the infection of a primary case and one of its secondary cases). The magnitude of this interval is determined by three time periods: the time from infection to onset of infectiousness (the latent period), the duration of infectiousness and the time from infection to clinical onset (the incubation period) [160]. The level of infectiousness can vary considerably during the course of the infectious period. This is particularly

the case for HIV (see Figure 1.1, Chapter 1). The actual number of transmission events and their distribution over time will reflect all of these factors. Therefore the pattern of infectiousness with stage of HIV infection will affect T_g and therefore the speed at which an epidemic progresses.

2.3 Compartmental models in epidemiology - the SIR model

The simplest dynamic infection transmission model, the SIR model, divides the model population into those who are susceptible to the disease ($S_{(t)}$), those who are infected ($I_{(t)}$) and those who have recovered or are immune ($R_{(t)}$), the numbers of which vary with time t. These subdivisions of the population are called compartments, and constitute the state variables of the system. The SIR model is illustrated in Figure 2.1, with boxes representing the compartments.

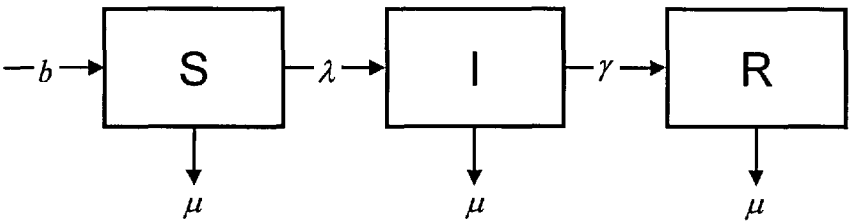


Figure 2.1 Flow diagram illustrating the classic SIR model.
There are three categories: S = susceptible, I = infected, R = recovered. λ represents the force of infection and γ represents the average rate of loss of infectiousness.

The movements of people in the population between compartments (transition rates) are represented by arrows. Susceptibles are lost by 'natural' deaths (deaths not associated with the infection in question) at a rate μ, or they are transferred to the infected class at a rate λ, the force of infection. The force of infection is the rate at which susceptible individuals become infected by an infectious disease (that is, the probability per unit time for a susceptible to become infected). It is analogous to the law of mass action from chemical kinetics; the number of new cases of a disease in a time interval is proportional to the product of numbers of infected and susceptible hosts in the previous time interval, so the force of infection is assumed to be proportional to I, the number of infecteds at time t. Infected individuals either die (naturally at rate μ) or recover into the immune or recovered class (at rate γ). The model assumes that an infected individual immediately becomes infectious; that is, there is no latent period. Infecteds have a constant probability per unit time of being removed. Thus the infectious period has a negative exponential distribution with parameter $\gamma+\mu$, so that the probability of still being infectious per unit time after infection is $e^{-(\gamma+\mu)\tau}$, where τ is time since infection, and the average duration of infection is $1/(\gamma+\mu)$. There is also an inflow of new members of the population (e.g. newborns, or newly sexually active) into the susceptible class at rate b. The

population is assumed to mix homogeneously (i.e., each individual has the same probability of contacting each other individual). Contacts are assumed to have no duration.

This flow diagram can be turned into a set of ordinary differential equations. An ordinary differential equation represents the instantaneous rate of change in a state variable with respect to another variable, in this case time. There is an equation for each of the state variables. The system of ordinary differential equations for this model is shown in (2.2).

$$\begin{aligned}\frac{dS}{dt} &= \mu N_{(t)} - S_{(t)}(\mu+\lambda)\\ \frac{dI}{dt} &= \lambda S_{(t)} - \gamma I_{(t)} - \mu I_{(t)}\\ \frac{dR}{dt} &= \gamma I_{(t)} - \mu R_{(t)}\end{aligned} \qquad (2.2)$$

where for an STI

$\lambda = c\beta I_{(t)}/N_{(t)}$

and more generally

$b = \mu N$ (for a stationary population only i.e. no population growth)

$S_{(t)} + I_{(t)} + R_{(t)} = N_{(t)}$

The SIR model is typically used for infections conferring long-lasting immunity, such as measles. There are other types of models, such as SEIR and SIS models, with different categories for subgroups of the population. SEIR models include the addition of a latent compartment upon infection, before the individual becomes infectious. SIS models assume there is no immunity generated as a result of previous infection, and are more appropriate for bacterial STIs. Greater detail and realism can be achieved by adding more compartments or categories to the model. Each additional compartment adds an equation to the system. The SIR could in theory be used to model HIV, if the $R_{(t)}$ compartment is assumed to represent deaths from infection rather than those who have recovered from infection. By removing the background death rate from this compartment, it would represent the cumulative number of deaths from infection over time.

The SIR model for endemic rather than epidemic conditions has been used here, meaning that births and (natural) deaths are incorporated, because the duration of HIV infection is sufficiently long that demographic processes become important. In the context of STIs, the force of infection λ for each susceptible is related to the number of sexual contacts per unit time (c, the partner change rate), the probability that each sexual partner is infected with the disease ($I_{(t)}/N_{(t)}$) and the probability of transmission of the pathogen (β) from an infected individual. To complete a description

of the system, sets of initial or boundary conditions are required. These conditions are usually provided by specifying values for $S_{(t)}$, $I_{(t)}$ and $R_{(t)}$ at time zero.

There can be other expressions for the force of infection, and the relevant term will depend on the characteristics of the infection to be modelled. The spread of STIs within a population is dependent on the number of sexual contacts of individuals; the spread of these diseases is therefore frequency dependent (dependent on the number of contacts). Other diseases may be density dependent, where the number of contacts each individual experiences is dependent on the density or "crowding" of that population, in which case $\lambda = \beta I_{(t)}$. For STIs, R_0 depends on the average rate at which new sexual partners are acquired, which usually has no direct dependence on $N_{(t)}$, the total population; doubling the population size does not affect sexual habits, except perhaps indirectly through social changes precipitated by greater crowding. Therefore all models in this thesis are frequency dependent.

2.4 Models of sexually transmitted infections

Mathematical models provide an explicit framework within which to develop and communicate an understanding of infectious disease transmission dynamics [158]. Once the transmission dynamics of an infectious disease are appropriately described by a model, the potential impact of proposed interventions can be evaluated. While models such as the SIR model described in section 2.3 assume homogeneous, random mixing, in reality this is unlikely to occur for any mode of transmission of human infections. Factors such as spatial proximity will influence the patterns of contacts between individuals. In the case of STIs, many factors are likely to influence the patterns of sexual contacts within a population, leading to non-random, heterogeneous mixing. A network is a system or group of interconnected elements, composed of a combination of two or more individuals and the connecting links between them. A sexual network is a network that is defined by the sexual relationships between a set of individuals. Much of our initial understanding of the epidemiological consequences of the natural history of STIs has been based on studies using population averages [161], but these techniques cannot capture the complexity of connections between cases. The understanding of more detailed sexual network data has required individual based simulation models [162].

Models can be categorised by a number of key criteria. Linear models treat the state variables of a model as simple functions of one another with more predictable results, whereas non-linear models are more complex. For infectious diseases, the transmission term is assumed to be non-linear because it is a function of the interaction between infectious and susceptible individuals. Many health economic models make linear assumptions, where treating one more individual simply reduces the number of cases by one. However, there are knock on effects which depend upon the epidemiological context and to take account of these, all the models described in this thesis, including

the SIR model described in section 2.3 are dynamic, non-linear transmission models which depend on the prevalence of infection.

Dynamic models can be discrete or continuous; i.e. changes in the model population can take place in discrete steps of time, or as a smooth continuous process. In continuous models, differential calculus is used to explore changes in one variable with a diminishingly small change in another variable, whereas in discrete models, difference equations, which reflect the change over the whole time step, are used. The sexual interactions allowing the spread of STIs occur continually, so most models of STIs are continuous.

Models can be deterministic or stochastic. In a deterministic model, events are not subject to chance and all outcomes are predetermined (two realisations of a model, using the same parameters and exact starting conditions, will produce exactly the same results). In stochastic models, chance is taken into account, with uncertainty at the level of the unit of analysis and determined by a probability distribution, and so each realisation is different. The most common and rigorous method for this is Monte Carlo simulation, where the set of possible next events is defined with a probability attached to each. A random number generator is then used to calculate when the next event will occur and which of the range of possible events it will be. One of the advantages of stochastic models is that the distribution of expected outcomes following from a given set of parameters can be generated, allowing an exploration of the ability of a model to explain observed infection patterns. The increased speed of computers has led to stochastic models becoming more convenient.

An important distinction in the modelling of STIs is whether the population is represented in groups with average rates of contact, risk of transmission, and progress through stages of infection (population-based, compartmental models) or whether individuals and their contacts are explicitly simulated (individual-based models). While compartmental models may be stochastic, they are most often deterministic. Individual-based models are almost always stochastic – the chance that a simulated individual experiences each event is determined according to predetermined probabilistic rules. For individual-based models, people are stepped through time and are exposed to the risk of experiencing various events, such as partnership formation and dissolution, infection, recovery or death, during each time step. The random variation introduced by such a pseudo Monte Carlo method means that the collection of simulated histories exhibits a degree of heterogeneity akin to that in a real population. This approach was volunteered by Blanchard et al [163] and has since been developed by Kretszchmar et al [164]. Through tracking individuals and their partnerships, the models enable the complete sexual network structure at any point in time to be reconstructed [165-168]. The host contact network determines the transmission pathways available to the disease.

A difficulty with individual-based network simulation models is determining when the sexual network simulated is representative of the true sexual network under study, in part due to difficulties in measuring sexual networks of humans [169]. In recent years, STI research has focused increasingly on population-level or network measures of risk rather than simply on individuals [162,

170, 171], as the infection risk of an individual is determined, among other factors, by their position in a network. It is not only their local position that is important, but the overall structure of the network also determines an individual's risk of infection, especially the behaviour of their nearest neighbours [162]. The much-cited example is the effect of network position for monogamous women whose husbands visit CSW and, in turn, transmit HIV infection to their wives. Here, individuals who do not practice risky behaviour themselves are at risk of infection because of their location in the network at a short distance from the high-risk core group [172]. Prevention efforts directed toward these people alone would have little effect. Only prevention that targets the partnerships between those women and their husbands or the contacts of husbands with CSW would reduce the risk to their wives. Therefore, prevention has to be viewed in a larger context than the behaviour of individuals. The more widespread existence of long-lasting concurrent partnerships in sub-Saharan Africa is one possible reason for the fast spread of HIV in heterosexual populations in this region [17, 173].

Another difficulty is that individual-based models are conceptually and computationally more complex than large population approximations. Such models carry significant costs in identifying parameter values, interpreting which measures are significant in generating results, and for rigour require a large number of simulation runs with statistical analysis of results. Although a network can be visualised well as a graph, where the nodes represent individuals of the population and the links represent their sexual partnerships, the mathematical analysis of the structure of such a graph that could contribute to the understanding of disease transmission is still in its infancy. Modelling has to be developed further to gain a better understanding of the relationship between network structure and the spread of specific STIs.

The particular choice of model structure depends on the nature of the research question. Some situations require investigation using particular model structures in order to simulate infection patterns realistically. For example, in exploring the elimination of syphilis, stochastic models that represent individual infections are required because deterministic large population models produce an impossibly tiny fraction of infectious individuals which could persist and subsequently reintroduce infection. However, deterministic, compartmental models are the simplest to formulate and analyse. Often for simple models, exact mathematical solutions are possible, which provide powerful insights into the relationship between parameter values and results. However, as models become more complex, for example by stratifying the model population by age, sex and sexual activity, it is often necessary to resort to numerical solution only. Hethcote and Yorke first used deterministic, compartmental models for analysing gonorrhoea in the U.S. [174]. They are useful for examining large-scale effects and for initial insights into problems where parameters are poorly estimated, as sensitivity analysis can be performed quickly.

In between the extremes of a homogeneous population and individual-based simulation it is possible to divide the population into groups with similar characteristics – for example, of a similar

age, sex, or patterns of sexual activity. Thus, some of the observed heterogeneity in the population can be captured by stratifying the model population. Mixing models, which describe the contact rates within and between the population groups with different sexual activity levels, were first introduced by researchers who coined the term "core group" for a small but highly sexually active subgroup in a population [174]. The core group concept has since been successful in explaining the continuing persistence of STIs at relatively low levels of prevalence in populations where, on average, the rate of partner change is low, as shown by early modelling work on gonorrhoea in the U.S. [174]. This core group concept has remained a powerful influence in understanding STIs. A distinction can be drawn between those individuals who are at risk of acquiring disease from their partner and those who are likely to transmit infection further to additional partners [162].

The pattern of mixing within a population will determine the sexual network structure and accordingly, the epidemiology of STIs. An important component of mixing is the degree of assortativity (like-with-like mixing). Empirical studies have suggested that there is a tendency for humans to choose sexual partners that are similar to themselves in various ways, such as age, ethnicity, geographic location and possibly rate of sexual partner change [175, 176].

Mixing patterns between the highest activity group and the rest of the population will affect the overall prevalence of disease in the population. Garnett et al suggest that mixing between individuals belonging to different sexual activity groups is near random [177], but other studies have demonstrated a preference for assortative mixing, where high activity individuals report partnerships with other people with higher numbers of partnerships [178]. While behavioural heterogeneity is frequently incorporated into deterministic models, these necessarily incorporate adjustments to reported distributions of behaviour or partner selection, with the commonly observed difference in reported numbers of sexual partnerships between males and females, in order to maintain a balance of partnerships between males and females in the modelled population. Garnett and Anderson define mixing preferences for males and females separately, and a constraint is applied to force the number of partnerships of males of a specified type (age, sexual activity level) to equal the number formed by females of a specified type with those males [179, 180]. These two numbers are not usually equal and so it is necessary to force one or the other to conform to the opposite sex. The dynamics of the pairing process are dominated by the sex that is chosen to determine the number of pairs that will form, although this can be circumvented by splitting the difference between each gender's preferred mixing pattern so that both compromise. Individual-based models can implement pairing in such a way that avoids the need for such procedures, with algorithms to determine the "next best preference" when certain "preferred" individuals for partnership formation are not available.

Population-based models also have the limitation of instantaneous partnership formation. This can be overcome by the use of pair models, which explicitly take partnership duration into account [181]. In addition to being susceptible, infected or removed, an individual in a pair model is

also described as being single or paired with another individual in the population. The model describes the transition between the "single" and "pair" state in terms of pair formation and separation rates. A pair can consist of two susceptible individuals, two infected individuals, or one susceptible and one infected individual. The inclusion of the pair-formation mechanism has a number of effects; for example, two susceptible individuals in a long-term partnership are essentially protected from infection. The average duration spent as a single influences the risk of being infected or transmitting the infection to others. Bacterial STIs are of relatively short duration, and so may resolve if there are long gaps between partnerships. When comparing models with and without pair formation, Dietz concluded that in a situation with pair formation, the rise of HIV prevalence toward the endemic equilibrium is much slower and the eventual endemic prevalence lower than estimates in a model that ignores partnership duration [182]. Similar results were obtained with a model that included long-term partnerships and incidental contacts with CSWs [183].

A limitation of pair models is that they cannot take into account concurrency. The slower rise in prevalence that Dietz observed using the pair model [182] is unlikely to be replicated if the model allowed individuals to form more than one partnership at a time. Modifications to such models to remove this constraint while retaining the deterministic structure rapidly lead to large increases in complexity [184] and models become intractable. The most convenient and thus commonly used method to account for this overlap in partnerships is through individual-based models.

Mathematical models have played a central role in illustrating the importance of different aspects of the sexual network in disease transmission and persistence, including mixing patterns, concurrency and network structures. In the past few years, perhaps in response to some of the conclusions drawn from mathematical models, there has been an increasing number of studies of patterns of sexual behaviour that have attempted to describe the mixing patterns found in populations [168, 177, 185]. Although it might be an unattainable goal to describe patterns of sexual mixing with the complexity that they exhibit within human populations, modelling can help to obtain insight into the patterns of disease transmission and, therefore, may provide valuable understanding of why some prevention measures work better than others. It is the abstraction and possible simplicity of models that renders them unrealistic, but it is often not necessary to include in full detail the complexity of the system to generate valid results; only sufficient complexity is required. Such simplification also provides the power to isolate the essential features of the dynamics of disease transmission in different settings. Validation of models is important when appropriate data are available to test the models, as well as comparing results of different models which vary in structure, or in the simplifying assumptions that they make.

Deterministic models have the advantage of being potentially analytically tractable, while individual-based models simulate the interactions between individuals, who are indivisible units, so these models cannot be expressed analytically. Individual-based models are appropriate for situations where there is substantial heterogeneity in risk of infection and transmission between

various individuals within the population. However, these models are limited by the large number of parameters required as inputs. The combined uncertainty in the estimates of all parameters is substantial and higher than for simpler deterministic models; therefore it is good practice to begin by producing a population-based deterministic model which can be used as a comparison. Certainly the increasing interest in network models has not led to neglect of deterministic model development [186, 187]. This thesis uses a series of deterministic compartmental models to investigate the impact of ART in resource-poor settings, but the need for models with alternative, more complex structures to complement this work and to compare predictions is recognised as important future work.

2.5 ART Models

The epidemiological impact of wide scale use of ART among HIV patients in industrialised countries has been explored in a number of mathematical modelling studies [188-192]. Mathematical models can be used to address questions regarding the potential impact and effectiveness of various treatment strategies. In terms of ART use, they can be used to investigate:

1) optimising the efficient use of ART;
2) the epidemiological consequences of ART and interaction with behavioural changes/interventions;
3) the likely course of the evolution of drug resistance
    a. within the individual;
    b. between individuals;
4) achievable levels of coverage and effectiveness;
5) the effective and efficient use of second line treatments; and
6) demographic/health care impact.

The following sections, based on a review by Baggaley, Ferguson & Garnett [193], describe a range of models investigating the impact of ART use in various settings and evaluate the utility of dynamic models in addressing some of the questions posed above. The publication of this work can be found in Appendix A.

A range of ART models was constructed, primarily as precursors to the finalised models used in this thesis, but here used for illustrative purposes. The simplest, one stage models, ART Models 1 and 2, are described below. Full descriptions of the other models can be found in Appendix C. ART Model 3 stratifies HIV infection by stages (primary infection, incubation, pre-AIDS and AIDS). ART Model 4 remains a one-stage model but incorporates heterogeneous sexual activity, with four risk groups.

2.6 Defining the basic reproductive number R_0

Defining and calculating R_0 for heterogeneous populations is more complicated than calculations for simpler, homogeneous models such as the simplest version of the SIR model as described in section 2.3. To derive R_0, an operator known as the "next-generation operator" is used to map generations of infected individuals into each other, as distributed over the possible individual characteristics, in the situation where a very small number of infecteds enter a very large population of susceptibles [194]. A demonstration of this method is presented here, using ART Model 1 to derive R_0.

2.6.1 ART Model 1 description

A compartmental, deterministic mathematical model describing HIV transmission and ART use was constructed. The structure of the model is illustrated in Figure 2.2, with state variables and transmission equations given below. Descriptions of parameters are given in Table 2.1. The model assumes one stage of HIV infection and use of a single, standard triple combination therapy regimen. The model tracks two HIV strains, one resistant to the ART regimen and one sensitive, and four categories of HIV-infected individuals according to virus phenotype and treatment status. Each compartment of infected individuals has a defined infectiousness determined by treatment status and virus type. Resistance evolution occurs at rate κ. It is a one sex model with no stratification by sexual activity class. In order to simplify derivation of R_0, individuals with ARV-resistant infection are assumed to transmit resistant virus only, despite often having a mixed infection with wild-type, ART-sensitive virus present.

2.6.1.1 State variables

From this point, the subscript t will not be used when referring to state variables in order to keep the notation clear.

S = susceptible individuals

I_S^U = ART-sensitive HIV infected individuals, untreated

I_S^T = ART-sensitive HIV infected individuals, treated

I_R^T = ART-resistant HIV infected individuals, treated

I_R^U = ART-resistant HIV infected individuals, untreated

N = total population

2.6.1.2 Other terms

λ_S = force of infection for ART-sensitive virus phenotype

λ_R = force of infection for ART-resistant virus phenotype

2.6.1.3 Transmission equations

From this point onwards, all differential equations are denoted by S' rather than dS/dt.

$$S' = \sigma N_0 - S(\lambda_S + \lambda_R + \mu) \quad (2.3)$$

$$I_S^{U'} = \lambda_S S - I_S^U(\mu + \nu_S^U + \gamma_S) \quad (2.4)$$

$$I_S^{T'} = \gamma_S I_S^U - I_S^T(\mu + \nu_S^T + \kappa) \quad (2.5)$$

$$I_R^{T'} = \kappa I_S^T + \gamma_R I_R^U - I_R^T(\mu + \nu_R^T) \quad (2.6)$$

$$I_R^{U'} = \lambda_R S - I_R^U(\mu + \nu_R^U + \gamma_R) \quad (2.7)$$

$$N = S + I_S^U + I_S^T + I_R^T + I_R^U \quad (2.8)$$

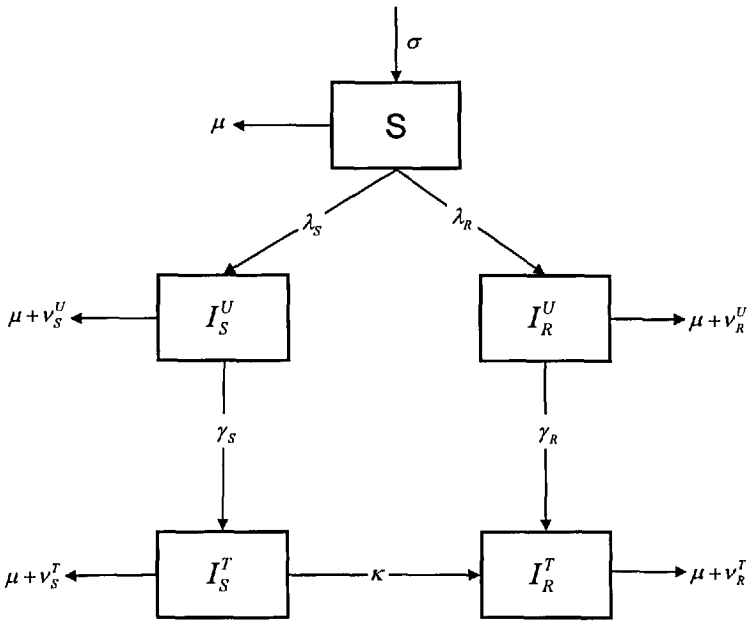
$$\lambda_S = \frac{c}{N}(\beta_S^U I_S^U + \beta_S^T I_S^T) \quad (2.9)$$

$$\lambda_R = \frac{c}{N}(\beta_R^U I_R^U + \beta_R^T I_R^T) \quad (2.10)$$

Table 2.1 Model parameters and values used for analytical analysis.

Symbol	Description	Value	Symbol	Description	Value
ν_S^U	HIV death rate, untreated (ART-sensitive)	0.1 year^{-1}	β_S^U	HIV transmission probability per partner, untreated (ART-sensitive)	5%
ν_S^T	HIV death rate, treated (ART-sensitive)	0.05 year^{-1}	β_S^T	HIV transmission probability per partner, treated (ART-sensitive)	0.1%
ν_R^U	HIV death rate, untreated (ART-resistant)	0.1 year^{-1}	β_R^U	HIV transmission probability per partner, untreated (ART-resistant)	4%
ν_R^T	HIV death rate, treated (ART-resistant)	0.1 year^{-1}	β_R^T	HIV transmission probability per partner, treated (ART-resistant)	2%
γ_S	Treatment uptake rate, ART-sensitive infections	0.1 year^{-1}	c	Partner change rate	2.5 year^{-1}
γ_R	Treatment uptake rate, ART-resistant infections	0.1 year^{-1}	κ	Rate of resistance evolution	0.3 year^{-1}
μ	Background death rate	0.02 year^{-1}	σ	Fertility rate	0.03 year^{-1}
			N_0	Population size at time t=0	1,000,000 individuals

Figure 2.2 Structure of ART Model 1, a one-stage model of HIV transmission and ART.



2.6.2 Calculating R_0

It has been shown that the value of R_0 is the dominant eigenvalue of the next-generation operator because it defines whether an infected population will grow or decline in size, it has a threshold size of one and it has the interpretation of expected number of new cases produced per (typical) infected individuals (the average contribution to the next generation) [194-196]. There are three steps to determining R_0 using this method: 1) identifying the relevant heterogeneous characteristics; 2) constructing the elements of the next-generation operator in terms of basic parameters and ingredients; and 3) computation of the dominant eigenvalue of the operator.

The only relevant characteristics are those that distinguish between individuals at the moment they are "born" (in the epidemiological sense). Only infected individuals and the state of the individual at birth (called the "type-at-birth") are taken into account during this step. In the case of a discrete number of types-at-birth, the next-generation operator is an $n * n$-matrix, where n is the number of types-at-birth. In this case, there are two types-at-birth for infection (i.e. routes of infection): an individual can become infected with ARV-sensitive or -resistant virus.

Individuals can be infected via two routes: with ARV-sensitive virus (route 1) or ARV-resistant virus (route 2). The next-generation operator is a 2x2 matrix of the form:

$$\begin{pmatrix} R_{11} & R_{12} \\ R_{21} & R_{22} \end{pmatrix}$$

where 1 and 2 represent infection from the ARV-sensitive and -resistant routes respectively. The elements R_{ij} represent the expected number of type j infections generated by type i infections. While type 1 infections can generate type 2 infections (those on ART develop resistance at rate κ), the opposite is not the case (the simplified model does not allow mixed infections to transmit ARV-sensitive virus), so R_{21} is zero.

$$R_{11} = \frac{c\beta_S^U}{\gamma_S + \mu + \nu_S^U} + \frac{\gamma_S}{\gamma_S + \mu + \nu_S^U} \frac{c\beta_S^T}{\kappa + \mu + \nu_S^T} \quad (2.11)$$

$$R_{12} = \frac{\gamma_S}{\gamma_S + \mu + \nu_S^U} \frac{\kappa}{\kappa + \mu + \nu_S^T} \frac{c\beta_R^T}{\mu + \nu_R^T} \quad (2.12)$$

$$R_{21} = 0 \quad (2.13)$$

$$R_{22} = \frac{c\beta_R^U}{\gamma_R + \mu + \nu_R^U} + \frac{\gamma_R}{\gamma_R + \mu + \nu_R^U} \frac{c\beta_R^T}{\mu + \nu_R^T}. \quad (2.14)$$

Therefore the next generation

$$\begin{pmatrix} R_{11} - \psi & R_{12} \\ 0 & R_{22} - \psi \end{pmatrix} = 0 \quad (2.15)$$

is the eigenvalue equation, where ψ represents the eigenvalues. The overall value for R_0 is calculated as the dominant eigenvalue [194-196]. Therefore $R_0 = Max(R_{11}, R_{22})$.

Using the baseline parameters given in Table 2.1 and equations (2.11) and (2.14), R_{11} is 0.57 and R_{22} is 0.64. Therefore R_0 is 0.64 and there is no epidemic (showing that parameter values must be revaluated). Higher partner change rates are required to cause an epidemic because a homogeneous model such as this cannot account for higher transmission rates among more active groups of the population.

The model is also a simplification because there is no transmission from infection route 2 to route 1, whereas in reality mixed infections could result in transmission of either ARV-sensitive or -resistant strains, meaning that R_{21} would no longer be zero. This would lead to a considerable increase in complexity of the expression for R_0, illustrating how small changes in assumptions to increase realism can limit the analytical tractability of models.

2.7 ART Model 2

The structure of ART Model 2 is illustrated in Figure 2.3, with state variables and transmission equations given below. Descriptions of parameters and baseline values used are given in Table 2.2.

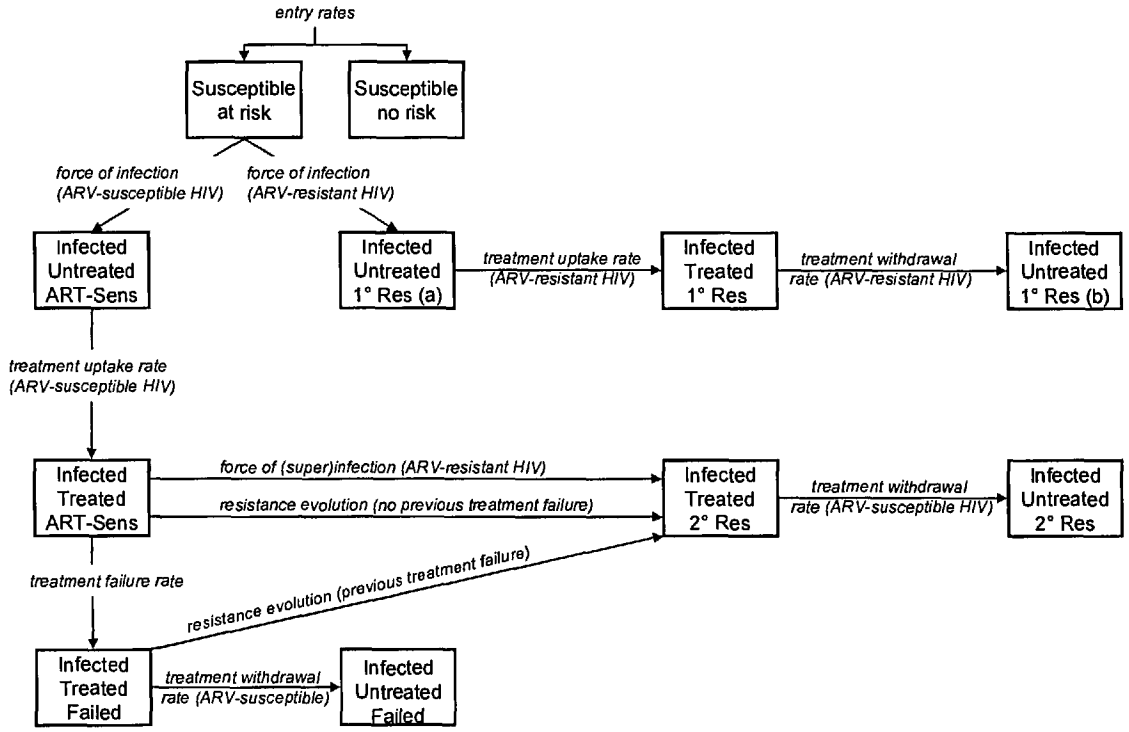
The model is a more complex version of ART Model 1, with an extra four categories of HIV-infected individuals according to virus phenotype and treatment status. Modifications were made to allow investigation of the impact of withdrawing treatment and to model the consequences of ART, such as treatment failure, more realistically. Rather than failure of ART always assigned to resistance emergence, treatment failure can occur with (κ) or without (f) the evolution of drug resistance. Superinfection with an ART-resistant strain is possible for individuals undergoing successful treatment only (I_S^T, S = ART-sensitive, T = treated), as these are the only individuals without viral outgrowth, and thus will have a pool of target cells rendering them susceptible to reinfection. While emergence of ART-resistant virus due to superinfection should be defined as primary infection, in the model, such individuals transfer to the secondary resistance, treated compartment because, like patients with secondary resistance, they are dually infected with wild-type and resistant virus. Individuals who have developed treatment failure not accompanied by resistance (I_S^{TF}, F = treatment failure) are at increased risk of developing drug resistance (at rate κ_F) because of viral replication in the presence of continued drug pressure. ART patients may also be withdrawn from treatment.

Another change from the previous model is the addition of a group of individuals that are not at risk of infection, S_2. Initially a fraction ϖ of the population is at risk, with the same fraction of those entering the population at each time step being assigned to this category. An alternative would be to model the fraction recruited into the "at risk" class being a function of the existing proportion at risk, which allows prevalence to stay high or fall in response to HIV-associated mortality. However, with the exception of South Africa, heavily affected countries have still seen population growth, and so the fraction ϖ remains constant. The S_2 population could have been included in the denominators of the force of infection equations (2.28) and (2.29). This would have then implied that the partnerships of the S_1 population included in the partner change rate include "safe" partnerships with those in group S_2. This may be the case if there was consistent condom use within a partnership between individuals in S_2 and the rest of the population, for example. However, the aim of the model is to simulate a high prevalence epidemic in a resource-poor setting such as sub-Saharan Africa, where consistent condom use tends to be low, at least until recently [197, 198], and so it is more appropriate to remove the S_2 group from the force of infection denominators and assume that this group are in "safe" partnerships with each other (probably mutually monogamous) and/or are not sexually active. The S_2 is therefore only used in the denominator to calculation population-level prevalence.

The model is run twice, once with treatment initiated 20 years after infection is introduced and once 30 years after, to produce two scenarios. This times the intervention to be introduced shortly

before and shortly after the peak of the epidemic, respectively. The post-20 year intervention scenario may reflect what will occur in regions where the HIV epidemic is still growing rapidly and where there may be time to intervene before it saturates, reflecting the situation of a country such as India. The post-30 year intervention reflects the situation in many sub-Saharan African countries, which have been living with the epidemic for the past 20 years and may now be experiencing the peak prevalence of infection, and may receive ART on a substantial scale in the next decade.

Figure 2.3 Schematic illustration of the structure of ART Model 2, a one-stage model of HIV transmission and ART.



"1° Res" denotes those with primary (transmitted) resistance, while "2° Res" denotes those with secondary (acquired) resistance. "ART-Sens" denotes people infected with ART-sensitive virus. For clarity, death rates are not shown.

2.7.1 State variables

S_1 = susceptible individuals, "at risk"

S_2 = susceptible individuals, "no risk"

I_S^U = ART-sensitive HIV infected individuals, untreated

I_S^T = ART-sensitive HIV infected individuals, treated

I_S^{TF} = ART-sensitive HIV infected individuals, treated but viral rebound

I_S^{UF} = ART-sensitive HIV infected individuals, suffered viral rebound, withdrawn from treatment

I_{R2}^T = ART-resistant HIV infected individuals (acquired, secondary resistance), treated

I_{R2}^U = ART-resistant HIV infected individuals (acquired, secondary resistance), untreated

I_{R1a}^U = ART-resistant HIV infected individuals (transmitted, primary resistance), untreated

I_{R1}^T = ART-resistant HIV infected individuals (transmitted, primary resistance), treated

I_{R1b}^U = ART-resistant HIV infected individuals (transmitted, primary resistance), withdrawn from treatment

λ_S = force of infection for ART-sensitive virus phenotype

λ_R = force of infection for ART-resistant virus phenotype (and force of (super)infection for ART-resistant virus phenotype, infecting an HIV wild type infected individual under treatment pressure)

2.7.2 Transmission equations

$$S_1' = \sigma N_0 \varpi - S_1\left(\lambda_S + \lambda_R + \mu\right) \tag{2.16}$$

$$S_2' = \sigma N_0 \left(1-\varpi\right) - \mu S_2 \tag{2.17}$$

$$I_S^{U'} = \lambda_S S - I_S^U\left(\mu + \nu_S^U + \gamma_S\right) \tag{2.18}$$

$$I_S^{T'} = \gamma_S I_S^U - I_S^T\left(\mu + \nu_S^T + f + \kappa + \lambda_R\right) \tag{2.19}$$

$$I_S^{TF'} = fI_S^T - I_S^{TF}\left(\mu + \nu_S^U + \alpha_S + \kappa_F\right) \tag{2.20}$$

$$I_S^{UF'} = \alpha_S I_S^{TF} - I_S^{UF}\left(\mu + \nu_S^U\right) \tag{2.21}$$

$$I_{R2}^{T\,\prime} = I_S^T\left(\kappa + \lambda_R\right) + \kappa_F I_S^{TF} - I_{R2}^T\left(\mu + \nu_R^T + \alpha_S\right) \tag{2.22}$$

$$I_{R2}^{U\,\prime} = \alpha_S I_{R2}^T - I_{R2}^U\left(\mu + \nu_R^U\right) \tag{2.23}$$

$$I_{R1a}^{U\prime} = \lambda_R S - I_{R1a}^{U}\left(\mu + \nu_R^U + \gamma_R\right) \quad (2.24)$$

$$I_{R1}^{T\prime} = \gamma_R I_{R1a}^{U} - I_{R1}^{T}\left(\mu + \nu_R^T + \alpha_R\right) \quad (2.25)$$

$$I_{R1b}^{U\prime} = \alpha_R I_{R1}^{T} - I_{R1b}^{U}\left(\mu + \nu_R^U\right) \quad (2.26)$$

$$N = S_1 + S_2 + I_S^U + I_S^T + I_S^{TF} + I_S^{UF} + I_{R2}^T + I_{R2}^U + I_{R1a}^U + I_{R1}^T + I_{R1b}^U \quad (2.27)$$

The forces of infection are determined by the infectiousness of individuals in each class (β) and the probability that ART-resistant rather than ART-sensitive virus is transmitted in the case of mixed infections (ω).

$$\lambda_S = \frac{c}{N - S_2}\left(\begin{array}{l}\beta_S^U\left(I_S^U + I_S^{UF} + \iota I_S^{TF}\right) + \beta_S^T I_S^T + \beta_R^T\left(\left(1-\omega_2^T\right)I_{R2}^T + \left(1-\omega_1^U\right)I_{R1}^T\right) \\ + \beta_R^U\left(\left(1-\omega_2^U\right)I_{R2}^U + \left(1-\omega_1^U\right)\left(I_{R1a}^U + I_{R1b}^U\right)\right)\end{array}\right) \quad (2.28)$$

$$\lambda_R = \frac{c}{N - S_2}\left(\beta_R^T\left(\omega_2^T I_{R2}^T + \omega_1^T I_{R1}^T\right) + \beta_R^U\left(\omega_2^U I_{R2}^U + \omega_1^U\left(I_{R1a}^U + I_{R1b}^U\right)\right)\right) \quad (2.29)$$

Models were programmed in Berkeley Madonna version 8.0.1 and solved using the Runge-Kutte 4 algorithm. ART Model 2 was also solved in MS Excel 2003 and compared to the Berkeley Madonna code using Euler's method to ensure the model had been coded correctly. The default values below were assigned after a brief review of parameter values used in other HIV transmission models; more realistic parameter values used in Chapters 5 and 6 were arrived at after a more detailed literature review, as described in Chapters 3 and 4.

Table 2.2 Baseline parameter values used in ART Model 2.

Parameter	Definition	Baseline value
c	Contact rate (rate of partner change per year)	5 per year
ϖ	Fraction of the population assigned to the "at risk" class	60%
β_S^U	HIV transmission probability per partnership for an untreated ART-sensitive infection	10%
β_S^T	HIV transmission probability per partnership for a treated ART-sensitive infection (=0.02 β_S^U)	0.2%
β_R^U	HIV transmission probability per partnership for an untreated ART-resistant infection (=0.95 β_S^U)	9.5%
ι	Factor change in transmission probability for treated ART-resistant infections or infections with other treatment failure	50%

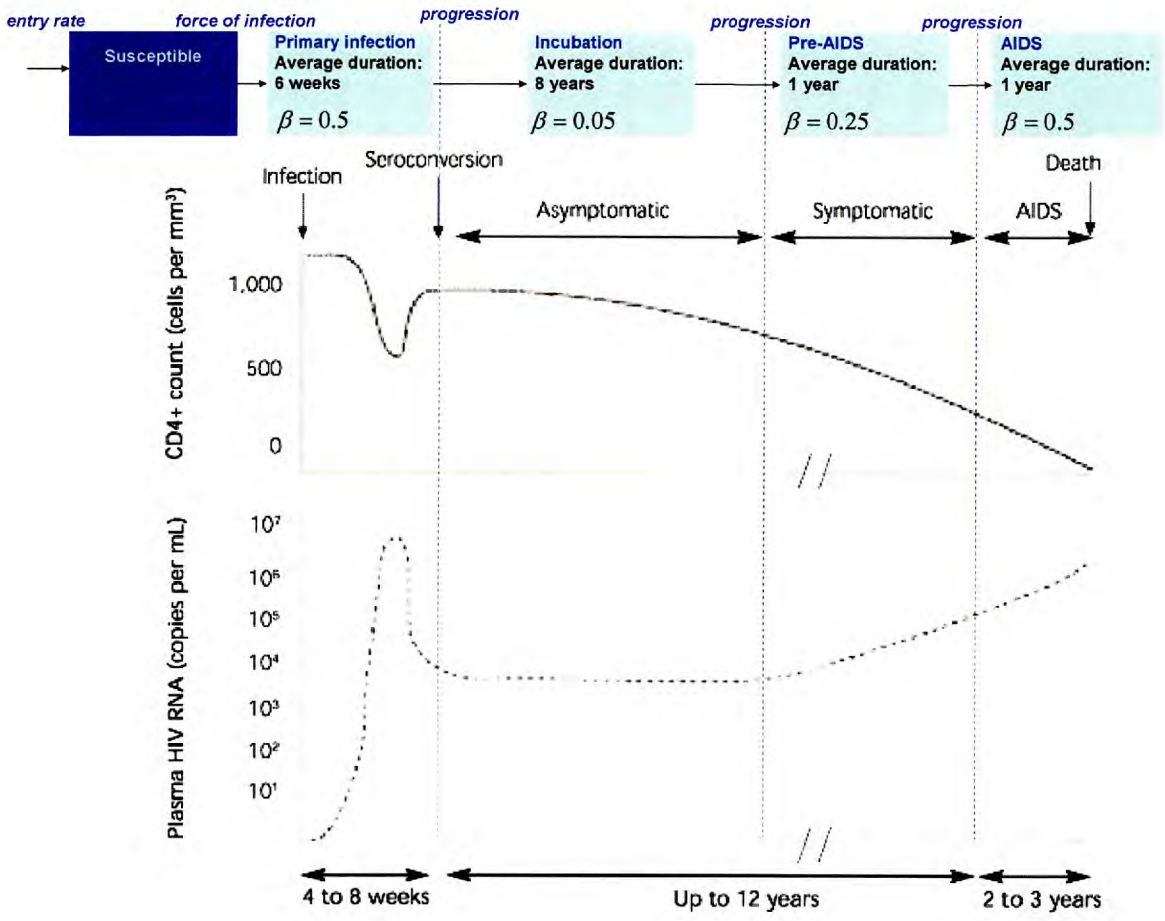
Parameter	Definition	Baseline value
β_R^T, β_S^{TF}	HIV transmission probability per partnership for a treated ART-resistant infection or ART-sensitive infection with viral rebound (= $\iota\beta_R^U$)	4.8%
κ	Rate of resistance evolution without previous viral rebound	0.3 year^{-1}
κ_F	Rate of resistance evolution with previous viral rebound	0.4 year^{-1}
f	Rate of treatment failure (without resistance evolution)	0.1 year^{-1}
μ	Natural model exit rate (assumes an average sexual lifetime of 35 years)	1/35 year^{-1}
ν_S^U	Excess death rate due to HIV infection with ART-sensitive virus in an untreated individual	1/10.125 year^{-1}
ν_S^T	Excess death rate due to HIV infection with ART-sensitive virus in a treated individual (=0.5 ν_S^U)	1/20.25 year^{-1}
ν_R^U	Excess death rate due to HIV infection with ART-resistant virus in an untreated individual (0.95 ν_S^U)	1/10.658 year^{-1}
ν_R^T	Excess death rate due to HIV infection with ART-resistant virus in a treated individual (0.90 ν_S^U)	1/11.25 year^{-1}
γ_S	Treatment uptake rate for individuals infected with ART-sensitive virus	0.5 year^{-1}
γ_R	Treatment uptake rate for individuals infected with ART-resistant virus	0.5 year^{-1}
α_S	Rate of withdrawal of ineffective treatment for individuals initially infected with ART-sensitive virus	0 year^{-1}
α_R	Rate of withdrawal of ineffective treatment for individuals initially infected with ART-resistant virus	0 year^{-1}
σ	Fertility rate	0.03 year^{-1}
N_0	Size of model population at time t=0	1,000,000 individuals
ω_1^U	Fraction of infections transmitted by untreated individuals with primary resistance which are also resistant phenotype	100%
ω_1^T	Fraction of infections transmitted by treated individuals with primary resistance which are also resistant phenotype	100%
ω_2^U	Fraction of infections transmitted by untreated individuals with secondary resistance which are also resistant phenotype	5%
ω_2^T	Fraction of infections transmitted by treated individuals with secondary resistance which are also resistant phenotype	80%

2.8 Multistage model – ART Model 3

2.8.1 Model description

ART Model 3 is essentially ART Model 2 divided into four stages of HIV infection (primary infection, incubation, pre-AIDS and AIDS) as shown in Figure 2.4. The substantial variation in pVL over the course of HIV infection is thought to result in markedly different infectiousness of infected individuals over time. Furthermore, ART is only initiated at later stages of infection. Therefore it is appropriate to stratify the model into infection stages. The forces of infection are determined by the infectiousness of individuals in each class, the probability that ART-resistant rather than ART-sensitive virus is transmitted in the case of mixed infections and the rates of sexual partner change, which decrease as individuals reach AIDS. A full description of ART Models 3 and 4 with parameter values is provided in Appendix C.

Figure 2.4 Schematic illustration of the structure of the stages of HIV infection for the four-stage model, ART Model 3.



Individuals progress from one stage to the next exponentially, with an average duration in each stage as shown in Figure 2.4. The HIV transmission probability per partnership at each infection stage j is given by β_j. The figure includes a graph of the natural history of HIV infection in terms of CD4 count and pVL and is described in Chapter 1 section 1.2. Adapted from Sande MA and Volberding P. The medical management of AIDS. 4th ed. Philadelphia: Saunders, 1995:40.

2.8.2 Patterns of infectiousness and epidemic growth

The distribution of infectiousness through the various stages of HIV infection, which can be investigated using ART Model 3, plays a key role in the timing of epidemics because it will affect the generation time T_g and therefore also impact on the exponential growth rate r (see section 2.2.2). For an infection where infectious individuals are characterised in terms of their infectiousness as a function of time (τ) since infection $\beta(\tau)$, R_0 can be defined by

$$R_0 = c\int_0^\infty \beta(\tau)\,d\tau \tag{2.30}$$

where it is assumed that the partner change rate c does not change with time since infection. The generation time T_g is given by the mean of the infectiousness distribution $\beta(\tau)$,

$$T_g = \int_0^\infty \tau\beta(\tau)\,d\tau \Big/ \int_0^\infty \beta(\tau)\,d\tau \tag{2.31}$$

as described by Fraser et al [159].

ART Model 3, as described in Appendix C, incorporates differential HIV infectiousness by stage of infection rather than as a continuous function with time since infection. The model is divided by stage of infection into 11 separate compartments ($j = 1..11$). The first compartment represents primary infection. The next eight compartments represent the incubation period, which has been subdivided in order to produce a more realistic progression of infection, using a gamma function rather than an exponential progression rate to pre-AIDS. Pre-AIDS and AIDS stages represent the final two stages. For simplicitly for this illustration, ART Model 3 is used without the incorporation of treatment and is therefore an SI model with stages of infection progression. There is homogeneous mixing between all compartments, and so an alternative to the next generation operator method can be used to calculate R_0 as defined in equation (2.30):

$$R_0 = \sum_{j=1}^{11} \frac{c_j \beta_j q_j}{\mu + \phi_j} \tag{2.32}$$

where

$$q_j = 1 \quad \{j = 1\} \qquad q_j = \prod_{k=1}^{j-1} \frac{\phi_k}{\mu + \phi_k} \qquad \{j = 2..11\} \tag{2.33}$$

and c_j is the partner change rate by stage of infection j, β_j is the stage-specific transmission probability per partnership, ϕ_j is the progression rate to the next stage for individuals in infection stage j and μ is the model exit rate. (For clarity, the notation c_{AIDS} for partner change rate of AIDS patients that is used in Appendix C is referred to as c_{11} in this section.)

The generation time can be characterised as

$$T_g = \sum_{j=1}^{11} \frac{c_j \beta_j q_j p_j}{\mu + \phi_j} \Big/ R_0 \tag{2.34}$$

where p_j represents the average time since infection at which stage j makes its contribution to the number of secondary cases that are generated:

$$p_j = \frac{1}{2(\mu + \phi_j)} \sum_{k=1}^{j-1} \frac{1}{\mu + \phi_k}. \tag{2.35}$$

Using ART Model 3 but in the absence of treatment, baseline parameters as detailed in Appendix C were varied to produce epidemics with the same value for R_0 but different values for the generation time T_g, by varying the distribution of infectiousness over time, β_j for $j = 1..11$, the duration of infection stages and the relative sexual activity of individuals by stage of infection c_j. Baseline values from Appendix C and parameters changed for scenarios 1 to 4 are shown in Table 2.3. The R_0 calculated for baseline parameters according to equation (2.32) is 3.2. Keeping this value constant, transmission probabilities were altered so that primary infection was more infectious relative to the late stages of pre-AIDS and AIDS in Scenario 1. Scenario 2 increases the contribution of AIDS to HIV transmission by increasing the contact rate of AIDS patients, c_{11}, while retaining the value for R_0 by decreasing infectiousness during the incubation period. Scenario 3 substantially increases the duration of primary infection and retains the value of R_0 by substantially reducing the infectiousness of AIDS, pre-AIDS and incubation stages. Scenario 4 demonstrates the effect of homogeneous infectiousness throughout all HIV infection stages (i.e. analogous to ART Model 2). The resultant epidemics produced by ART Model 3 are shown in Figure 2.5.

Table 2.3 Summary of parameter values used for Scenarios 1 to 4, investigating the impact of varying patterns of HIV infectiousness on the timing of epidemics.

Symbol	Parameter description	Baseline	Scenario			
			1	2	3	4
β_1	HIV transmission probability per partnership, primary infection	50%	100%	50%	50%	6%
$\beta_2 .. \beta_9$	HIV transmission probability per partnership, incubation	5%	5%	1%	2%	6%
β_{10}	HIV transmission probability per partnership, pre-AIDS	25%	16%	25%	10%	6%
β_{11}	HIV transmission probability per partnership, AIDS	50%	50%	50%	10%	6%
c_{11}	Partner change rate per year, AIDS patients	0.5 $year^{-1}$	0.5 $year^{-1}$	2.0 $year^{-1}$	0.5 $year^{-1}$	0.5 $year^{-1}$
ϕ_{S1}^{U}	Rate of transition from primary infection to incubation	8 $year^{-1}$	8 $year^{-1}$	8 $year^{-1}$	2 $year^{-1}$	8 $year^{-1}$
R_0	Basic reproductive number	3.2	3.2	3.2	3.2	3.2
T_g	Generation time	5.6 years	5.1 years	6.6 years	2.9 years	4.3 years

Greyed cells refer to parameter values varied from baseline.

Changing patterns of infectiousness and sexual activity throughout the stages of HIV infection, and the durations of these stages, has a substantial impact on the timing of HIV epidemics by affecting the generation time of the infection T_g. R_0 is kept constant, and so properties of the epidemic that relate to R_0 only remain constant between scenarios, such as the prevalence at equilibrium (Figure 2.5). However, parameter values that increase the contribution of primary infection to HIV transmission shorten the generation time and lead to a faster epidemic which reaches a higher peak prevalence (Scenarios 1, 3 and 4), while the converse is true if the contribution to R_0 of advanced stages is increased (Scenario 2). HIV is transmitted at a faster rate, which leaves less time to react to disease spread and prepare interventions. This deterministic model cannot capture all the complexities of the sexual network. A higher infectiousness during primary infection is likely to result in even higher transmission rates if there is a high degree of concurrency within the population, with infection likely to spread rapidly through the branches of the network.

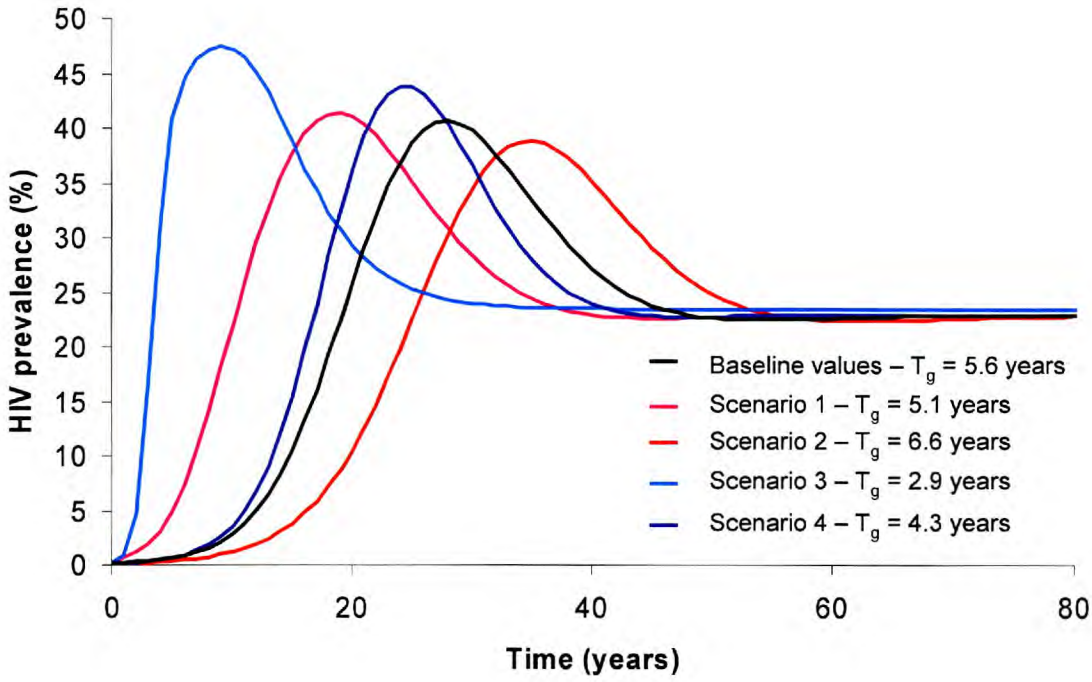


Figure 2.5 Comparison of modelled HIV epidemics with different patterns of infectiousness with stage of infection but equal values for R_0.

This exercise has demonstrated the sensitivity of models to changes in parameters. The uncertainty regarding factors such as sexual behaviour and infectiousness, which is discussed further in chapters 3 and 4, means that models are often calibrated to empirical data on epidemics (which is used later in this thesis).

2.9 Calculation of R_0 for heterogeneous sexual mixing

The simplest method of calculating R_0 for a model with heterogeneous sexual activity uses the simple formula $\beta \bar{c} D$, where $\bar{c}$ is the effective number of sexual partners per unit time and is defined as:

$$\bar{c} = m + \sigma^2 / m \qquad (2.36)$$

where m is the mean number of sexual partners per unit time and σ^2 is the variance in the distribution of numbers of partners:

$$m = \sum_i c_i \theta_i \qquad (2.37)$$

$$\sigma^2 = \sum_i (c_i - m)^2 \theta_i \qquad (2.38)$$

where i represents sexual activity classes, c_i is the number of partners per unit time for class i and θ_i is the proportion of the population in class i [158]. The effective number of partners, $\bar{c}$, is used rather than the mean number of partners so that, if the variance is high and there is therefore a large amount of heterogeneity in numbers of partners by activity group, the effective number can be significantly larger than the mean number, which takes more appropriate account for the disproportionate role that high activity individuals play in the transmission of infection.

This method assumes random mixing between sexual activity groups. To estimate R_0 for assortative mixing requires an alternative method. It can be derived analytically using the next generation operator method, as described in section 2.6.2.

Introducing an individual as the index case into one of the sexual activity groups will result in a mixture of sexual activity groups for the secondary cases, the ratio of which depends on the assigned group for the index case. Therefore a 'characteristic' or 'typical' index case is chosen, which is essentially one person, but divided into fractions within each sexual activity group. The definition of R_0 for heterogeneous mixing is the number of secondary characteristic cases generated by such a characteristic index. R_0 is calculated as the largest eigenvalue of the next generation operator, where the next generation operator is the reproduction number for each sexual activity group (separated into the number of secondary infections produced in each sexual activity group). Therefore, as an example, the 3x3 matrix of next generation operators for a one infection stage and one sex model of HIV with three sexual activity groups would be:

$$M = \begin{pmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{pmatrix} \qquad (2.39)$$

where R_{ij} is the risk group reproduction number and R_{12}, for example, is the average number of secondary infections in sexual activity group 2 resulting from a primary index case in risk group 1 [194-196].

For the one stage model, there is by definition no change in sexual behaviour or infectiousness during infection. Therefore the risk-group reproduction numbers are:

$$R_{ij} = \frac{\beta c_i \rho_{ij}}{\mu + \nu} \qquad (2.40)$$

where

ρ_{ij} denotes the probability that, given an individual in sexual activity class i forms a sexual partnership, the partnership is with a member of sexual activity class j. Therefore:

$$\sum_j \rho_{ij} = 1$$

The value of ρ_{ij} depends on the pattern of mixing which could vary in the model from fully assortative, where partnerships only form within the same activity class, to random, where partnerships form randomly between different activity classes. (In reality, there could be more complex patterns of mixing than this, with different tendencies for assortative mixing for each sexual activity class.)

$$\rho_{ij} = \varepsilon\delta_{st} + (1-\varepsilon)\frac{c_j N_j}{\sum_j c_j N_j} \quad (2.41)$$

where $\delta_{st} = 1$ when $i = j$ and $\delta_{st} = 0$ when $i \neq j$. ε describes the pattern of mixing between individuals by sexual activity class (0 = fully assortative, 1 = random).

$N_i = S_i + I_i$

Figure 2.6 compares R_0 calculated using the effective number of partners with R_0 calculated using the next generation operator with varying degrees of assortative mixing. For simplicity, a one infection stage model is assumed. It demonstrates that using the effective partner change rate method underestimates the value of R_0 when there is some degree of assortative mixing.

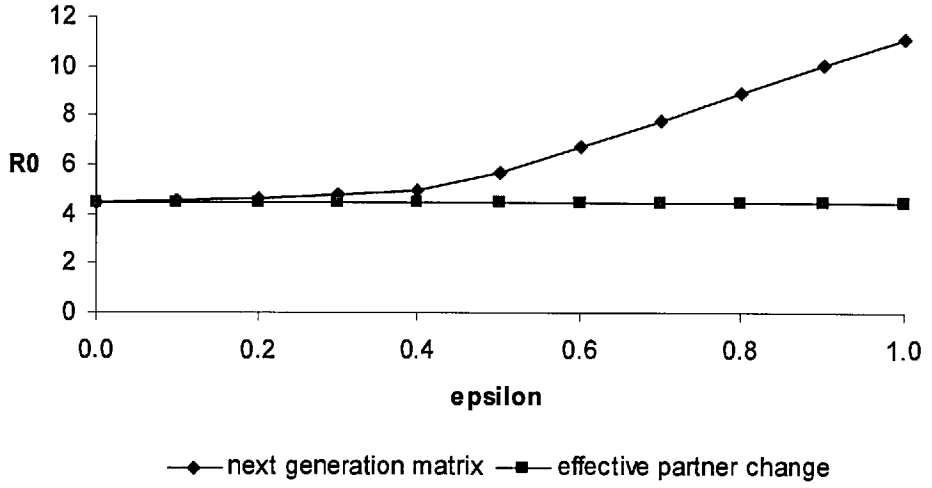


Figure 2.6 Comparison of R_0 calculation methods.

The advantage of one-stage models of infection is that they are relatively simple and analytically tractable; that is, the relationship between each parameter and the outcome of the models, for example in terms of R_0 [189], can be exactly specified without recourse to simulation and sensitivity

analysis. However, while a model should not incorporate complexity for its own sake, stages of HIV infection play a crucial role in the impact of ART, because treatment is only initiated at late stages of infection, and infectiousness and sexual activity vary with the course of infection. Similarly, incorporating heterogeneous sexual activity within a model is more important for some research questions than for others. If investigating the potential impact of a transmissible ART-resistant HIV strain through a population, its spread would appear very different in a model of homogeneous sexual activity, compared to one with heterogeneity and various assumptions regarding mixing between activity classes, where infection would travel through core groups first before spreading into the general population. Therefore there is always a trade-off between realism and complexity in model design. The ART models described in later chapters incorporate both stages of infection and heterogeneous sexual activity.

2.10 The range of ART models

Mathematical models examining the epidemiological impact of ART broadly fall into two categories; those incorporating HIV transmission dynamics as described in this chapter and used in this thesis, where incidence of new infections is dependent on HIV prevalence [188-190, 192], and simpler linear models [199-201]. Throughout this thesis, "dynamic" refers to models with a transmission term dependent on prevalence of infection, while "linear" refers to models without this dependency. A summary of ART models is provided in Table 2.4, at the end of this chapter. Aalen et al [200] constructed a model describing MSM in England and Wales and the use of ART. This Markov multi-stage model represented stages of HIV infection based on CD4 count. The authors considered a variety of treatment scenarios, and incorporated asymptomatic and symptomatic individuals and the concept of eligibility for treatment, making the simulation of treatment uptake and its impact more realistic than previous work. Wood et al [199] constructed a health economic model to predict the future impact of low-level ART use in South Africa from 2000 to 2005. The authors modelled total drug cost, cost per life year gained and the proportion of per person healthcare expenditure required to finance ART in each scenario. The study involved a cost effectiveness analysis comparing the epidemiological impact of ART with other interventions such as PMTCT. Freedberg et al [201] also used stages of disease determined by CD4 count and predicted the incremental cost per quality-adjusted year of life gained by ART in the US. Wilson and Blower [156] used a spatial mathematical model to explore ART allocation strategies among health care facilities in the province of KwaZulu-Natal, South Africa, with an emphasis on maximising equity in access to treatment.

In an investigation into the impact of an expanded response (incorporating prevention interventions and care and support activities) on the HIV/AIDS pandemic, Stover et al 2002 did not include the effect of ART, stating, "there is little empirical data available on the magnitude of the preventive effect of treatment (reduced viral load and hence infectiousness) and care" [202]. However, in a later publication, the authors investigated the effects of combining treatment with

prevention efforts, using the same model (the Goals model [203]), calibrated to sub-Saharan Africa [204]. The Goals model is a Microsoft Excel™ spreadsheet model using linear equations, designed to improve resource allocation for national HIV/AIDS programmes. It feeds into the dynamic epidemic projection package (EPP) and Spectrum, used by the UNAIDS/WHO to produce national HIV/AIDS estimates [205, 206], to predict the impact of an intervention. The authors concluded that a prevention-centred strategy provides greater reductions in incidence, but more modest mortality benefits, than treatment-centred scenarios. A combined approach would yield further benefits, but focusing on treatment at the expense of prevention could diminish this effect. Auvert et al 2004 used a linear model to estimate the proportion of the South African population requiring ART under the then current WHO guidelines (treating all individuals with a CD4 count less than 200 cells/mm^3 [108]). The model was also used to predict the impact of ART on the short term spread of HIV in this setting [207].

Such linear models have generally been used to inform policy makers on issues such as resource allocation, and typically involve only short-term predictions of the effect of ART for health care providers, as estimated by cost-effectiveness analysis [199, 201]. The models are relatively straightforward in that they include the health states of individuals, associated treatments and events that individuals experience, but fail to take account of the non-linear feedback process underlying infectious disease epidemics, as discussed in section 2.4. Linear models are limited by the accuracy of estimates of HIV incidence used to parameterise the models, which is all the more important because their predictions and conclusions are usually more quantitative in nature than those provided by dynamic models, which have tended to be used to give more qualitative insight. Models incorporating HIV transmission dynamics typically investigate the impact of ART over a longer time frame and are used to address more general questions surrounding ART use, such as whether the benefits of ART provision outweigh the problems and risks, and which approaches to ART provision are most effective. Both types of model are required, to inform policy makers in resource-poor settings about the costs of ART provision in the short term (Wood et al [199], for example), as well as to predict the likely impact of scaling up ART use.

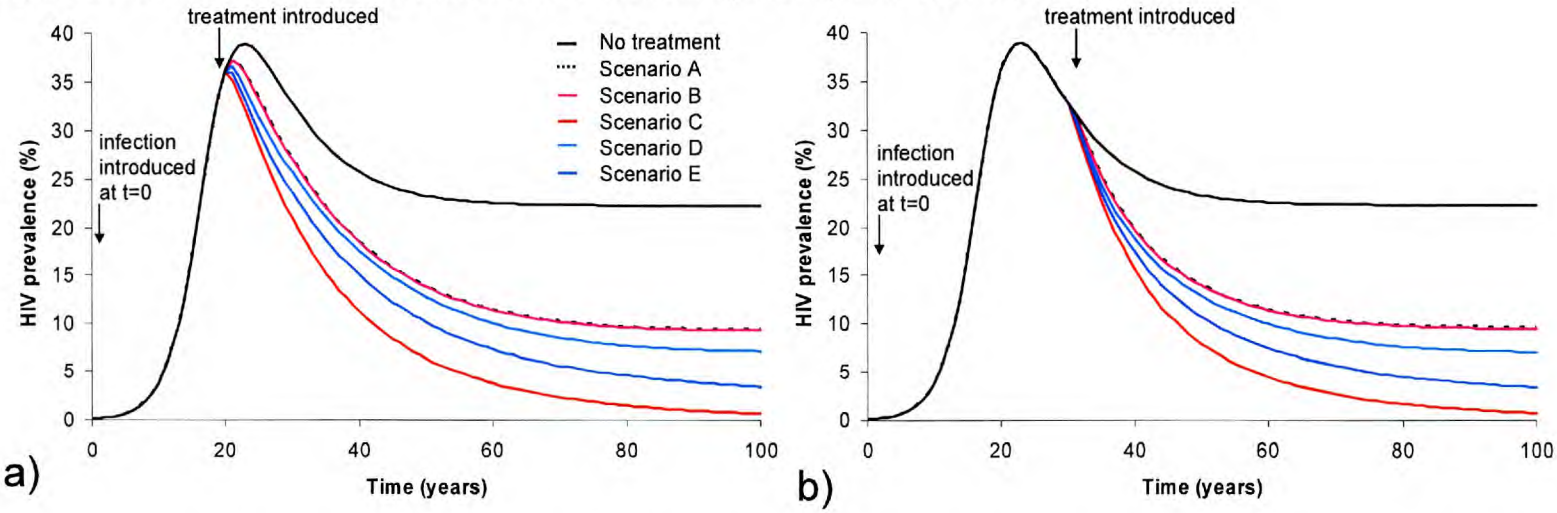
2.11 Dynamic model structures

Most dynamic models of HIV transmission investigating the impact of ART are deterministic, with a frequency-dependent (density-independent) transmission term, as discussed in section 2.4. HIV transmission models often incorporate relatively complex patterns of sexual behaviour, with model populations stratified into sexual activity groups by rate of partner change, and assuming different degrees of mixing between groups. However, to date most models specifically designed to examine ART impact have assumed homogeneous risk behaviour (although some of these models have investigated changes in risk behaviour of the general population as a result of ART introduction and/or a change upon diagnosis of HIV [188, 192]). More realistic incorporation of sexual behaviour

is likely to improve the ability of models to capture the observed timescale of African HIV epidemics, namely steady state being reached over decades rather than centuries [193]. Figure 2.7 shows projections from ART Model 2, which assumes homogeneous sexual activity. With a homogeneous population, realistic prevalence levels (representing epidemics in sub-Saharan Africa) can only be reached over unrealistically long timescales, unless they are assumed to represent only the 'at-risk' proportion of the total population. This means that the population is crudely divided into two groups; one group practices no risky behaviour at all, whereas the other has a relatively high rate of (unprotected) sexual partner change. This structure produces an epidemic curve over a realistic timeframe (decades rather than centuries), without producing unreasonably high prevalence levels for the entire population (at-risk and not at-risk). The model is too simple to draw conclusions, especially considering the unrealistically high treatment uptake rates, which imply that ART is initiated far earlier in infection than is warranted clinically. Such simple models suggest that ART alone cannot eliminate an epidemic. In contrast, Figure 2.8 shows the impact of full coverage of all infected individuals, but at an appropriate stage of infection: that is, pre-AIDS and AIDS. The average infectiousness of infected individuals remains at 0.1, as used for the model runs in Figure 2.7, but the partner change rate has had to be increased to produce an epidemic over a realistic timescale. However, even in these unrealistically optimistic scenarios, the main impact on prevalence comes from changes in risk-taking behaviour rather than ART (Figure 2.8).

More sophisticated models incorporating sexual behaviour include partner models [208, 209] and network models [186, 210]. Gray et al use a stochastic simulation incorporating individuals and their contacts, although some assumptions are not clear in the available publication [190]. The need for complexity will depend on the nature of the research question [161]. For example, where changes in sexual behaviour as a result of ART are to be investigated, a more sophisticated description of sexual behaviour is required [186]. Where the effect of ART on transmission is to be investigated, a more realistic pattern of infectiousness is required [190, 192]. However, while increased complexity can make models more realistic, it also makes them more difficult to parameterise and more difficult to analyse and interpret model output.

Figure 2.7 Model predictions of the effect of ART on a mature epidemic, under various assumptions.



Model simulations of the potential impact of ART on a mature epidemic, varied by treatment uptake rate, reduction in infectiousness due to treatment and impact on risk behaviour at the population level, using ART Model 2. Figures a) and b) show the impact if ART is introduced 20 and 30 years after the start of the epidemic, respectively. The model used only incorporates one stage of HIV infection and so individuals initiate treatment at an earlier stage of infection than is realistic, and there is homogeneous sexual mixing.

Scenario A – ART uptake = 50% per year, sexual activity post ART = unchanged (5 partners per year), reduction in infectiousness due to ART = 50-fold

Scenario B – ART uptake = 50% per year, sexual activity post ART = unchanged (5 partners per year), reduction in infectiousness due to ART = 1000-fold

Scenario C – ART uptake = 50% per year, sexual activity post ART halves (2.5 partners per year), reduction in infectiousness due to ART = 50-fold

Scenario D – ART uptake = 90% per year, sexual activity post ART = unchanged (5 partners per year), reduction in infectiousness due to ART = 1000-fold

Scenario E – ART uptake = 90% per year, sexual activity post ART = reduced by 20% (4 partners per year), reduction in infectiousness due to ART = 1000-fold

2.12 Behaviour change in ART models

Given that it is difficult to predict how individuals might change their sexual behaviour as a result of ART introduction in different regions, models are faced with either estimating behavioural parameters from epidemiological data or exploring pessimistic and optimistic scenarios using parameter values assumed to be at the ends of the spectrum of possible outcomes. Law et al in 2001 modelled the effect of ART on the HIV epidemic in Australia in 1996 among the homosexual population and predicted the outcome of the competing effects of increased life expectancy, decreased infectiousness and increases in unsafe sex of uninfected MSM on HIV incidence [192]. Their assumption of a range of no change to a doubling of risky sex was essentially arbitrary, but demonstrated that increases in sexual behaviour (and life expectancy) could negate the beneficial impact of decreased infectiousness on incidence. Blower et al 2000 produced similar results for the homosexual population in San Francisco [188], again using the range of no change to a doubling in sexual risk-taking.

Velasco-Hernandez et al have investigated the conditions under which ART in HIV infected individuals may drive an epidemic to extinction [189], but it is highly unlikely that ART could eliminate HIV in any setting because it is likely that an extensive reduction in risk activity would be required to counteract the increased opportunity for transmission allowed by extending patients' life expectancy (see [193], Figures 2.7 to 2.9, Chapter 5). As behaviour change is notoriously difficult to elicit and initial coverage rates for ART in resource-poor settings are likely to be low, this optimistic scenario is highly unlikely.

The early impact of wide scale ART use in resource-poor settings where HIV prevalence is currently high will probably not involve substantial population-level increases in risky behaviour. The effectiveness of local ART programmes will probably need to be demonstrated across a broad range of the population before the perceived threat of AIDS as a disease declines. In lower prevalence regions where high coverage rates are feasible, such changes may occur. Careful monitoring of potential changes in risk behaviour would be very useful, if feasible. Ideally, a model designed to explore the impact of sexual behaviour change in resource-poor settings, be it an increase or a decrease, should explicitly model HIV diagnosis separately from treatment initiation, as shown by Law et al [192], because 1) it is knowledge of HIV status and the associated counselling that may change behaviour, 2) the advent of therapy in the sick may change their desire and/or ability for sexual functioning and 3) the attitude of those who know they are infected with HIV may change between not being treated, where they perceive a risk of transmitting to partners, to being treated, where the magnitude of risk may be perceived as smaller. This is one area where the introduction of ART could be used for prevention as well as treatment, through facilitating VCT.

2.13 Stage of HIV infection

Researchers have suggested that ART could be used as a direct prevention tool due to its effect on pVL leading to a decrease in infectiousness and therefore incidence [207, 211, 212]. However, the competing effects of increasing prevalence due to the effect of ART on life expectancy and potential behavioural disinhibition would make this a risky strategy. Furthermore, models that predict dramatic reductions in incidence due to ART have used unrealistic treatment uptake rates. As described, some have argued that even high prevalence (30%) epidemics can be driven to extinction by ART, when assuming a treatment coverage rate of 50% to 90% [188, 189]. The 50% level was estimated from data collected in a telephone sample interview of 462 MSM from four US cities conducted between November 1996 and February 1998 [213]. This was when triple ART was in its infancy and treatment was initiated in a large proportion of HIV positive individuals, regardless of infection stage or CD4 count, because a "hit hard, hit early" consensus existed for patient management. Furthermore, the study only included self-identified, HIV-positive MSM, and so individuals unaware of or reluctant to admit their serostatus would have been missed. It is now more common to initiate treatment at a later stage of infection, due to side-effects and the risk of evolution of drug resistance. The proportion of HIV-infected people currently being treated, even in industrialised countries, is likely to be substantially below that required for any prospect of disease elimination.

More realistic patterns of ART use are incorporated in the models of Law et al [192, 214] and Gray et al [190], where the proportion of individuals treated increases with severity of HIV disease as determined by CD4 count [192] or pVL [190]. By explicitly modelling changes in infectiousness and sexual activity over time, it has been shown that ART alone cannot be relied upon as a prevention tool.

Gray et al [190] and Nagelkerke et al [215] explicitly modelled the impact of ART in resource-poor settings (Uganda, and Botswana and India, respectively). Nagelkerke et al assumed that those receiving ART and infected with drug-sensitive virus had zero infectiousness, which does not reflect the true situation, despite pVL being substantially reduced [215]. Assumed rates of resistance evolution seem optimistically low for ART use in resource-poor settings, only being varied between 5% and 25% of those on ART failing treatment per year, whereas rates as high as 60% have been predicted by others [81, 216, 217]. Despite this the model predicted that after transient success, ART would be rendered ineffective within 30 years due to wide-scale emergence of drug resistance, based on resistant virus being as transmissible as sensitive virus.

Gray et al's conclusions were also relatively pessimistic [190] compared with Blower et al [188]. Gray et al concluded that ART alone cannot control mature HIV epidemics such as that in Rakai, Uganda. This conclusion concurs with Garnett et al [18], who believe that ART cannot make an impact on a mature epidemic unless treatment is initiated with high coverage and earlier in infection (i.e. with higher CD4 counts) than is currently recommended in treatment guidelines. Such early treatment is unfeasible financially and unwarranted clinically, since it would lead to earlier

evolution of resistance and treatment failure, leaving individuals running out of treatment options, perhaps even before the onset of AIDS.

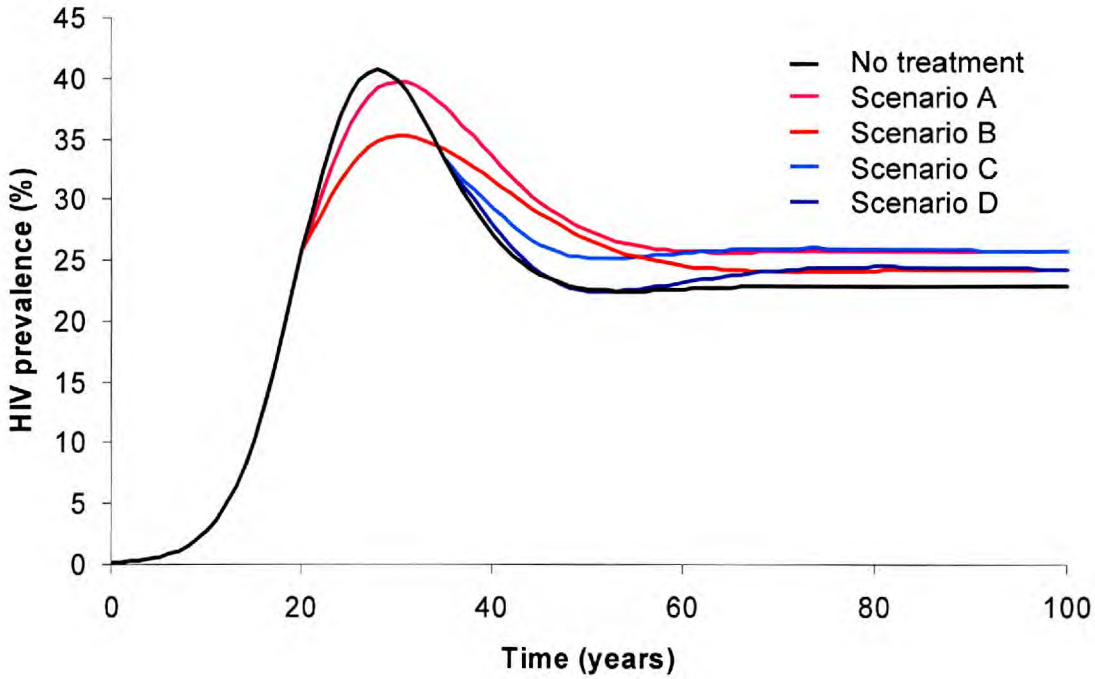
While some studies aim to evaluate the effect of treating individuals in primary infection [191], the vast majority of HIV infections are not diagnosed until well into the incubation period or later. If primary infection is defined as the period before detectable antibodies against the virus emerge, then standard tests of serostatus can only identify those who have completed the primary stage. However, if primary infection is used to describe the high initial viraemia then infection could be diagnosed before this has ended. Treatment could not start earlier than the incubation stage which follows primary infection except in rare circumstances where exposure is known to have occurred. In resource-poor settings, diagnosis is frequently at a very late stage of infection, and so initiating treatment at diagnosis or when CD4 counts descend to a certain benchmark, such as 200 or 350 cells/mm^3, will mean that the highly infectious period of primary infection and the long period of incubation escape the controlling effects of treatment.

In models examining the impact of ART on HIV incidence, inclusion of the variation in infectiousness as a function of infection stage is crucial for producing realistic predictions. As ART can only be initiated upon HIV diagnosis, it will have no effect on transmission from most individuals undergoing primary infection, when risk of transmission is high. By the time an individual has developed AIDS, their sexual activity will have decreased, and so this group of infected individuals will not contribute as much to HIV transmission as the duration of this phase would suggest. Figure 2.9 shows runs from ART Model 3, a four-stage HIV infection model, with various treatment coverage scenarios, determined by stage of infection. Treatment is introduced into a population with a mature HIV epidemic, so it is not surprising that that even aggressive implementation of ART to individuals, regardless of stage of infection, cannot lead to elimination. Figure 2.9 illustrates that ART under more realistic assumptions regarding treatment delivery, in terms of treatment initiation, will have far less impact on incidence. In this model, there is high, but plausible, rates of drug resistance evolution (30% per year), meaning that the effects on transmission are short-lived, coinciding with the effectiveness of the regimen (details of other parameter values are given in Appendix C). This illustrates the urgent need for cheap and reliable second-line treatment options to be available for ART roll-out, an issue further explored in Chapter 6.

Despite the results of Blower et al being rather over-optimistic [188], Gray et al's assumptions of the effects of ART may similarly be over-pessimistic [190]. The authors assume that ART leads to an average proportional reduction in HIV log pVL of between 26.8% and 43.6%, based on data from the Women's Interagency HIV Study [218] and the John Hopkins Clinic [219], respectively. However, other studies distinguish between patients who respond to a regimen (who typically experience reduction in pVL to undetectable levels (<50 copies/ml)), those who do not respond and those who subsequently experience treatment failure (viral rebound). With these distinctions, an individual responding successfully to ART will have a far greater reduction in pVL than Gray et al assume. Furthermore, the proportion reduction was the value recorded one month

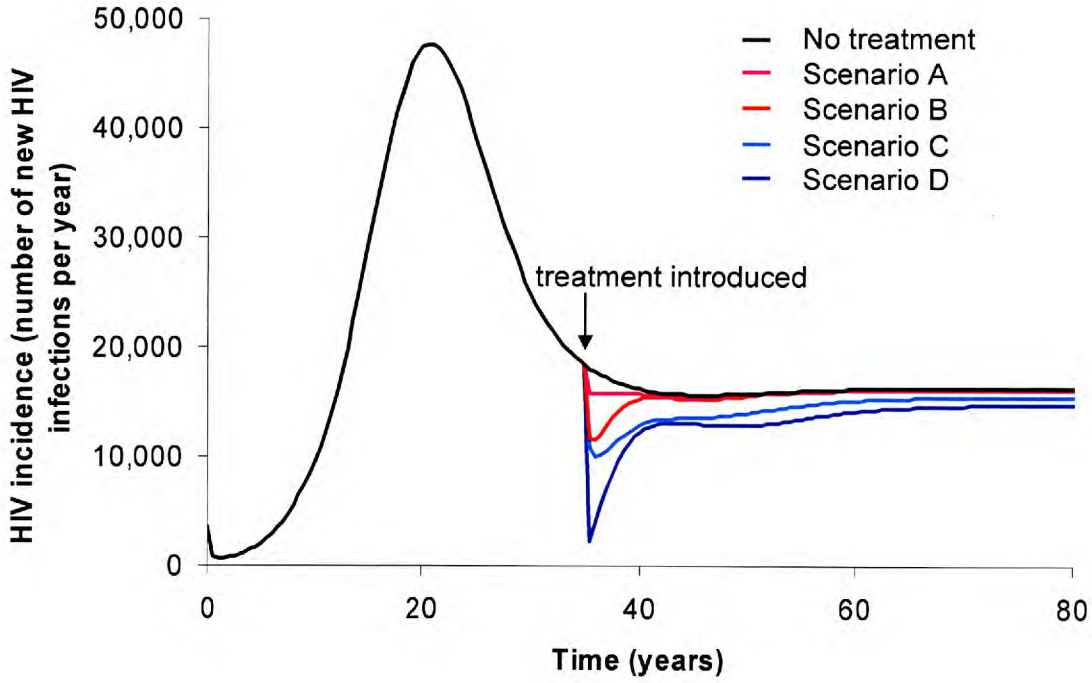
and three months after treatment initiation for the WIHS and John Hopkins Clinic patients, respectively. It can take much longer than this for complete reduction of pVL, often to undetectable limits [27] (models generally do not incorporate a delay between treatment initiation and effect, but it can be assumed that this is implicitly accounted for in the treatment uptake rate). Gray et al also included the possibility of behavioural disinhibition; the average number of partners for those on treatment was increased by 50% or 100%. Again, the values appear pessimistic and were essentially chosen arbitrarily, probably in order to complement other models [188, 192].

Figure 2.8 Model predictions of the effect of ART on a mature epidemic using more realistic timing of initiation of ART.



Results generated using the staged progression model, ART Model 3, details of which can be found in Appendix C. The model assumes only pre-AIDS and AIDS patients qualify for treatment. ART uptake for these stages is 12 year^{-1} (patients start ART after an average of one month), representing maximum coverage and therefore the most optimistic scenario. Scenarios A and C model prevalence if ART is introduced 20 and 35 years after the start of the epidemic, respectively. Scenarios B and D are as for A and C, respectively, but sexual activity of healthy individuals (all non-AIDS members of the "at risk" population) is reduced by 20% (from 7 to 5.6 partners per year).

Figure 2.9 Predictions of the impact of ART by stage of infection at which treatment is initiated.



Predictions of the impact of the introduction of ART in terms of HIV incidence, by stage of infection at which treatment is initiated.

Scenario A – ART uptake: AIDS patients only (after a mean of 1 month)

Scenario B – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months)

Scenario C – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months) and incubation stage (after mean 4 years)

Scenario D – ART uptake: all four stages, after mean 1 month

2.14 Emergence of ART drug resistance

Many models of ART have concentrated on predicting the emergence and spread of ART drug resistance. Once again it is very difficult to make such predictions, as the spread of drug-resistant virus is highly dependent on the replicative fitness of the resistant strains that evolve and their ability to superinfect individuals infected with wild-type strains. Mathematical models may have the ability to predict best- and worst-case scenarios for resistance spread [215, 220], but it must be conceded that the degree to which drug resistance and risky behaviour increase as ART use rolls out in Africa and other resource-poor areas cannot yet be quantified.

Blower et al 2001 predicted that acquired resistance will continue to rise, but transmitted resistance is likely to increase only gradually, with a doubling time of around four years and a predicted median of 15.6% of new HIV infections likely to be resistant to ARV drugs by 2005 [220]. This conclusion was due to an assumption that of all possible ART-resistant HIV strains that could possibly evolve, none could be as transmissible as wild-type. The study also assumed that individuals infected with ART-sensitive virus undergoing treatment cannot be co-infected or superinfected by an ART-resistant strain.

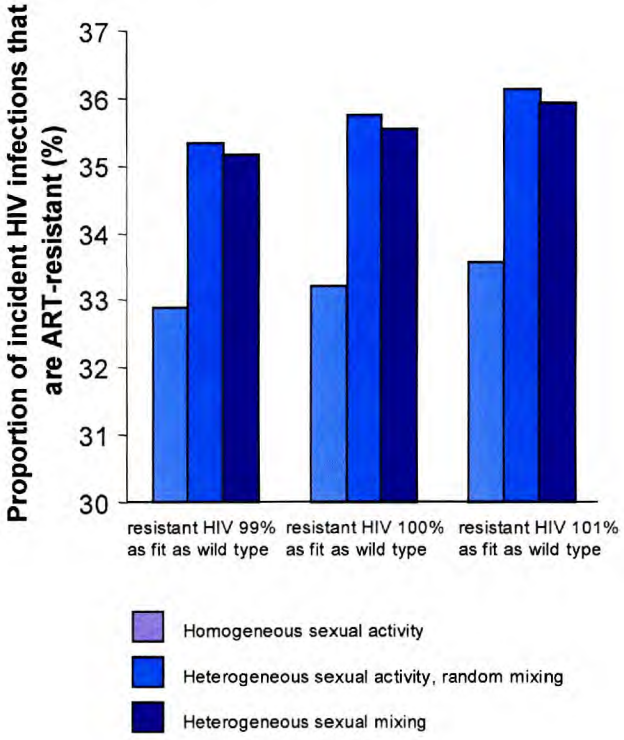
Despite the conclusion that transmitted ART resistance will stabilise at low levels, the predicted range around the 15.6% value is very wide (0.05% to 73.21%) [220]. The authors argue that the higher values in the range generated from their sensitivity analysis have a very low probability. However, the choice of parameter distributions in the Monte Carlo sampling of parameter space undertaken in their study was arbitrary (in the sense of not being motivated by prior data) and entirely determines the probability of pessimistic scenarios.

The authors themselves acknowledge that they are "predicting the unpredictable" [220], but argue that their theoretical predictions [188] are in close agreement with empirical data [221]. Both display an increase in primary resistance between 1997 and 2001, but this is a short time period and the increase may reflect the expansion in use of ART over this time. Furthermore, the uncertainty interval around predictions made by the authors is large enough for a wide range of empirical data to fit the model. Blower et al acknowledge that transmission of ART resistance may vary widely by location and that frequent comparison to empirical data is necessary. However, Blower et al in 2005 recommend that large-scale surveillance for detecting transmitted resistance in Africa will be unnecessary for the next decade because transmitted drug resistance will not reach more than 5% during that time [71]. This is due to the assumption that ART use will remain at low levels, although the authors suggest that in urban locations rates of treatment may be higher. They recommend close monitoring of treated patients, but in areas where resources are constrained, this is unlikely to be practicable (WHO guidelines do not consider resistance testing, or even pVL testing, to be a priority in these regions [108, 136]). Surveillance of the prevalence of drug resistance among patients is required in all locations where ART is used [87], and the predictive utility of models with high degrees of uncertainty in their input parameters, and hence also their results, is limited.

If one relaxes the assumption that no resistant strain can exceed the transmission fitness of wild-type, even in the presence of ART use, even greater variation in predicted levels of transmitted drug resistance after 10 years of ART provision is possible (Figure 2.10). The results suggest that if a relatively fit variant emerged, the effectiveness of current ART regimens could be compromised after a very short period. When heterogeneous sexual activity is incorporated, resistance transmission is predicted to emerge more rapidly. This is partly due to superinfection allowing resistance to be transmitted through core groups receiving ART. Incorporating assortative mixing has comparatively little impact, but slightly decreases transmission of resistance due to saturation of resistance transmission through high activity groups.

These results do not suggest a likelihood of drug resistance transmission, but merely demonstrate the potential effects of various scenarios (as with the other models in this chapter, the results are purely illustrative). It is more for biological studies (in particular resistance testing) and within-host models of HIV infection to examine the possibility that such strains could emerge [222]. Ongoing treatment pressure in the presence of viral outgrowth could lead to sequential mutations increasing the fitness of a resistant strain; therefore, there is an argument for close monitoring of patients and implementation of drug resistance surveillance systems as ART is rolled out in resource-poor settings.

Figure 2.10 Model predictions of transmission of ART drug resistance by relative fitness of strains and model structure.



Predictions of the spread of transmitted (primary) ART resistance under various scenarios, using ART Model 2 with stratification into four sexual activity classes (ART Model 4, details in Appendix C). The model is run for 40 years before ART introduction, with model output 10 years after. For homogeneous sexual activity, all classes have a partner change rate of 5 partners per year with random mixing. For heterosexual sexual activity, the partner change rate for classes 1 to 4 is 40, 10, 2 and 0.5 respectively. For heterogeneous sexual mixing, the assortative mixing parameter is set to 0.5; for random mixing it is set to 0.0. Relative fitness refers to the transmission probability per partnership of ART-resistant β_R^U compared to ART-sensitive β_S^U infection for untreated individuals and the probability that untreated individuals with mixed infections transmit ART-resistant rather than ART-sensitive virus (ω_2^U , details in Appendix C).

2.15 Parameterisation

To aid the design of successful ART programmes in resource-poor settings, more information on the impact of ART provision is crucial – data on morbidity and mortality, tolerability, treatment failure and the possible emergence of drug resistant strains are very important. This information also increases the reliability of model predictions by providing more accurate ranges of parameter estimates. Population-level monitoring for changes in risk behaviour and patterns of ARV drug resistance are also required. Information on the performance of ART programmes in these settings is starting to be generated. However, data generated from industrialised countries should be interpreted with care when assessing the applicability of results. Modelling provides the tools to predict the consequences of possible activity; by constraining ourselves to examining only those scenarios that are supported by current, gathered data, we may be ignoring other, distinct possibilities, such as the case in which an ART-resistant strain as fit as wild-type could evolve.

2.16 Discussion

HIV transmission models predicting the impact of ART use should incorporate a realistic progression through stages of HIV infection in order to capture the timing of treatment initiation. Further elaboration of models is required (depending on the research question being posed), in areas such as time of diagnosis, sexual behaviour and assumptions regarding drug resistance evolution and transmission. In view of the complexity of the problem, mathematical models of ART use would be difficult to analyse analytically.

All modelling studies are ultimately dependent on the availability of setting-specific surveillance and behavioural data, and collection of such data is important for all regions where large scale ART use is introduced. More investigation is required in order to determine the effect of introducing ART on a substantial scale in resource-poor settings with different stages and magnitudes of HIV epidemic. Models addressing questions of ART implementation in such settings, utilising data from fledgling ART projects where possible, will be of great use in designing cost effective programmes.

Table 2.4 Summary of existing ART models, by date of publication.

Study	Model structure	Setting	Assumptions	Key outcomes (pertaining to ART) and comments
Zaric et al 1998 [223]	Dynamic, difference equations	MSM and IDU, US cities/regions	Infection stratified into HIV and AIDS stages. Allows acquired and transmitted drug resistance. Rate of resistance evolution: 95% per year for non-adherents, 5% per year for adherents. Increased life expectancy due to ART: 1.5-fold for adherents, 1.2-fold for non-adherents, 1.2-fold for adherents infected with drug resistant HIV.	The most important factor affecting emergence of drug resistance is adherence to ART.
Aalen et al 1999 [200]	Linear model	MSM, England and Wales, 1990s	Markov multi stage model (stage based on CD4 count). Explicit diagnosis and treatment. Estimated HIV incidence in the MSM population, which was fixed at 1200 cases/year for all but one scenario, where incidence was halved from 1995 onwards.	Decrease in AIDS incidence due to ART. Number receiving treatment will increase 50-100% by 2001 compared to pre-1996.
Wood et al 2000 [224]	Linear model	IDU, Vancouver, Canada 1999-2006	Treatment uptake: 80% (scenario 1), 20% (scenario 2). Median increase in life expectancy due to ART: 7 years. No drug resistance or stratification by infection stage or sexual activity class. Prevalence estimates used in DemProj, part of the Spectrum suite of models (information at http://www.futuresgroup.com/software/Goals/goals.pdf) (3 scenarios: prevalence reduced from 7% in 1999 to 5% in 2006, prevalence remains at 7%, prevalence increases to 9% in 2006).	Calculated life expectancy and AIDS deaths 1999-2006 for each scenario. Concluded that low level ART use is not sufficient to increase life expectancy in this population and called for expansion in ART coverage.
Wood et al 2000 [199]	Linear health economic model (based on previous model [224])	South Africa 2000-2005	Median increase in life expectancy due to ART: 6 years (range: 5-7). Treatment uptake: 25% of infected adults. Spectrum AIDS Impact model was used to adjust the population projections for current and projected HIV-associated mortality.	Providing ART for 25% of the infected population could prevent a 3.1 year decline in life expectancy and more than 430,000 incident cases, but with disproportionate expenditure ($19 billion at 2000 prices) compared to preventing mother-to-child transmission.
Blower et al 2000 [188]	Dynamic, deterministic	MSM, San Francisco, US, up to 2010	Changes in sexual behaviour: no change to doubling of risk. Treatment coverage rates: 50-90% uptake per year. ART reduces infectiousness 2- to 100-fold. Acquired drug resistance: 10-60% per year (infections can revert back to ART-sensitive). Resistance is transmitted, but is less fit than wild type. No stratification by stage of infection or sexual activity class. Increased life expectancy due to ART: 1.5- to 3.0-fold.	Increasing ART usage would decrease the death rate and substantially reduce HIV incidence (wide range of results due to uncertainty in parameter estimations).
Blower et al 2001 [220]	Dynamic, deterministic (used previous model [188])	MSM, San Francisco, US, 1996-2005	Treatment uptake and drug resistance evolution rates as for [188]. No change in risk behaviour. Assumed no resistant strains could arise that were as transmissible as wild type. Transmissibility range: 1-90% as fit as wild type. Implicitly allows superinfection with wild type virus of subjects with primary resistance.	Prevalence of ART resistance is already high in San Francisco and will continue to increase substantially through 2005. Transmitted drug resistance will remain low, only increasing gradually, with a doubling time of around 4 years and a predicted median 15.6% (range 0.05-73.21%) new infections resistant to ARVs by 2005.
Freedberg et al 2001 [201]	Linear health economic model	US	Monte Carlo simulation of a hypothetical cohort of infected patients. Disease progression predicted by CD4 count (6 categories) and pVL (5 categories). Detailed description and associated costs of HIV-related morbidity, opportunistic infections and death. Virological failure represented as 0.5 log increase in pVL for 2 consecutive months. Increased life expectancy due to ART: 2 years.	The cost-effectiveness ratio for ART was $13,000-$23,000 per quality-adjusted life year gained. Initial CD4 count and drug costs were the most important determinants of costs, clinical benefits, and cost effectiveness.

Study	Model structure	Setting	Assumptions	Key outcomes (pertaining to ART) and comments
Tchetgen et al 2001 [225]	Dynamic, deterministic	MSM (assumes same population as Blower et al [188])	No stratification by sexual activity or stage of infection (model is for all stages except AIDS; progression to AIDS exits an individual from the model population). Models diagnosis separately from treatment initiation. No sexual behaviour change due to ART. Drug resistance emerges at 1.2-13.5% per year for adherent patients and 67.3-85.9% per year for non-adherent patients. Resistant strains are half as transmissible as wild type. Untreated resistant infections may revert to wild type infections (10% per year). 60% of treated patients adhere. Increased life expectancy due to ART: approximately 3-fold. ART reduces infectiousness by 74%. Withdrawal rates also vary by adherence.	Although screening for adherence is likely to reduce levels of drug resistance compared to treating all patients, HIV and AIDS incidence rates are likely to increase unless screening accuracy is extremely high.
Dangerfield et al 2001 [226]	Dynamic, deterministic	MSM, UK 1981-1998	Five stages of infection with varying infectiousness broadly corresponding to primary infection, incubation, pre-AIDS and early and late AIDS. Three levels of sexual activity with proportionate mixing. No drug resistance. Proportion initiating ART at each stage (models 1, 2 and 3 respectively): Incubation = 0%,0%,60%; preAIDS = 0%,10%,25%; early stage AIDS = 0%,10%, 35%. No uptake for late stage AIDS, which is defined as the final few months of care – authors assume patients only reach this stage as a result of treatment failure. Infectiousness decreases to a constant level for all those treated, which is 35-40-fold less than for pre-AIDS.	Three models were designed, differing by prognosis of patients experiencing treatment failure for models 1 and 2. Model 3 stratifies life expectancy on ART by stage of infection at which treatment is initiated.
Law et al 2001 [192]	Dynamic, deterministic	MSM, Australia 1996	Population-level changes in sexual behaviour: no change to doubling of risk. Decrease in infectiousness due to ART: 10-fold (range: 100-fold to none). Proportion of individuals diagnosed and treated increases with progression of disease, as determined by CD4 count. HIV diagnosis modelled separately to ART initiation, median 2-fold decrease in risk behaviour upon diagnosis (range: 25-75% reduction). No stratification by sexual activity group. No incorporation of drug resistance. Stratified by stage of infection in terms of CD4 count (>500 cells/ml, 200-500, <200, AIDS). Proportion treated by disease stage: >500=35%, 200-500=52%, <200=72%, AIDS=90%.	Changes in risk behaviour were linearly associated with increases in incidence, while decreases in infectiousness were non-linearly associated with decreases in incidence. Decreases in infectiousness of 2-, 5- and 10-fold would be counterbalanced (in terms of incidence) by increases in risk behaviour of 40, 60 and 70%, respectively.
Velasco-Hernandez et al 2002 [189]	Dynamic, deterministic (used previous model [188])	MSM, San Francisco, US,	Previous model [188] is used to derive an analytical expression for R_0. Used assumptions as for the previous model. Changes in risk behaviour: 50% reduction to 100% increase (whole population). Relative fitness of resistant strains: 1% to "approximately as transmissible".	Median R_0=0.90 if risky sex decreased, 1.0 if risky sex remained stable, and 1.16 if risky sex increased. R_0 decreased as ART coverage increased. The probability of epidemic eradication is high (85%) if risky sex decreases (median 25% reduction), moderate (50%) if it remains stable, and low (13%) if it increases (median 50% increase). Concluded that ART can function as an effective HIV prevention tool, even with high levels of drug resistance and risky sex, and could eradicate a high prevalence (30%) HIV epidemic.
Law et al 2002 [227]	Dynamic, deterministic (extension of previous model [192])	MSM, Australia 1996	Incorporation of other STIs, but not dynamically – assumed 100% increase in prevalence of STI among all MSM regardless of HIV status due to increased risk behaviour as a result of ART introduction. STI infection increased HIV infectiousness 3.5-fold (range: 2-5-fold).	Decreases in infectiousness of 2-, 5- and 10-fold would be counterbalanced (in terms of incidence) by increases in risk behaviour of 30, 50 and 65%, respectively i.e. even more modest increases than in previous publication [192]. Even small increases in STI as a result of increased risk behaviour could have an important multiplicative effect increasing HIV incidence.

Study	Model structure	Setting	Assumptions	Key outcomes (pertaining to ART) and comments
Johnson & Dorrington 2002 [228]	ASSA2000 Interventions Model (dynamic, deterministic spreadsheet model)	South Africa	Stages of infection: stages I to IV of the WHO clinical staging system, with decline in sexual activity at advanced stages. Includes VCT with a corresponding (though transient) decrease in risk behaviour for both infected and uninfected individuals. Reduction in pVL due to ART: 1.76 $\log_{10}$. Reduction in infectiousness: 67% per log reduction in pVL. Four sexual activity classes. Only AIDS patients qualify for treatment. Model assumes a phased roll-out achieving 90% coverage by 2006. First six months of ART: death rate=8.2%, discontinuation rate=9.1%. Thereafter: death rate=5.8%/year, discontinuation rate=5.8%. Resistance not explicitly modelled.	ART provision is highly effective at preventing new infections, through reduced infectiousness and assumed impact of VCT, and the high coverage level. ART plus VCT reduces incidence of AIDS, but because of increasing numbers starting treatment, the overall number of AIDS cases increases to a peak in 2015. Approximately one million deaths would be averted between 2001 and 2015 if ART is added to a set of AIDS prevention initiatives.
Nagelkerke et al 2002 [229]	Dynamic, deterministic	Botswana and India	Stratified by gender and two sexual activity groups (higher group represents CSWs and their clients). No changes in sexual behaviour due to ART, but "effective counselling" of those on ART could decrease infectiousness of those developing drug resistance by 50%. ART reduces infectiousness to zero. Rate of acquired resistance: 25% per year (range: 5-25%). Transmitted resistance possible (resistant strains appear to be as transmissible as wild type). Rate of treatment uptake: all those infected are recruited at rate 50% per year. No stratification by stage of infection.	Compared impacts of ART programmes to other HIV interventions. Concluded that after transient success, ART would be ineffective within 30 years due to widespread drug resistance. Assumes high treatment uptake rates and pessimistic assumptions regarding transmission of drug resistant strains.
Gray et al 2003 [190]	Dynamic, stochastic	Rakai, Uganda, 2000-2020	Assumes ART reduces HIV log pVL by 27.0-42.5%, representing decreases in log pVL from 5.32 to 3.06 $\log_{10}$ copies/ml [219], and 5.23 to 3.82 $\log_{10}$ copies/ml [218]. These generate an average decrease in infectiousness of 95.7% (0.0023 to 0.0001 per coital act) and 43.5% (0.0023 to 0.0013) respectively. Sexual activity decreases with increasing pVL. Behavioural disinhibition: increased risk by 50-100% (among those on ART only). Treatment uptake: scenario 1: all with pVL >55,000 copies/ml; scenario 2: all subjects, irrespective of pVL (20% of infected persons in Rakai had pVLs >55,000 copies/ml [230]). Range of treatment coverage: 0-100%.	Concluded that ART alone cannot control mature HIV epidemics such as that in Rakai. Behavioural disinhibition would counter decreases in HIV infectiousness due to ART.
Xiridou et al 2003 [231]	Dynamic, deterministic	Young MSM, Amsterdam, The Netherlands	Steady and casual partnerships. Stages of infection: primary, incubation, AIDS. Sexual activity assumed to cease after development of AIDS. 42% subjects in incubation stage are diagnosed. Diagnosis during incubation results in a 25% (0-50%) reduction in risky behaviour. ART reduces infectiousness by 74.5%. Increased life expectancy (before development of AIDS) due to ART: 9.5 years.	A 75-99% reduction in infectiousness due to ART will be counterbalanced by increases of 50% (range: 30-80%) in risky behaviour with steady partners, but not by increases of up to 100% with casual partners. Increasing HIV testing from 42% to 80% and ART coverage from 70% to 85%, would mean even a 100% increase in risk taking with steady partners would not outweigh the effect of ART on HIV incidence.
Xiridou et al 2004 [191]	Dynamic, deterministic (extension of previous model [231])	Young MSM, Amsterdam, The Netherlands	Extension of original model [231] to allow for initiation of ART during primary infection. Proportion of men diagnosed during incubation and successfully treated: 60-80%. Proportion initiating ART during primary infection: 1-10%. ART reduces infectiousness during incubation by 50-99%. Population-level increase in risk behaviour for both steady and casual partnerships: 0-100%. Mean incubation time to AIDS for initiating ART during incubation: 15-30 years. Decreases in infectiousness and increases in life expectancy for those initiating ART during primary infection were forced to be larger than for those initiating ART during incubation.	Investigates the role of primary infection in HIV transmission. Estimates that among all new infections only 11% occur during primary infection. The effect of ART during primary infection on transmission is therefore limited. However, in a community with higher risk behaviour among casual partnerships, the fraction of transmission attributed to primary infection increases to 25%.

Study	Model structure	Setting	Assumptions	Key outcomes (pertaining to ART) and comments
Clements et al 2004 [214]	Dynamic, deterministic (based on previous models [192, 227])	MSM, Australia 1995-2006	Assumed a 10% annual increase in population-level risk behaviour from 1996. A stable proportion receive ART from 1998, which then declines from 70% in 2001 to a median of 50% of diagnosed on ART by 2006.	HIV incidence was predicted to have declined during 1996-1998 due to ART, with a slow increase 1998-2001 due to increased risk behaviour while ART usage remained fairly stable. From 2001, a continued increase in risk behaviour coupled with a moderate decline in ART use would lead to a 50% increase in incidence by 2006.
Auvert et al 2004 [207]	Linear	Township near Johannesburg South Africa, 2002	Used results from a cross-sectional study. Under WHO guidelines, all with CD4 counts <200 cells/mm^3 initiated treatment. Under USDHHS guidelines, all with CD4 counts <350 or pVL >55,000 copies/mL initiated treatment. Reduction in infectiousness due to ART calculated using infectiousness estimates by pVL category used by Gray et al [190] and comparing change in distribution of pVL in the community with and without ART.	Investigated short term impact of ART on incidence. The proportion of infected subjects eligible for ART was 9.5% (95% CI 6.1-14.9%) under WHO guidelines and 56.3% (95% CI 49.1-63.2%) under USDHHS guidelines. The population impact of ART on HIV transmission is small (reduction in annual risk of transmission 11.9% (95% CI 7.1-17.0%)) under WHO guidelines, but higher under USDHHS guidelines (71.8% (95% CI 64.5-77.5%)).
Boily et al 2004 [186]	Dynamic, deterministic	MSM population	STI (gonorrhoea) increasing HIV infectiousness is modelled dynamically. Stratified into six sexual activity groups with proportionate mixing. Two stages of HIV infection: incubation and AIDS. AIDS patients treated with ART resume the sexual activity of asymptomatic individuals within their activity class. ART reduces infectiousness by 25% (pessimistic), 50-90% (moderate), 99% (optimistic). Treatment uptake rates: 10-90% per year, for AIDS patients only, or for all infected subjects Withdrawal rate (due to treatment failure, resistance and toxicity): 0-50% per year.	Zero to 55% new bacterial STI could be attributed to wide-scale ART use, due to more modest increases in risky behaviour (0-25%) at the population level. These increases have a negative impact on HIV if coverage is too low. Increasing ART coverage helps to prevent more HIV infections despite larger increases in risk behaviour and STI that is predicted to ensue. No individual-level increase in risk behaviour; population-level increases in risk behaviour over time are due to ART slowing the depletion of high-risk infected individuals, so these populations are replenished.
Salomon et al 2005 [204]	The Goals model (linear spreadsheet model) (based on previous models [202, 203])	Sub-Saharan Africa, calibrated to three regions: East, West/Central and Southern, up to 2020.	Goals model adjusts UNAIDS/WHO EPP (epidemic projection package) and Spectrum model incidence and prevalence estimates. Five different risk groups (single and married men and women, and CSWs). Median increase in life expectancy due to ART: three years. No drug resistance. Includes STI transmission. Three stages of infection: primary, incubation and symptomatic. ART reduces infectiousness by 99% (optimistic) or 66% (pessimistic). Number of partners reduced by 50% plus two times higher condom use (optimistic) or no change (pessimistic) for those treated. Risk behaviour of the general population does not change (optimistic), or condom use declines by 10% (pessimistic). Treatment uptake: 50% ART coverage (of those in need) by 2005, increasing to and remaining at 80% from 2010-2020. This "treatment-centred" response, where little prevention activity occurs, was compared to a "prevention-centred" response where no ART scale-up occurred, and a "combined response", with optimistic and pessimistic assumptions of the effect of ART on prevention efforts being investigated.	Explored the potential impact of ART in the context of a broader strategy for HIV/AIDS control, comparing deaths and new infections averted to baseline projections without interventions. A prevention-centred strategy provides greater reductions in incidence and mortality reductions similar to those of treatment-centred strategies by 2020, but more modest mortality benefits over the next 5-10 years. If treatment scale-up leads to reduced effectiveness of prevention efforts, benefits (in terms of infections and HIV/AIDS deaths averted) are considerably smaller than for initiatives which complement each other. The number receiving ART in 2020 ranges from 9.2 million in a pessimistic treatment-only scenario, to 4.2 million in a combined response scenario with positive treatment-prevention synergies.
Wilson & Blower 2005 [156]	Spatial model	KwaZulu-Natal, South Africa	Incorporates heterogeneity in treatment accessibility with distance to health care facilities, and heterogeneous distribution of people infected with HIV.	Determining the optimal ART allocation strategy among health care facilities, aiming to maximise equity. Authors' strategy gave more equal access to ART than allocating therapy to the state capital only, or equal allocation to all health care facilities.

Abbreviations: IDU – intravenous drug use(r); MSM – men who have sex with men; STI – sexually transmitted infection; VCT – voluntary counselling and testing.

Chapter 3 Sexual HIV transmission probabilities

Summary

The estimation of HIV-1 infectiousness for different modes of transmission is important epidemiologically, not only to assess the infection risk to susceptible individuals when exposed to the virus, but also to make predictions of the potential spread of HIV infection in a population, as well as to interpret current epidemiological patterns of HIV prevalence between populations and settings. Since the beginning of the HIV epidemic, a number of studies have provided a wide range of estimates for infectiousness, partly due to differences in methods between studies and differences in the distribution of risk factors between the populations studied.

This chapter reports the results of a systematic review and meta-analysis of the literature on HIV-1 infectiousness for heterosexual and homosexual intercourse. It includes both per partnership and per contact transmission probability estimates. The purpose was to parameterise HIV infectiousness in the models used in this thesis, reviewing the literature in a similar way to all other model parameters, as described in Chapter 4. While results from this review have aided parameterisation of infectiousness for the models described in the following chapters, future models incorporating an explicit partnership duration will be able to make more direct use of these empirical estimates.

Estimates of both per partner and per contact sexual HIV transmission probabilities show considerable heterogeneity. While a meta-analysis for per partner infectiousness is presented, the production and use of summary estimates from such heterogeneous data and from studies with such different patterns of risk factors present, is not appropriate. While a random effects model can moderate the effect of heterogeneity for some analyses, in the case of HIV transmission, the influence of risk factors is so great that only analyses on subsets of similar studies may be reliable. The meta-analysis presented here is informative at a qualitative level, identifying trends in estimates between risk groups, such as between research settings or by direction of transmission, M→F or F→M. The results suggest that per partner transmission probabilities are higher in resource-poor than in industrialised research settings, higher for M→F than F→M transmission and higher for symptomatic rather than asymptomatic infection of the index case, yet these patterns generally were not statistically significant because of the high degree of heterogeneity.

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3.1 Abbreviations and acronyms

The following additional abbreviations and acronyms are used in this chapter:

AI	Anal intercourse
ARC	AIDS-related conditions/complex
CDC	Centers for Disease Control and Prevention (US)
CPS	California Partners' Study
F→M	Female to male (transmission)
GUD	Genital ulcer disease
HTLV-III	Human T-lymphotropic virus type III
LAV	Lymphadenopathy-associated virus
M→F	Male to female (transmission)
NLM	National Library of Medicine
UIAI	Unprotected insertive anal intercourse
URAI	Unprotected receptive anal intercourse

3.2 Background

HIV-1 (hereafter referred to as HIV) infectiousness, or transmission probability, is the proportion of HIV exposures that results in transmission of infection. The definition of "exposure" depends on the mode of transmission. For HIV, examples of types of infectiousness include per sexual contact, per sexual partnership, per injection, per blood transfusion, and per live birth. The estimation of HIV infectiousness for different modes of transmission is very important epidemiologically, not only to assess the infection risk to susceptible individuals when exposed to the virus, but also to make predictions on the potential spread of HIV infection in a population, as well as to interpret current epidemiological patterns of HIV prevalence between populations and settings. The scope of this project increased to incorporate a review of parenteral and blood transfusion transmission in order to parameterise collaborators' models investigating the impact of these modes of HIV transmission in resource-poor settings. The results are presented in Baggaley et al 2006 [232] (Appendix A).

HIV infectiousness is usually quantified as a transmission probability following single unit exposure to an infectious source, which may be defined in a number of ways. Exposure to HIV may be defined as a single blood transfusion, a single accidental needlestick injury, a single sexual contact or a single partner. For the first three examples of exposures, the transmission probability measures an instantaneous risk of infection following a single contact, whereas in the per partnership case, the transmission probability reflects a cumulative risk of infection over the duration of the relationship i.e. for a given follow-up duration or a given number of sexual contacts. In all cases, the transmission probability describes the risk of transmission of the virus from an infected individual to a susceptible partner. Transmission of HIV will therefore inherently include risk factors for the individual transmitting the virus (infectiousness) and of their partner acquiring it (susceptibility). Ideally, studies should aim to disentangle the risk factors affecting infectiousness and susceptibility on HIV transmission estimates. However, it is often methodologically difficult, with the result that estimates can display large variability.

Transmission probabilities are notoriously difficult to quantify for most modes of transmission of HIV infection (with the possible exception of perinatal transmission), and especially for sexual transmission. However, these measures are key to understanding the different patterns of spread of HIV in different settings, including addressing claims of different infectivities by subtype and by prevalence of STIs at various locations. These estimates are also required to parameterise mathematical models of HIV transmission more accurately, and therefore increase the reliability of the conclusions from a wide range of research questions that these models are designed to address. The variation in transmission probability due to STI cofactors and stage of infection is particularly important in investigating the wide disparity in size of HIV epidemics in different geographical locations. The high infectiousness during primary infection means that it is not only the number of partners that an individual has, but the number of concurrent partners and their positions within the wider sexual network which determine rates of HIV (and other STI) spread [233].

Fundamentally, the estimation of HIV transmission probability per sexual exposure relies on determining as exactly as possible the change in HIV status between two partners and the number of units of exposure. However for HIV, the long incubation period during which the person remains infectious means that the date of seroconversion is rarely known. Thus, the duration of exposure is also unknown. Furthermore, self-reported data on sexual behaviour are often inaccurate due to recall bias and misreporting, leading to imprecise estimates of condom use, frequency of sexual contacts or monogamous partnerships. Finally, HIV infectiousness is determined and influenced by a number of risk factors affecting both susceptibility and infectiousness [234]. For example, biological factors postulated to affect HIV infectiousness include mutation of chemokine-receptor genes [235], ART [236], viral subtype [237, 238], local STI infections (inflammation or ulceration of the reproductive tract, rectum or oral mucosa [239]), type of sexual act [240, 241], presence of cervical ectopy [242], circumcision [239, 243], method of contraception (barrier, hormonal contraceptives, spermicidal agents, intrauterine devices [240, 241]), intercourse during menses [241], factors lowering cervicovaginal pH [244] and genital tract trauma [245]. Therefore average transmission probabilities will depend on the distribution of risk factors in the population sampled, and estimates may not be appropriate to generalise across populations, especially if derived from limited or unrepresentative samples. Although the association with infectiousness has not been proved for all factors, they need to be taken into account in the interpretation of studies estimating transmission probabilities. HIV transmission probabilities for sexual transmission are important parameters to estimate accurately in mathematical models.

3.3 Methods

Searching: The systematic review was undertaken according to the MOOSE checklist for review of observational studies [247]. The MEDLINE database (at PubMed National Library of Medicine (NLM) http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) was searched for any titles containing keywords: "HIV transmission probability" OR "HIV transmission probabilities" OR "HIV infectivity" OR "HIV infectiousness" NOT "perinatal" NOT "mother-to-child" NOT "mother to child" which yielded 222 articles. Additional articles were identified from title and abstract searches using "LAV" and "HTLV-III", which were used prior to universal acceptance of "HIV". Complementary searches on www.sciencedirect.com using keywords "HIV AND transmission probability" OR "HIV AND transmission probabilities" identified another seven relevant articles and on NLM Gateway (http://gateway.nlm.nih.gov/gw/Cmd) using: ("HIV transmission probability" OR "HIV transmission probabilities" OR "HIV infectivity" OR "HIV infectiousness") AND ("heterosexual" OR "homosexual") in order to identify conference abstracts not available on Medline. Bibliographies of relevant articles, including reviews and mathematical modelling studies investigating HIV transmission probabilities, were perused to find additional relevant publications. The search which covered the period up to May 2005 was not restricted to any language of publication. Titles (and abstracts, where available) were scanned for relevance to the objective, identifying papers requiring closer study. Bibliographies of

relevant articles, including reviews and mathematical models investigating HIV transmission probabilities, were used to find additional relevant publications.

Selection: All studies with relevant transmission probability estimates identified in PubMed MEDLINE, NLM Gateway and Science Direct up to May 2005 were included. Studies of transmission through oral sex were excluded because the risk is believed to be very low [248]. Where more than one study examined the same data to provide transmission probability per contact using different statistical techniques, all estimates were included for comparison. Where reports at different time points for the same prospective study were identified, the most recent study only was selected for analysis. The methodological limitations of transmission probability studies imply that the quality of most of the data collected is variable and often limited. For example, in resource-poor settings, enrolling monogamous subjects has often proved difficult. Therefore, in order to retain a sufficiently large number of studies, the only exclusion criteria were: all abstracts pre-1990 with no follow-up publication; transmission probability estimates for HIV-2; and estimates for heterosexual transmission based on sample sizes of less than ten. All studies without these limitations have been included, despite other limitations in study design such as control for STIs, which are discussed. Data from resource-poor settings have been presented separately from those from industrialised countries for comparison. Five authors were contacted to obtain complementary information but only three of them replied.

Quantitative data synthesis: Summary tables of study design and date of publication, study population and results were constructed for each transmission probability estimate for vaginal and anal intercourse (AI). Estimates of the transmission probability of AI for heterosexual transmission were also presented because this practice would increase infectiousness among couples. Summary tables of excluded studies with reasons were also compiled.

There are several methods for calculating 95% confidence intervals (CIs) for proportions [249]; transmission probabilities per partner were recalculated using the Wilson 'score' method [250] as recommended by Newcombe 1998 [249], so that results would be comparable (summary per contact transmission probability could not be calculated because the required data were not available). Forest plots were constructed using MS Excel (Microsoft Corp., Redmond, WA, US) and Adobe Illustrator version 10 (Adobe Systems Incorporated).

Meta-analysis: A meta-analysis was undertaken for per partnership transmission probability estimates but not for per contact estimates because estimates for variance were often not available. The analysis was performed in STATA version 8.0 using the `meta` user-written "add-on" commands. The `meta` command uses inverse-variance weighting to calculate fixed and random effects model summary estimates. The random effects model uses the DerSimonian and Laird method [251]. It requires variables containing the effect estimate and its corresponding standard error for that study. The standard error for each estimate was calculated using the `ciwi` command (part of the CIW STATA module for binomial CIs for proportions using Wilson scores, downloaded from Boston College Department of Economics,

http://econpapers.repec.org/software/bocbocode/s429802.htm). The meta-analysis commands in STATA have been designed to assess comparative outcomes (relative risk, odds ratio, risk difference etc.). To ensure the correct calculation for this dataset of single outcomes, results were compared to the same fixed and random effects models programmed in MS Excel, and were in agreement.

For studies with no transmission events the standard error calculated by STATA is zero, potentially giving infinite weight to the study. The `meta` command will not accept standard error entries of zero. For the three studies with a 0.0% estimate for combined, M→F or F→M transmission [252-254], a proxy for the standard error was calculated as the upper 95% CI for the Wilson score method divided by z (=1.96, denoting the standard Normal deviate associated with a two-tailed probability α =5%), as used in the meta-analysis of HIV transmission probabilities for iatrogenic modes of transmission detailed in Baggaley et al 2006 [232] (Appendix A). The estimates produced by fixed and random effects models were compared to estimates produced using sample sizes for weights (pooled estimates). Meta-regression was conducted using the `metareg` command which performs random effects meta-regression on study-level summary data using the default method for estimating the between studies component of variance (restricted maximum-likelihood).

3.4 Summary of search

In total, 232 studies were identified using the database search criteria in May 2005, but a large majority were biomedical and microbiological studies, and the majority of epidemiological studies were investigating cofactors of HIV infectiousness or the effect of HIV infection on TB infectiousness, rather than quantifying HIV transmission probability per se. A breakdown of the type of studies located by the search is shown in Figure 3.1. A total of 28 relevant articles were found using internet searches; all other relevant papers were traced using citations from relevant papers and from review articles and mathematical models of transmission probabilities also traced by the search.

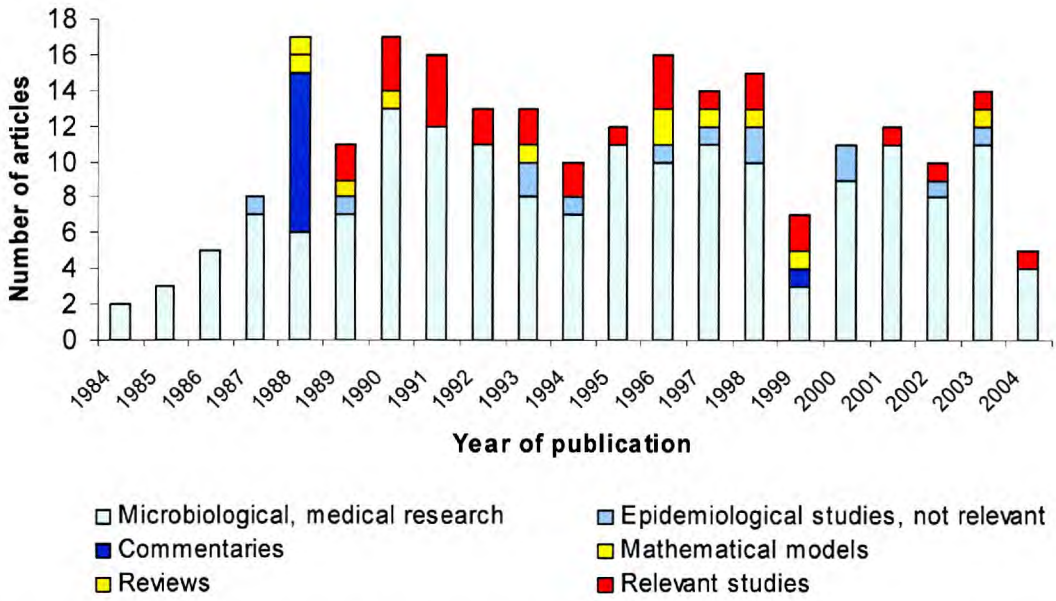


Figure 3.1 Breakdown of search results for articles describing HIV transmission probabilities based on publication type.

After exclusion of reports from prospective studies which have been superseded by more recent updates, a total of 83 papers and conference abstracts with transmission probability estimates for heterosexual or homosexual HIV transmission were identified. Of these, 18 were excluded according to our pre-specified criteria. The breakdown of studies by type is shown in Table 3.1.

Table 3.1 Number of identified studies of HIV transmission probabilities for heterosexual transmission and anal intercourse

	Included studies		Excluded studies
	Industrialised settings	Resource-poor settings	
Heterosexual infectiousness (per partner)			
Combined M→F and F→M	18	5	2
M→F	25	10	8
F→M	10	3	2
Risk factor categories	7	3	0
Total	**31**	**10**	**10**
Heterosexual infectiousness (per contact)			
Combined M→F and F→M	7	1	0
M→F	12	5	2
F→M	4	3	1
Risk factor categories	4	4	0
Total	**16**	**10**	**2**
Anal intercourse (per partner)			
Total	5		4
Anal intercourse (per contact)			
Total	4		2

Many studies provided estimates for more than one transmission probability category and so are counted more than once.

3.5 Heterosexual transmission

Estimates of HIV transmission probabilities for sexual modes of transmission broadly fall into two classes: those assigning a cumulative probability of infection per sexual partnership (or per partnership per unit time), disregarding the specific number of sexual contacts that occur (Tables 3.2 to 3.6), and those assigning a probability of infection per sexual contact (Tables 3.6 to 3.10).

All studies attempted to estimate the risk of HIV infection of susceptible individuals exposed to a known infected partner (index case). The design of partner studies is typically of two sorts: cross-sectional (retrospective) or prospective. With cross-sectional studies, the duration of infection and the direction of transmission (i.e. identification of the index case) is usually inferred retrospectively from an important risk event or risk factors in one partner, such as haemophilia, blood transfusion, or occasionally intravenous drug use (IDU) [255-259]. One problem is that this method of distinguishing

direction of transmission may not be reliable in high prevalence settings such as Africa, where different sources of exposure can be quite frequent. Furthermore, when retrospectively reporting sexual behaviour, recall bias may affect the study results.

Prospective studies follow couples discordant by HIV status, following the diagnosis of the index case. This is usually achieved by enrolling monogamous couples, which avoids having to account for variable number of partners, potentially of unknown serostatus. This alternative to a cross-sectional study provides more reliable information with less recall bias on type (anal, vaginal, orogenital intercourse) and frequency of contact, condom use and other variables. The time of seroconversion of the susceptible partner, if and when it occurs, can be determined more accurately (typically assumed to be the midpoint between follow-up visits), whereas cross-sectional partner studies can only report current infection status, with a vaguely-determined time of infection and number of contacts before transmission, with no proof of the true direction of transmission. However, individuals in monogamous relationships may tend to have more sex acts during their relationship than individuals reporting higher numbers of partners. Thus per partner transmission probability estimates derived from prospective studies may not be representative of all types of partnerships. On one hand, these estimates may represent an overestimate of the average transmission probability per partnership due to higher than average number of contacts. On the other hand, they may represent an underestimate by missing the period of high infectiousness associated with primary infection, before seroconversion of the index partner. If there is significant heterogeneity in infectiousness or susceptibility between partnerships, couples for which transmission occurred early in the course of disease of the index case will be excluded, whereas in retrospective studies, they will not. Other factors which differ between long-term monogamous couples and other types of partnership will also influence transmission probability estimates, with possible bias in either direction. Discordant couple studies have been criticised by some on ethical grounds [260].

3.5.1 Per partner transmission

Summaries of studies estimating transmission probability per heterosexual partnership are shown in Tables 3.2 to 3.6. Risk categories relate to HIV disease stage for the index partner (such as symptomatic versus asymptomatic, AIDS, AIDS-related complex (ARC)) [230, 261, 262] or pVL [263], number of acts per partnership [254], presence versus absence of STIs or circumcision status. Details of excluded studies are presented in Table 3.6.

Table 3.2 and Figure 3.2 show the 23 estimates of the combined male to female (M→F) and female to male (F→M) transmission probabilities from the 22 studies that satisfied the inclusion criteria. Overall, the combined M→F and F→M per partnership transmission probability estimates vary between 0.0% [252] and 71.4% [259] (median = 21.3%) (Table 3.2). Eighteen (78%) estimates are below 50%. Five estimates are above 50% [256, 259, 264-266]. Combined M→F and F→M per partnership transmission probabilities range from 0.0% [252] to 57.8% [265] (median = 20.1%) for studies in industrialised countries and from 15.1% [267] to 71.4% [259] (median = 30.6%) for studies from resource-poor settings. Thus, there is considerable heterogeneity in transmission probability

estimates between studies from both industrialised countries and resource-poor settings. This is confirmed by the values of the Q statistic for heterogeneity performed as part of the meta-analysis presented in Table 3.7 ($Q = 237$ for all studies, $p<0.001$). The large heterogeneity between estimates may partly be explained by differences in the distribution of risk factors in sampled populations (duration of exposure to an infected partner, frequency of sexual contacts, presence of STIs, condom use, stage of HIV infection and others) or different study designs. First, the highest transmission probability estimates were found by studies carried out in the early and mid eighties [256, 258, 259, 264-265], when risk factors and infectiousness of HIV positive individuals may have been different due to the early stage of the HIV epidemic and lack of awareness of HIV/AIDS. Except for Fischl et al [265], these studies were mostly cross-sectional, enrolled partners of AIDS patients or those at higher risk of HIV infection (e.g. not monogamous, expatriates in tropics, possible STI), which may have biased estimates upwards. The estimate from Luzi et al [264], for example, may well have been confounded by partners underreporting other risk factors such as IDU and engaging in CSW.

The results of the meta-analysis, presented in Table 3.7, indicate that a fixed effects model is not appropriate for this analysis because of the large heterogeneity of per partner transmission probability estimates ($Q = 237$, $p<0.001$). The random effects model is an alternative way to combine estimates that explicitly accounts for heterogeneity. Fixed effect models assume that all studies are estimating the same "true" effect, and that the variation in estimates observed by different studies is solely due to chance. In contrast, random effects models assume that the estimates from individual studies are a random sample from a "population" of different effect sizes that follows a normal distribution. In view of the myriad of risk factors affecting HIV transmission, a random effects model is more appropriate. Weights for studies with different sample sizes are more similar than using a fixed effects model and the CIs are typically wider because the heterogeneity in estimates adds an additional source of uncertainty to the CI calculations. The difference in summary estimates between the model types is striking, particularly for F→M estimates (Table 3.7, transmission probability estimate 8.8% (95% CI 7.0-10.7) fixed effects model, 17.7% (95% CI 10.4-24.9) random effect model). The pooled estimates are similar to the random effects model estimates because both methods give relatively more weight to studies with small samples than with the fixed effects model.

The substantial heterogeneity between studies and estimates cannot fully be addressed, even using a random effects model, because of the very different risk patterns between studies, such as prevalence of STIs. Therefore the summary estimates generated by the random effects model should be interpreted bearing in mind the limitations in data quality and the extent of confounding. However, the results can be used to identify trends in estimates between risk groups, such as between research settings or by direction of transmission, M→F or F→M.

The results of the meta-regression, investigating differences in transmission probability estimates by stage of infection of the index case (asymptomatic versus symptomatic) and research setting (industrialised versus resource-poor), are shown in Table 3.8. The regression coefficients represent the estimated absolute increase in transmission probability for resource-poor compared to

industrialised settings for investigation by research setting, and symptomatic compared to asymptomatic HIV infection in the index case for investigation by stage of infection. Only one study provided an estimate for F→M transmission stratified by stage of infection of the index case, so no meta-regression was performed. Despite transmission probability estimates spanning a similar range in both types of settings, those from resource-poor settings appear somewhat higher than those from industrialised countries. This is suggested by the random effects model summary estimates in Table 3.7 and the results from the meta-regression presented in Table 3.8, but only reaches significance for M→F transmission ($p<0.001$), although this may be due to the limited number of studies for combined and F→M transmission estimates. Estimates by Mann et al [256] and Sewankambo et al [259] are the highest among those from resource-poor settings, and may be due to decreased frequency of monogamy and potentially high levels of STIs in these populations. These estimates may also partly be explained by the cross-sectional design used compared to the other prospective studies on initially serodiscordant couples [230, 267, 268]. Although the studies by Mann et al [256] and Sewankambo et al [259] are likely to overestimate per partner transmission probability due to lack of monogamy, the other studies may underestimate risk because these estimates, by definition, did not take into account the period of primary infection, which is believed to be more infectious. In contrast, some of the early prospective studies in industrialised settings are unlikely to have consisted of initially discordant couples [265]. These studies took into account the prevalence of HIV in partners of assigned index cases at study entry, thus leading to estimates that included primary infection and potentially leading to higher estimates. Interestingly, these studies also found that very few or no seroconversions took place prospectively [253, 254]. Three prospective studies of discordant couples from resource-poor settings produced transmission probability estimates over one to two years' exposure comparable to cross-sectional partnerships from industrialised settings (15.1% to 30.6%) [230, 267, 268]. This suggests that per partner transmission probability in resource-poor settings is higher than in industrialised settings. However, conversely, the absence of monogamy among many of these partners effectively means that no conclusions can safely be drawn from this evidence.

Table 3.3 and Figure 3.3 show that M→F per partnership transmission probability estimates vary from 0.0% [253] to 59.3% [288] (median = 18.2%) for studies in industrialised countries compared to 20.0% [267] to 66.7% [259] (median = 44.9%) for those in resource-poor settings. However, transmission probability estimates have been shown to vary between studies. For example, 28 of 35 studies (80%) provided estimates below 50%. The high estimates by Fischl et al [265], Laga et al [258], Mann et al [256] and Sewankambo et al [259] can be explained by the same reasons as discussed above. Estimates by N'Gbichi [259] were also based on a cross-sectional study which enrolled partners of AIDS patients who were not all monogamous. As indicated by the range, estimates from resource poor settings also appear to be higher than for industrialised countries, with minimum estimates of 20.0% by Allen et al [267] and relatively high estimates from Brazil and Thailand who enrolled patients with AIDS [269] or high pVL [263, 270] respectively. Lower estimates were obtained from studies carried out later during the course of the HIV epidemic [230, 268].

There are fewer studies examining F→M transmission than for M→F transmission (13 fit the inclusion criteria compared to 35 for M→F transmission). A number of F→M estimates derived from the early stage of the epidemic when most infections reported in industrialised countries were in men were excluded due to their small sample size [256, 259, 271, 272]. Furthermore, many studies of heterosexual HIV transmission have focussed on partners of infected haemophiliacs, who are usually men because it is a recessive X-chromosome linked disease. Eleven of the 13 studies (85%) included provided estimates below 40%. Even though F→M estimates from industrialised countries are more variable (0.0% [254] to 70.6% [265] (median = 11.0%)) than those from resource-poor settings (8.7% [267] to 35.5% [268] (median = 21.4%), Table 3.4 and Figure 3.4, and Q statistics, Table 3.7), they tend to be lower, with seven estimates out of 10 below 20% (70%) compared to one out of three (33%), respectively. Again the large estimate from Fischl et al [265] may be explained because all index cases were AIDS patients, rather than a mixture of AIDS patients and asymptomatic individuals. With the index case an AIDS patient, partners may be exposed to a higher transmission probability per sexual contact due to the disease stage, or if sexual relations have ceased upon development of symptoms, this still could be a proxy marker of a longer duration of exposure to HIV within the partnership. Furthermore, as stated in the study, partnerships have lasted at least one year, rather than at least three or six months as in other studies [240, 258], and partnerships have lasted up to 28 years – longer than stated in any other study.

Among all studies included, 50% of M→F per partnership transmission probability estimates were below 18.2% for studies in industrialised countries, compared to below 44.9% for those in resource-poor settings (Table 3.3, Figure 3.3). In contrast, 50% of F→M estimates were below 11.0% and 21.4% in industrialised and resource-poor settings, respectively (Table 3.4, Figure 3.4), suggesting a lower infectiousness from F→M than M→F, and especially for resource-poor settings. Studies that estimated both M→F and F→M transmission have often found M→F infectiousness to be higher than for F→M transmission. M→F infectiousness is higher for nine studies from industrialised countries [230, 240, 241, 245, 254, 257, 258, 262, 267], while F→M is higher for four studies [255, 265, 266, 268]. Only one of the studies from a resource-poor setting found F→M infectiousness to be higher [268]. However, the differences with direction of transmission were only significant at the 95% level for three studies [240, 245, 258]. The summary estimates presented in Table 3.7 have lower values for F→M infectiousness for all research settings, but the difference between M→F and F→M transmission probabilities never reaches statistical significance for the random effects model. Therefore, despite its biological plausibility, the results of these studies cannot reject the null hypothesis that M→F per partner transmission probability is no greater than that for F→M transmission, because of the heterogeneity in study estimates. The presence of risk factors differentially distributed between males and females (e.g. circumcision, STIs, pVL) may also have obscured the relationship. Indeed, inference on the impact of disease stage from these studies is difficult because of the lack of information provided by most, and the scarcity of details regarding risk factors for both the HIV infected index case and the susceptible partner.

When stratified by risk factors (Table 3.5), estimates to compare gender-specific transmission probabilities are only available from the European Study Group [241]. The estimate of M→F transmission compared to F→M transmission is significantly higher when the index case is in the symptomatic phase (M→F=19.6%, F→M=3.8%), but not significant when in the AIDS phase (M→F=34.8%, F→M=41.7%). Of special interest are the results of van der Ende et al [253] (Table 3.2) and O'Brien [254] (Table 3.3), who prospectively followed discordant couples for up to five years and did not observe any seroconversions. Furthermore, O'Brien et al [254] and Goedert et al [273] did not find any association between the time from infection of the index cases and diagnosis, and the probability of transmission to their partner (Table 3.5), which supports the idea that a large number of transmissions occur during the highly infectious primary infection stage. A longer duration of exposure may reflect an increased likelihood that the index partner has experienced an increase in infectiousness during the pre-AIDS and AIDS stages of infection, rather than a uniform increase in numbers of contacts over time. Therefore, a uniform per partner transmission probability per unit time throughout infection will not reflect changes in infectiousness adequately. A closer examination of the transmission probability estimates, which are stratified by stage of infection (Table 3.5), is more informative and shows an increase in infectiousness when the index case shows symptoms, although smaller sample sizes due to the numerous stratifications preclude drawing strong conclusions.

The results of the meta-regression by stage of infection suggest that for M→F transmission, stage of infection (symptomatic versus asymptomatic) has a significant effect on transmission probability (p=0.016, Table 3.8). An index patient with symptomatic infection increases the transmission probability by 12.1% (95% CI 2.3%-22.0%) compared to an asymptomatic index. The results for combined M→F and F→M transmission did not reach significance and a test for F→M transmission only could not be performed because only one study provides the relevant information. However, the heterogeneity of study estimates once again means that quantifying the difference in infectiousness by stage of infection from these data is not recommended.

Measuring per partner transmission probability for the primary infection stage is extremely difficult for many reasons, primarily because the initial phase cannot be identified serologically. Therefore the studies presented in Table 3.5 only distinguish between symptomatic and asymptomatic infection. Unsurprisingly, most studies highlight that per partner transmission probability estimates are lower when the index case was still asymptomatic at the time of study, than for index cases with AIDS or ARC [230, 241, 261, 262, 273, 274]. Estimates combining genders are 1.06 [262] to 2.5 [241] times larger when the index case is in the symptomatic phase. Excluding the results of Jason et al [274] where there was no infection among couples with asymptomatic infection, M→F estimates are 1.8 and 2.7 times larger when the male index case was in the symptomatic phase for the European Study Group [241] and Goedert et al [273], respectively. Although this difference did not reach statistical significance for the majority of these studies [230, 261, 262, 273, 274], authors usually ascribed this to insufficient sample size rather than a lack of association. The studies not

detecting any difference in infectiousness by phase of infection were cross-sectional, and so sexual activity may have decreased or stopped among couples with symptomatic index partners [261, 275].

Table 3.5 suggests that F→M infectiousness might be lower among circumcised than uncircumcised men – in other words, their susceptibility to HIV infection might be reduced. In Quinn et al [230, 268], per partner transmission probability was 29.2% among uncircumcised men compared to 0.0% among those circumcised. In the study by Fideli et al [268] (uncircumcised 37.8%, circumcised 26.7%), the difference did not reach statistical significance. The protective effect of circumcision has recently been supported by a randomised controlled intervention trial in sub-Saharan Africa [276].

Table 3.2 Transmission probabilities per partner for heterosexual intercourse – combined M→F and F→M transmission.

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
INDUSTRIALISED SETTINGS					
Jones et al 1985 [277]	UK cross-sectional, sexual partners of haemophilia patients 1985	Stage not specified One seroconverter had recently had multiple transfusions, but had already developed AIDS; no other risk factors. No cofactors specified	**8.3**	(3/36, 2.9-21.8)	Neither stated
Luzi et al 1985 [264]	Italy cross-sectional, partners of IDU, bisexuals, haemophiliacs, no date	Stage not specified No other risk factors No cofactors specified	**53.6**	(15/28, 35.8-70.5)	Neither stated
Fischl et al 1987 [265]	US prospective, spouses of AIDS patients (infected through IDU, heterosexual promiscuity, bisexual, blood transfusion, haemophilia, Haitian immigrants) 1983-1985	AIDS No other risk factors UC: condom	**57.8**	(26/45, 43.3-71.0)	DE: not stated DP: married ≥1 year (range 1-28 years)
Brettler et al 1988 [252]	US cross-sectional, sexual partners of haemophiliacs 1984-1987	AIDS and asymptomatic 1 needlestick injury No cofactors specified	**0.0**	(0/36, 0.0-9.6)	DE: Median 26 months (6.0-57 months)[4] DP: Median 66 months (6.0 months-41.3 years)
Berglund et al 1988 [278]	Sweden cross-sectional, sexual partners of transfusion recipients 1979-1985	Status not specified No risk factors specified No cofactors specified	**4.0**[2]	(1/25, 0.7-19.5)	Neither stated
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, spouses of transfusion recipients, no date	AIDS and asymptomatic One seroconverter (female) reported two other partners since 1978 (both low risk) and a history of STI	**15.0**	(12/80, 8.8-24.4)	DE: 1 to >200 sexual contacts DP: not stated
France et al 1988 [279]	UK prospective, regular sexual partners of IDU 1985-1986	Status not specified No other risk factor (deny IDU) No cofactors specified	**19.0**	(4/21, 7.7-40.0)	DE: not stated DP: ≥ 18 months
Laga et al 1989 [258]	Belgium cross-sectional, regular partners of attendees of a tropical medicine clinic (53% Europeans (generally travellers or expatriates of the tropics), 47% Africans) 1985-1988	71% asymptomatic, 29% symptomatic No other risk factors UC: STI	**45.0**[1]	(36/80, 34.6-55.9)	DE: not stated DP: ≥3 months
Johnson et al 1989 [257]	UK cross-sectional, heterosexual couples recruited from health clinics (index case primarily IDU or bisexual) 1986-1989	Large majority asymptomatic Majority of partners had at least one other partner in last 5 years UC: AI, condom, STI	**15.8**[1]	(15/95, 9.8-24.4)	DE: not stated DP: 1 – 420 months
Glaser et al 1989 [272]	US cross-sectional, spouses of index cases (index cases primarily IDU, 5 bisexuals, 1 transfusion-acquired, 1 heterosexually-acquired) 1984-1987	~2/3 ARC or AIDS, ~1/3 asymptomatic Contacts with history of homosexuality, IDU or receipt of blood products excluded No cofactors specified	**23.3**[1]	(7/30, 11.8-40.9)	DE: not stated DP: median 6 years (6 months – 23 years)

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
Padian et al 1991 [245]	US California Partners' Study (CPS), cross-sectional (entry-level data), index case bisexual, haemophiliac, IDU, transfusion-acquired 1985-1991	Stage not specified Not all partners monogamous, no other risk factors UC: AI	**16.4**	(62/379, 13.0-20.4)	DE: not stated DP: >70% couples monogamous for ≥6 years
Giesecke et al 1992 [261]	Sweden cross-sectional 1989-1990 Partner notification of all patients diagnosed in Sweden	7/61 index cases symptomatic when reported UC: AI, condom	**21.3**	(13/61, 12.9-33.1)	Recall bias meant this could not be recorded, but includes casual, short-term partners
European Study Group 1992 [241]	9 European countries, prospective, regular sexual partners of index cases (mainly IDU) recruited in health centres 1987-1991	AIDS and asymptomatic No other risk factors UC: STI	**13.1**	(52/397, 10.1-16.8)	DE: not stated DP: median 3 years (2 weeks – 20 years)
Seidlin et al 1993 [266]	US cross-sectional 1987-1992	Not all partners monogamous (25% females reported other sexual partners known to be at risk for infection); otherwise no other risk factor. UC: AI, circ, condom, STI	**52.3**	(80/153, 44.4-60.0)	DE: not stated DP: ≥ 10 to >1000 sexual contacts with index case
O'Brien et al 1994 [254]	US prospective, sexual partners of transfusion recipients, enrolment 1987-1992	AIDS and asymptomatic; some partners exposed during primary infection of index No other risk factors UC: condom, STI	**15.2**	(7/46, 7.6-28.2)	DE: <2 years to ≥ 5 years DP: not stated
Nicolosi et al 1994 [240]	Italy cross-sectional, sexual partners of index cases recruited from health clinics 1987-1992	Asymptomatic and AIDS No other risk factor UC: AI, condom, STI	**24.2**	(177/730, 21.3-27.5)	DE: 6 months to >7 years DP: ≥ 6 months
Operskalski et al 1997 [271]	US prospective, sexual partners of transfusion recipients 1986-1993	Clinical status not specified (CD4 < or ≥400 is examined). No transmission during primary infection. No other risk factor UC: AI	**31.6**	(6/19, 15.4-54.0)	DE: 18 – 100 months DP: not stated
Robertson et al 1998 [255]	UK prospective (population not specified, but appear to be mainly IDU), no date (mean duration of follow-up 2.79 and 3.00 years for M→F and F→M transmission, respectively)	Stage not specified Not all partners monogamous, IDU suspected UC: condom (no others specified)	**21.1**[1]	(32/152, 15.3-28.2)	DE: not stated DP: M→F: mean 52 months (max 313 months), F→M: mean 42 months (max 172 months)
RESOURCE-POOR SETTINGS					
Mann et al 1986 [256]	Zaire cases only from a case-control study (spouses of AIDS patients) 1984-1985	AIDS Not all partners monogamous UC: circ, STI	**61.1**[1]	(11/18, 38.6-79.7)	DE: not stated DP: ≥2 years
Sewankambo et al 1987 [259]	Uganda cross-sectional, cohabiting, sexual partners of AIDS patients, no date	AIDS Numerous injection, no other risk factors, no one admitted to other sexual contacts UC: circ, STI	**71.4**[1]	(10/14, 45.4-88.3)	DE: not stated DP: cohabiting for ≥3 months
Allen et al 1992 [267]	Rwanda prospective, cohabiting, discordant couples, from 1986	Status not specified Not all partners monogamous UC: circ, condom, STI	**15.1**	(8/53, 7.9-27.1)	DE: mean 2.2 years DP: not stated

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
Quinn et al 2000 [230]	Uganda prospective, discordant couples (retrospective identification of discordant couples during community-based trial) 1994-1998	Majority of index cases asymptomatic Not all partners were monogamous UC: circ, condom, STI (no information on AI)	**21.7**[3]	(90/415, 18.0-25.9)	DE: median 22.5 months DP: "culturally accepted long-term sexual relationships"
Fideli et al 2001 [268]	Zambia prospective, cohabiting discordant couples 1994-2000	Clinical status not specified Not all partners monogamous[5] UC: condom (no reported STI in index case for last 5 years)	**30.6**	(57/186, 24.5-37.6)	DE: median 15 months, mean 22 months (2-67 months) DP: ≥6 months

All CIs have been recalculated using the Wilson 'score' method [250].
[1] Direction of transmission inferred from distribution of risk factors
[2] Relatively elderly transfusion recipients (possible lower sexual activity)
[3] Rate ratio for risk of transmission associated with each log increment in pVL = 2.45 (95% CI 1.85-3.26).
[4] Median duration between index case's first known seropositive sample and their partners' most recent sample
[5] However, transmission from index case identified for 129 out of 162 seroconverting partners by epidemiological linkage analysis (see paper for details [268])
Abbreviations: AI – anal intercourse; CDC – Centers for Disease Control and Prevention (US); CPS – California Partners' Study; circ – circumcision; condom – condom use; DE – duration of exposure; DP – duration of partnership; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.3 Transmission probabilities per partner for heterosexual intercourse – M→F transmission.

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
INDUSTRIALISED SETTINGS					
Kreiss et al 1985 [280]	US cross-sectional, wives of haemophiliacs 1982-1984	Asymptomatic No other risk factor except 1 instance of blood transfusion since 1978; no needlestick injury UC: AI	**9.5**	(2/21, 2.7-28.9)	DE: not stated DP: mean 11 years (2 - 40 years)
Jason et al 1986 [274]	US cross-sectional, sexual partners of haemophiliacs 1983-1984	AIDS and asymptomatic (index cases of seroconverters AIDS/ARC) No risk factors UC: AI	**9.5**	(2/21, 2.7-28.9)	Neither stated
Allain 1986 [281]	France cross-sectional, sexual partners of haemophiliacs 1986	Stage not specified Risk factors and cofactors not specified	**6.8**	(10/148, 3.7-12.0)	Neither stated
Bardin et al 1986 [282]	France cross-sectional, spouses of haemophiliacs 1985	AIDS and asymptomatic No risk factors No cofactors specified	**11.8**	(2/17, 3.3-34.3)	Neither stated
Biberfeld et al 1986 [283]	Sweden cross-sectional, regular sexual partners of haemophiliacs 1985	Asymptomatic Other risk factors not specified. Cofactors not specified.	**10.0**	(4/40, 4.0-23.1)	DE: "probably ≥2 years" DP: ≥2 years
CDC 1987 [284]	US cross-sectional, sexual partners of haemophiliacs 1985-1987	HIV stage not stated No risk factors specified UC: condom	**10.0**	(77/772, 8.1-12.3)	Neither stated
Fischl et al 1987 [265]	US prospective, spouses of AIDS patients (infected through IDU, heterosexual promiscuity, bisexual, blood transfusion, haemophilia, Haitian immigrants) 1983-1985	AIDS No other risk factors UC: condom	**50.0**	(14/28, 32.6-67.4)	DE: not stated DP: married ≥1 year (range 1-28 years)
Goedert et al 1987 [273]	US cross-sectional, sexual partners of haemophiliacs 1984-1986	AIDS and (mainly) asymptomatic One seroconverter not monogamous, another had 1 needlestick injury UC: condom	**23.1**	(6/26, 11.0-42.1)	DE: 5 months - >59 months DP: not stated
Kim et al 1988 [285]	US cross-sectional, spouses of haemophiliacs 1986-1987	Seropositive for a mean of 46 ± 23 (SD) months; 6/14 had AIDS. No risk factors	**7.1**	(1/14, 1.3-31.5)	DE: 46 ± 23 (SD) months DP: 13.5 ± 10.5 (SD) years (range 3-36 years)
Smiley et al 1988 [286]	US cross-sectional, sexual partners of haemophiliacs 1984-1987	All index cases transmitting were symptomatic IDU excluded; no other risk factors UC: condom	**6.9**	(2/29, 1.9-22.0)	DE: not stated DP: >1 year
van der Ende et al 1988 [253]	The Netherlands prospective, spouses of haemophiliacs 1984-1987	7/13 index cases had become symptomatic Other risk factors not specified. UC: condom	**0.0**	(0/13, 0.0-22.8)	DE: 3-5 years DP: not stated
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, spouses of transfusion	AIDS and asymptomatic One seroconverter reported two other	**18.2**	(10/55, 10.2-30.3)	DE: 1 to >200 sexual contacts DP: not stated

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
	recipients, no date	partners since 1978 (both low risk) and a history of STI			
Ragni et al 1989 [287]	US Hemophilia Partner Study, cross-sectional, partners of haemophiliacs 1989	AIDS and (mainly) asymptomatic (all transmitters asymptomatic) Seroconverters more likely to have had >1 partner in last 5 years UC: condom	**13.3**	(6/45, 6.3-26.2)	DE: mean 10.4±3.0 months for seroconverters; 54.2 ±3.7 months for non-seroconverters DP: ≥6 months
Laga et al 1989 [258]	Belgium cross-sectional, regular partners of attendees of a tropical medicine clinic (57% Europeans (generally travellers or expatriates of the tropics), 43% Africans) 1985-1988	72% asymptomatic, 28% symptomatic No other risk factors UC: STI	**53.1**[1]	(34/64, 41.1-64.8)	DE: not stated DP: ≥3 months
Johnson et al 1989 [257]	UK cross-sectional, heterosexual couples recruited from health clinics (index case primarily IDU or bisexual) 1986-1989	62 asymptomatic, 15 ARC Majority of partners had at least one other partner in last 5 years UC: AI, condom, STI	**18.2**[1]	(14/77, 11.2-28.2)	DE: not stated DP: mean 52.1 months, median 33.5 months (1 to 420 months)
Glaser et al 1989 [272]	US cross-sectional, spouses of index cases (index cases primarily IDU, 5 bisexuals, 1 transfusion-acquired, 1 heterosexually-acquired) 1984-1987	~2/3 ARC or AIDS, ~1/3 asymptomatic Contacts with history of homosexuality, IDU or receipt of blood products excluded No cofactors specified	**22.2**[1]	(6/27, 10.6-40.8)	DE: not stated DP: median 6 years (6 months – 23 years)
Hewlett et al 1990 [288]	US cross-sectional, partners of haemophiliacs 1988	2 AIDS, 3 ARC, 22 asymptomatic Other risk factors not specified. UC: condom	**59.3**	(16/27, 40.7-75.5)	DE: not stated DP: median 7 years (1 - ≥10 years)
Lusher et al 1991 [289]	US Transfusion Safety Study, prospective, long-term partners of haemophiliacs 1985-1989	AIDS and asymptomatic Other risk factors not specified. UC: AI, condom	**10.4**	(21/201, 6.9-15.4)	Neither stated
Padian et al 1991 [245]	US CPS cross-sectional (entry-level data), index case bisexual, haemophiliac, IDU, transfusion-acquired 1985-1991	Stage not specified Not all partners monogamous, no other risk factors UC: AI	**19.9**	(61/307, 15.8-24.7)	DE: not stated DP: >70% couples monogamous for ≥6 years
European Study Group 1992 [241]	9 European countries, prospective, regular sexual partners of index cases (mainly IDU) recruited in health centres 1987-1991	AIDS and asymptomatic No other risk factors UC: STI	**13.6**[1]	(40/295, 10.1-17.9)	DE: not stated DP: median 3 years (2 weeks – 20 years)
Seidlin et al 1993 [266]	US cross-sectional 1987-1992	Not all partners monogamous (25% females reported other sexual partners known to be at risk for infection); otherwise no other risk factor. UC: AI, circ, condom, STI	**51.4**	(73/142, 43.3-59.5)	DE: not stated DP: ≥ 10 to >1000 sexual contacts with index case
O'Brien et al 1994 [254]	US prospective, sexual partners of transfusion recipients, enrolment 1987-1992	AIDS and asymptomatic; some partners exposed during primary infection of index No other risk factors UC: condom, STI	**21.9**	(7/32, 11.0-38.8)	DE: <2 years to ≥ 5 years DP: not stated
Nicolosi et al 1994 [240]	Italy cross-sectional, sexual partners of index cases recruited from health clinics 1987-1992	Asymptomatic and AIDS No other risk factor UC: AI, condom, STI	**29.8**	(156/524, 26.0-33.8)	DE: 6 months to >7 years DP: ≥ 6 months

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
Operskalski et al 1997 [271]	US prospective, sex partners of transfusion recipients 1986-1993	Clinical status not specified (CD4 < or ≥400 is examined). No transmission during primary infection. No other risk factor UC: AI	**36.4**	(4/11[2], 15.2-64.6)	DE: 18 – 100 months DP: not stated
Robertson et al 1998 [255]	UK prospective (population not specified, but appear to be mainly IDU), no date (mean duration of follow-up 3.00 years)	Stage not specified Not all partners monogamous, IDU suspected UC: condom (no others specified)	**21.2**[1]	(25/118, 14.8-29.4)	DE: not stated DP: mean 52 months (max 313 months)
RESOURCE-POOR SETTINGS					
Mann et al 1986 [256]	Zaire cases only from a case-control study (spouses of AIDS patients) 1984-1985	AIDS Not all partners monogamous UC: circ, STI	**53.3**[1]	(8/15, 30.1-75.2)	DE: not stated DP: ≥2 years
Sewankambo et al 1987 [259]	Uganda cross-sectional, cohabiting, sexual partners of AIDS patients, no date	AIDS Numerous injection, no other risk factors, no one admitted to other sexual contacts UC: circ, STI	**66.7**[1]	(8/12, 39.1-86.2)	DE: not stated DP: cohabiting for ≥3 months
Allen et al 1992 [267]	Rwanda prospective, cohabiting, discordant couples, from 1986	Status not specified Partners all reported being monogamous UC: condom, STI	**20.0**	(6/30, 9.5-37.3)	DE: mean 769 days (SD 338 days) DP: not stated
N'Gbichi et al 1995 [290]	Côte d'Ivoire cross-sectional, hospitalised male index cases, no date	AIDS Not all partners monogamous No cofactors specified	**50.4**[1]	(176/349, 45.2-55.6)	DE: not stated DP: >1 month and >1 contact
Guimaraes et al 1995 [269]	Brazil cross-sectional, sex partners of HIV-positive patients recruited from an STI clinic, 1990-1991	>60% AIDS No other risk factors UC: AI, condom, STI	**45.1**	(92/204, 38.4-52.0)	DE: not stated DP: ≥1 sexual contact
Nagachinta et al 1997 [270]	Thailand cross-sectional, regular partners of blood donors (index cases appear mainly to have been infected through heterosexual contact with a CSW) 1992-1995	97 of 387 index cases had CD4 count <200 No other risk factors UC: AI, circ, condom, STI HIV-1 CRF_01AE*	 **46.2**[1] **53.0**[1]	 (187/405, 41.4-51.0) (124/234, 46.6-59.3)	DE: not stated DP: >half partnerships were >24 months All partnerships Partnerships >24 months
Panda et al 2000 [291]	India cross-sectional, wives of IDU 1996-1997	HIV stage of index not specified. Wives denied IDU; only 5% reported having ever had a sexual partner other than their husband, some blood transfusions. UC: condom, STI	**44.7**[3]	(72/161, 37.3-52.4)	DE: not stated DP: median duration of marriage 5 years, mean 6 years (SD 4 years)
Quinn et al 2000 [230]	Uganda prospective, discordant couples (retrospective identification of discordant couples during community-based trial) 1994-1998	Majority of index cases asymptomatic Not all partners were monogamous UC: condom, STI (no information on AI)	**21.9**[4]	(50/228, 17.0-27.7)	DE: median 22.5 months DP: "culturally accepted long-term sexual relationships"
Fideli et al 2001 [268]	Zambia prospective, cohabiting discordant couples 1994-2000	Clinical status not specified Not all partners monogamous[5] UC: condom (no reported STI in index case for last 5 years)	**25.8**	(24/93, 18.0-35.5)	DE: median 15 months, mean 22 months (2-67 months) DP: ≥6 months

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)	Duration of exposure (DE)/duration of partnership (DP)
Tovanabutra et al 2002 [263]	Thailand prospective, married couples (index cases appear mainly to have been infected through heterosexual contact with a CSW) 1992-1998	CD4 counts indicate some AIDS, ARC and asymptomatic index cases No other risk factors UC: STI HIV-1 CRF_01AE*	**44.2**[1] (218/493, 39.9-48.6)	Neither stated

All CIs have been recalculated using the Wilson 'score' method [250]. *Formerly subtype E.
[1] Direction of transmission inferred from distribution of risk factors
[2] One man transmitted HIV to two regular partners
[3] Direction of transmission inferred from distribution of risk factors. Paper presented as a case-control study, therefore there could have been bias in study participant selection
[4] Rate ratio for risk of transmission associated with each log increment in pVL = 2.45 (95% CI 1.85-3.26)
[5] However, transmission from index case identified for 129 out of 162 seroconverting partners by epidemiological linkage analysis (see paper for details [268])
Abbreviations: AI – anal intercourse; CDC – Centers for Disease Control and Prevention (US); circ – circumcision; condom – condom use; CPS – California Partners' Study; CSW – Commercial sex worker; DE – duration of exposure; DP – duration of partnership; SD – standard deviation; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.4 Transmission probabilities per partner for heterosexual intercourse – F→M transmission.

Study	Setting/Study Design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
INDUSTRIALISED SETTINGS					
Fischl et al 1987 [265]	US prospective, spouses of AIDS patients (infected through IDU, heterosexual promiscuity, bisexual, blood transfusion, haemophilia, Haitian immigrants) 1983-1985	AIDS No other risk factors UC: condom	**70.6**	(12/17, 46.9-86.7)	DE: not stated DP: married ≥1 year (range 1-28 years)
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, spouses of transfusion recipients, no date	AIDS and asymptomatic No other risk factor 2 seronegative partners reported history of STI	**8.0**	(2/25, 2.2-25.0)	DE: 1 to >200 sexual contacts DP: not stated
Laga et al 1989 [258]	Belgium cross-sectional, regular partners of attendees of a tropical medicine clinic (38% Europeans (generally travellers or expatriates of the tropics), 62% Africans) 1985-1988	69% asymptomatic, 31% symptomatic No other risk factors UC: STI	**12.5**[1]	(2/16, 3.5-36.0)	DE: not stated DP: ≥3 months
Johnson et al 1989 [257]	UK cross-sectional, heterosexual couples recruited from health clinics (index case primarily IDU) 1986-1989	3 symptomatic, 15 asymptomatic No other risk factor No cofactors for seroconverter	**5.6**[1]	(1/18, 1.0-25.8)	DE: not stated DP: mean 45.6 months, median 39 months (6 to 109 months) (DP of seroconverter >5 years)
Padian et al 1991 [245]	US CPS cross-sectional (entry-level data), index case bisexual, haemophiliac, IDU, transfusion-acquired 1985-1991	Stage not specified Not all partners monogamous, no other risk factors UC: AI	**1.4**	(1/72, 0.2-7.5)	DE: not stated DP: >70% couples monogamous for ≥6 years
European Study Group 1992 [241]	9 European countries, prospective, regular sexual partners of index cases (mainly IDU) recruited in health centres 1987-1991	AIDS and asymptomatic No other risk factors UC: STI	**11.8**	(12/102, 6.9-19.4)	DE: not stated DP: median 3 years (2 weeks – 20 years)
Seidlin et al 1993 [266]	US cross-sectional 1987-1992	Not all partners monogamous (25% females reported other sexual partners known to be at risk for infection); otherwise no other risk factor. UC: AI, circ, condom, STI	**63.6**	(7/11, 35.4-84.8)	DE: not stated DP: ≥ 10 to >1000 sexual contacts with index case
O'Brien et al 1994 [254]	US prospective, sexual partners of transfusion recipients, enrolment 1987-1992	AIDS and asymptomatic; some partners exposed during primary infection of index No other risk factors UC: condom, STI	**0.0**	(0/14, 0.0-21.5)	DE: <2 years to ≥ 5 years DP: not stated
Nicolosi et al 1994 [240]	Italy cross-sectional, sexual partners of index cases recruited from health clinics 1987-1992	Asymptomatic and AIDS No other risk factor UC: AI, condom, STI	**10.2**	(21/206, 6.8-15.1)	DE: 6 months to >7 years DP: ≥ 6 months
Robertson et al 1998 [255]	UK prospective (population not specified, but appear to be mainly IDU), no date (mean duration of follow-up 2.79 years)	Stage not specified Not all partners monogamous, IDU suspected UC: condom (no others specified)	**20.6**[1]	(7/34, 10.3-36.8)	DE: not stated DP: mean 42 months (max 172 months)
RESOURCE-POOR SETTINGS					

Study	Setting/Study Design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
Allen et al 1992 [267]	Rwanda prospective, cohabiting, discordant couples, from 1986	Status not specified Not all partners monogamous UC: circ, condom, STI	**8.7**	(2/23, 2.4-26.8)	DE: mean 841 days (SD 304 days) DP: not stated
Quinn et al 2000 [230]	Uganda prospective, discordant couples (retrospective identification of discordant couples during community-based trial) 1994-1998	Majority of index cases asymptomatic Not all partners were monogamous UC: circ, condom, STI (no information on AI)	**21.4**[2]	(40/187, 16.1-27.8)	DE: median 22.5 months DP: "culturally accepted long-term sexual relationships"
Fideli et al 2001 [268]	Zambia prospective, cohabiting discordant couples 1994-2000	Clinical status not specified Not all partners monogamous[3] UC: condom (no reported STI in index case for last 5 years)	**35.5**	(33/93, 26.5-45.6)	DE: median 15 months, mean 22 months (2-67 months) DP: ≥6 months

All CIs have been recalculated using the Wilson 'score' method [250].
[1] Direction of transmission inferred from distribution of risk factors
[2] Rate ratio for risk of transmission associated with each log increment in pVL = 2.45 (95% CI 1.85-3.26).
[3] However, transmission from index case identified for 129 out of 162 seroconverting partners by epidemiological linkage analysis (see paper for details [268])
Abbreviations: AI – anal intercourse; CDC – Centers for Disease Control and Prevention (US); circ – circumcision; condom – condom use; CPS – California Partners' Study; DE – duration of exposure; DP – duration of partnership; SD – standard deviation; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.5 Transmission probabilities per partner for heterosexual intercourse – stratified by risk categories.

Study	Setting/Study design/Population/Date/Stage of HIV infection/Other risk factors, uncontrolled cofactors	Risk categories	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
INDUSTRIALISED SETTINGS					
Jason et al 1986 [274]	US cross-sectional, sexual partners of haemophiliacs 1983-1984, no risk factors, UC: AI	Asymptomatic (M→F) AIDS/ARC (M→F)	**0.0** **14.3**	(0/7, 0.0-35.4) (2/14, 4.0-39.9)	Neither stated
Goedert et al 1987 [273]	US cross-sectional, sexual partners of haemophiliacs 1984-1986 AIDS and (mainly) asymptomatic One seroconverter not monogamous, another had 1 needlestick injury UC: condom	Asymptomatic (M→F) AIDS/ARC (M→F) M→F: <24 months 24-47 months 48-59 months >59 months	**15.8** **42.9** **16.7** **0.0** **60.0** **0.0**	(3/19, 5.5-37.6) (3/7, 15.8-75.0) (1/6, 3.0-56.4) (0/7, 0.0-35.4) (3/5, 23.1-88.2) (0/5, 0.0-43.4)	DE: 5 months - >59 months DP: not stated
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, spouses of transfusion recipients, no date One seroconverter reported two other partners since 1978 (both low risk) and a history of STI.	Asymptomatic (combined M→F F→M) AIDS (combined M→F F→M)	**14.3** **15.2**	(2/14, 4.0-39.9) (10/66, 8.4-25.7)	DE: 1 to >200 sexual contacts DP: not stated
Giesecke et al 1992 [261]	Sweden cross-sectional, partner notification of all patients diagnosed in Sweden, 1989-1990 UC: AI, condom	Asymptomatic (combined M→F F→M) Symptomatic (combined M→F F→M)	**20.4** **28.6**	(11/54, 11.8-32.9) (2/7, 8.2-64.1)	Recall bias meant this could not be recorded, but includes casual, short-term partners
European Study Group 1992 [241]	9 European countries, prospective, regular sexual partners of index cases (mainly IDU) recruited in health centres 1987-1991 AIDS and asymptomatic index cases, no other risk factors, UC: STI	Asymptomatic (M→F) Asymptomatic (F→M) Asymptomatic (combined M→F F→M) AIDS (M→F) AIDS (F→M) AIDS (combined M→F F→M)	**19.6** **3.4** **14.6** **34.8** **41.7** **36.7**	(39/199, 14.7-25.7) (3/89, 1.2-9.4) (42/288, 11.0-19.1) (32/92, 25.8-44.9) (15/36, 27.1-57.8) (47/128, 28.9-45.3)	DE: not stated DP: median 3 years (2 weeks – 20 years)
Seidlin et al 1993 [266]	US cross-sectional 1987-1992 Not all partners monogamous (25% females reported other sexual partners known to be at risk for infection); otherwise no other risk factor. UC: AI, circ, condom, STI	No. acts (M→F): <200 200-499 500-999 ≥1000	**62.9** **62.9** **41.7** **38.9**	(22/35, 46.3-76.8) (22/35, 46.3-76.8) (15/36, 27.1-57.8) (14/36, 24.8-55.1)	DE: not stated DP: ≥ 10 to >1000 sexual contacts with index case
O'Brien et al 1994 [254]	US retrospective, sexual partners of transfusion recipients, enrolment 1987-1992 AIDS and asymptomatic; some partners exposed during primary infection of index, no other risk factors, UC: condom, STI	No. acts (M→F): 1-10 11-100 101+ Time from infection to diagnosis of index case (M→F): <2 years 2-4 years ≥5 years	**0.0** **36.4** **16.7** **33.3** **14.3** **26.7**	(0/3, 0.0-56.2) (4/11, 15.2-64.6) (3/18, 5.8-39.2) (1/3, 6.1-79.2) (2/14, 4.0-39.9) (4/15, 10.9-52.0)	Neither stated DE: <2 years 2-4 years ≥5 years
RESOURCE-POOR SETTINGS					
Quinn et al 2000 [230]	Uganda prospective, discordant couples (retrospective identification of discordant couples during community-based trial) 1994-1998 Majority of index cases asymptomatic Not all partners were monogamous UC: circ, condom, STI (no information on AI)	Asymptomatic (combined M→F F→M) AIDS (combined M→F F→M) Circumcised (M→F) Uncircumcised (M→F)	**20.9** **42.9** **0.0** **29.2**	(84/401, 17.2-25.2) (6/14, 21.3-67.4) (0/50, 0.0-7.1) (40/137, 22.2-37.3)	DE: median 22.5 months DP: "culturally accepted long-term sexual relationships"

Study	Setting/Study design/Population/Date/Stage of HIV infection/Other risk factors, uncontrolled cofactors	Risk categories	Transmission probability, % (x/n, 95% CI)		Duration of exposure (DE)/duration of partnership (DP)
Fideli et al 2001 [268]	Zambia prospective, cohabiting discordant couples 1994-2000 Clinical status not specified, not all partners monogamous UC: condom, STI	Circumcised (F→M) Uncircumcised (F→M)	**26.7** **37.6**	(4/15, 10.9-52.0) (62/165, 30.5-45.2)	DE: median 15 months, mean 22 months (2-67 months) DP: ≥6 months
Tovanabutra et al 2002 [263]	Thailand prospective, married couples (index cases appear mainly to have been infected through heterosexual contact with a CSW) 1992-1998 CD4 counts indicate some AIDS, ARC and asymptomatic index cases No other risk factors UC: STI, HIV-1 CRF_01AE*	DP (M→F): <24 months ≥24 months HIV RNA copies/mL (M→F): <500 500-1580 1581-4999 5000-15,810 15,811-49,999 50,000-158,110 158,114-499,999 500,000+	**39.6**[1] **46.1**[1] **0.0**[2] **7.1** **38.5** **33.7** **49.6** **48.6** **51.7** **60.0**	(44/111, 31.0-48.9) (176/382, 41.1-51.1) (0/3, 0.0-56.2) (1/14, 1.3-31.5) (15/39, 24.9-54.1) (32/95, 25.0-43.7) (70/141, 41.5-57.8) (67/138, 40.4-56.8) (30/58, 39.2-64.1) (3/5, 23.1-88.2)	Neither stated, but no significant difference in transmission for marriage <24 months and ≥24 months, or for sexual partnerships <12 months and ≥12 months

All CIs have been recalculated using the Wilson 'score' method [250]. *Formerly subtype E.
[1] Direction of transmission inferred from distribution of risk factors
[2] Each log(10) increment of HIV RNA in the male is associated with an 81% increased rate of HIV transmission to his wife
Abbreviations: AI – anal intercourse; CDC – Centers for Disease Control and Prevention (US); circ – circumcision; condom – condom use; CSW – Commercial sex worker; DE – duration of exposure; DP – duration of partnership; SD – standard deviation; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.6 Transmission probabilities for heterosexual intercourse – excluded studies.

Study	Setting/Study Design/Population/Date/Stage of HIV infection/Other risk factors, uncontrolled cofactors	Duration of exposure (DE)/duration of partnership (DP)	Transmission probability , % (x/n, 95% CI)		Reason for exclusion
PER CONTACT					
Stewart et al 1985 [292]	Australia cross-sectional (recipients of infected semen during artificial insemination) 1984-1985	Not applicable	M→F	**50.0** (4/8, 21.5-78.5)	Artificial insemination may not be a comparable mode of transmission to heterosexual intercourse
Steigbigel et al 1988 (abstract) [293]	Partners of IDU	Not applicable	M→F F→M	**0.07-38.60** **0.09-56.18**	Abstract pre-1990
PER PARTNER					
Harris et al 1983 [294]	US cross-sectional, sexual partners of IDU AIDS patients 1982-1983 All partners denied IDU and stated that they were monogamous. UC: AI	DE: not stated DP: 1.1 to 16 years	M→F	**85.7**[1] (6/7, 48.6-97.4)	Sample size <10
Redfield et al 1985 [295]	US, spouses of infected servicemen 1983-1984	DE: not stated DP: 2-14 years	M→F	**71.4** (5/7, 35.9-91.8)	Sample size <10
Harris et al 1985 [296]	Unknown	Unknown	Not specified	**47.6** (20/42, 33.4-62.3)	Conference presentation pre-1990
Melbye et al 1985 [297]	Denmark cross-sectional, long-term sexual partners of haemophiliacs 1984. Index partner had AIDS (stage of infection for other haemophiliacs not specified). No other risk factors. UC: AI	DE: not stated DP: mean 14.2 years (1 year for seroconverter)	M→F	**11.1** (1/9, 2.0-43.5)	Not all haemophiliacs in the 9 couples were seropositive, small sample size
Saltzman et al (abstract) 1986 [298]	Unknown	Unknown	M→F	**42.1** (32/76, 31.6-53.3)	Abstract pre-1990
Padian & Winkelstein (abstract) 1986 [299]	Unknown	Unknown	M→F	**18.6** (8/43, 9.7-32.6)	Abstract pre-1990
Smiley et al (abstract) 1986 [300]	Unknown	Unknown	M→F	**9.5** (2/21, 2.7-28.9)	Abstract pre-1990
Steigbigel et al (abstract) 1987 [301]	Unknown	Unknown	M→F F→M	**44.7** (51/114, 35.9-53.9) **50.0** (7/14, 26.8-73.2)	Abstract pre-1990
Taelman et al (abstract) 1987 [302]	Unknown	Unknown	Unknown	Unknown	Abstract pre-1990
Davidson et al (abstract) 1989 [303]	UK prospective, partners of IDU (discordant couples), HIV stage not specified, no other risk factor (IDU excluded) UC: AI, STI	Unknown	M→F F→M	**15.8** (6/38, 7.4-30.4) **"5"**[2]	Abstract pre-1990

All CIs have been recalculated using the Wilson 'score' method [250]

[1] Diagnosis made on the basis of clinical status and CD4 count (therefore possible underestimate)

[2] 15 index cases can be deduced from the abstract, which is not consistent with the quoted 5% transmission provided in the results section

Abbreviations: AI – anal intercourse; circ – circumcision; condom – condom use; DE – duration of exposure; DP – duration of partnership; SD – standard deviation; STI – sexually transmitted infection; UC – uncontrolled cofactors

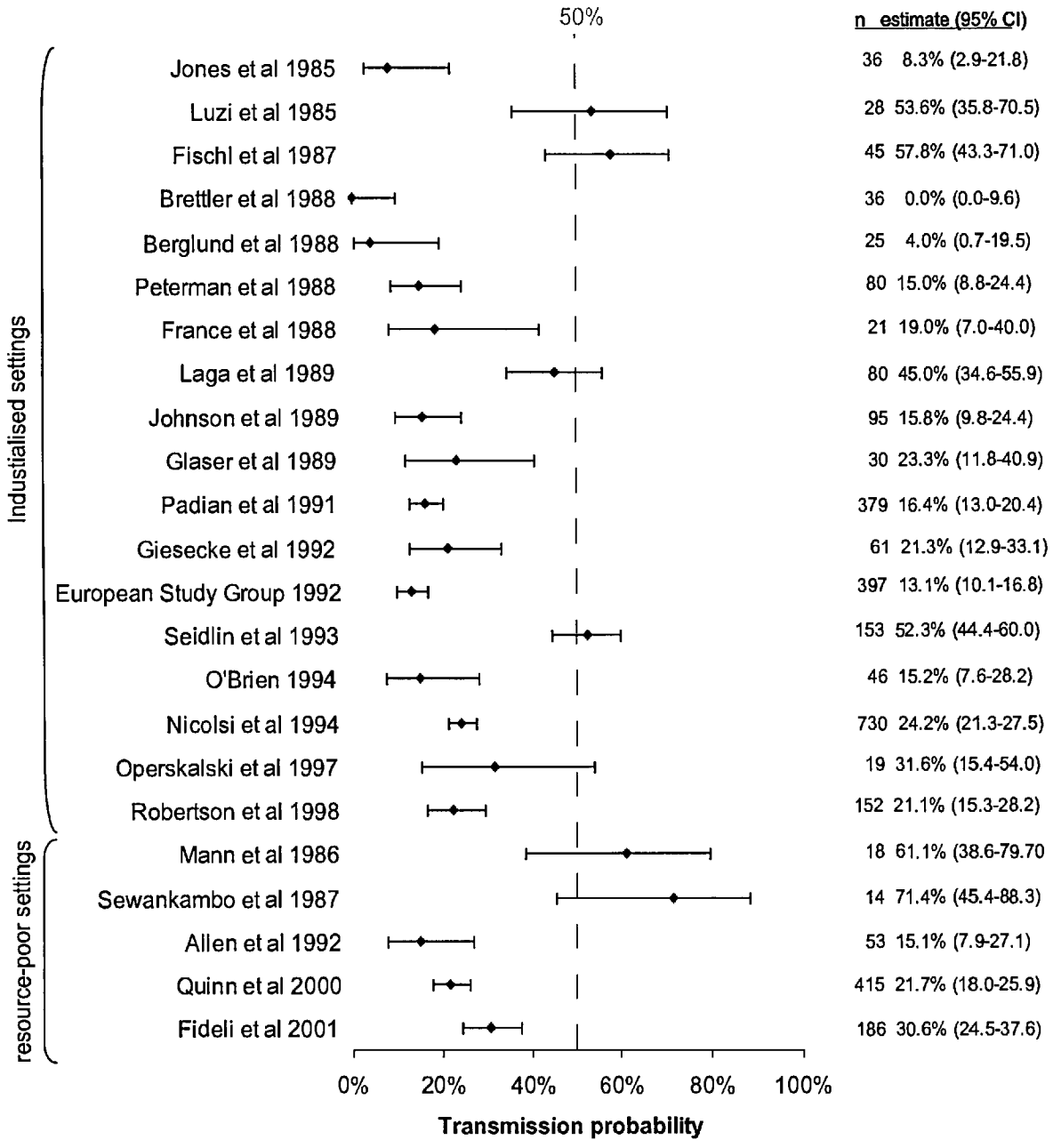


Figure 3.2 Summary of studies estimating HIV transmission probability per heterosexual partnership for combined M→F and F→M transmission, with 95% confidence intervals.

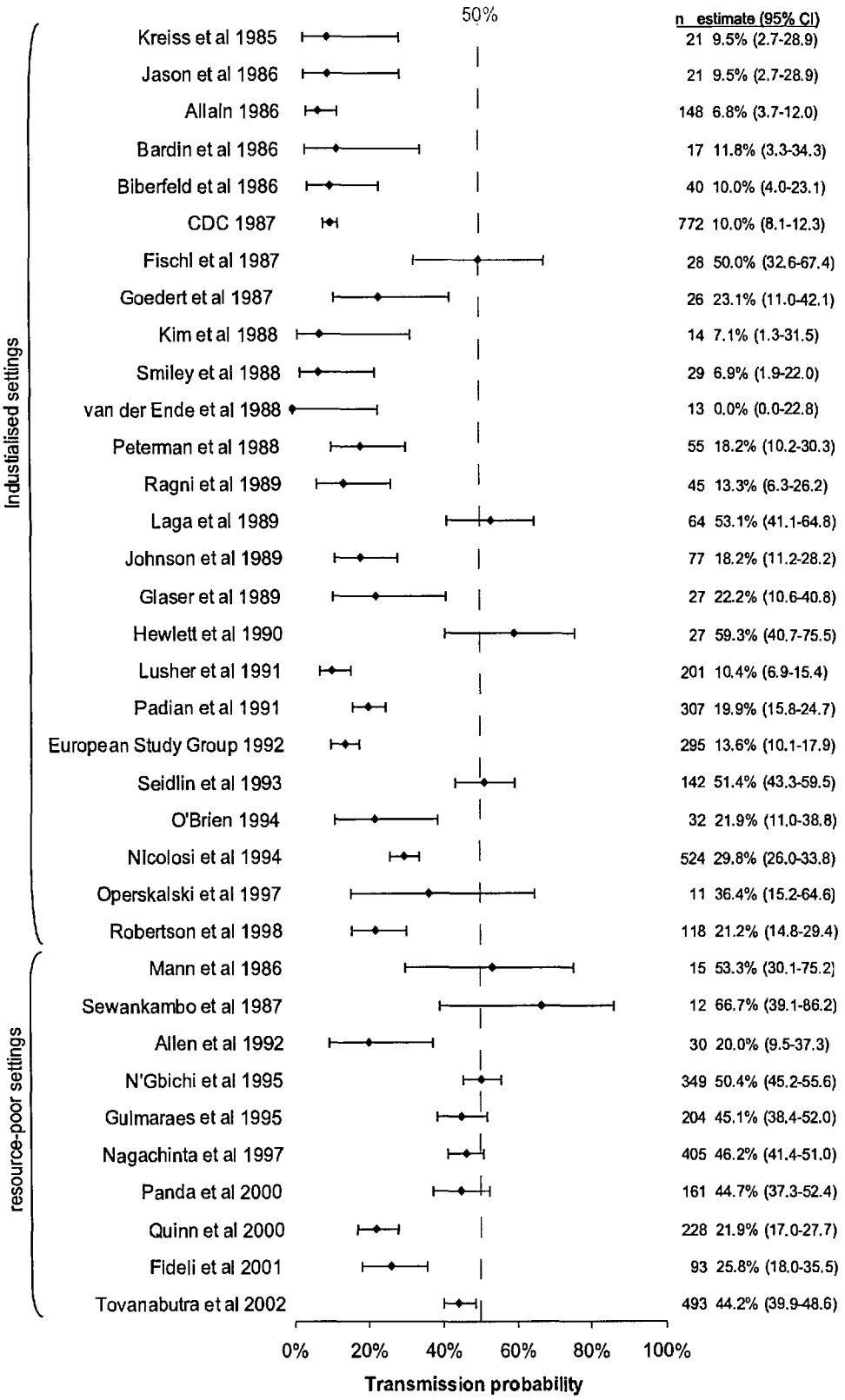


Figure 3.3 Summary of studies estimating HIV transmission probability per heterosexual partnership for M→F transmission, with 95% confidence intervals.

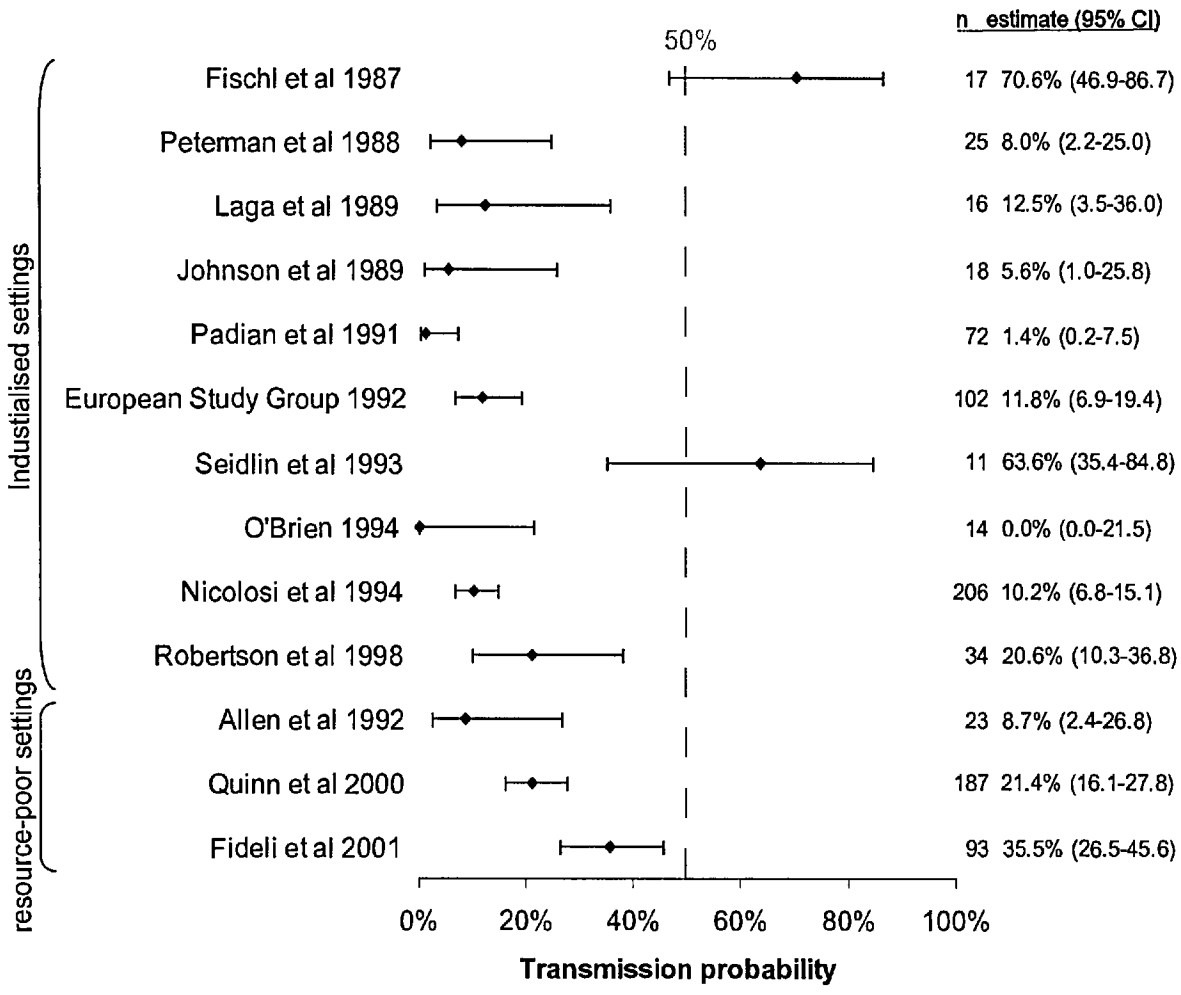


Figure 3.4 Summary of studies estimating HIV transmission probability per heterosexual partnership for F→M transmission, with 95% confidence intervals.

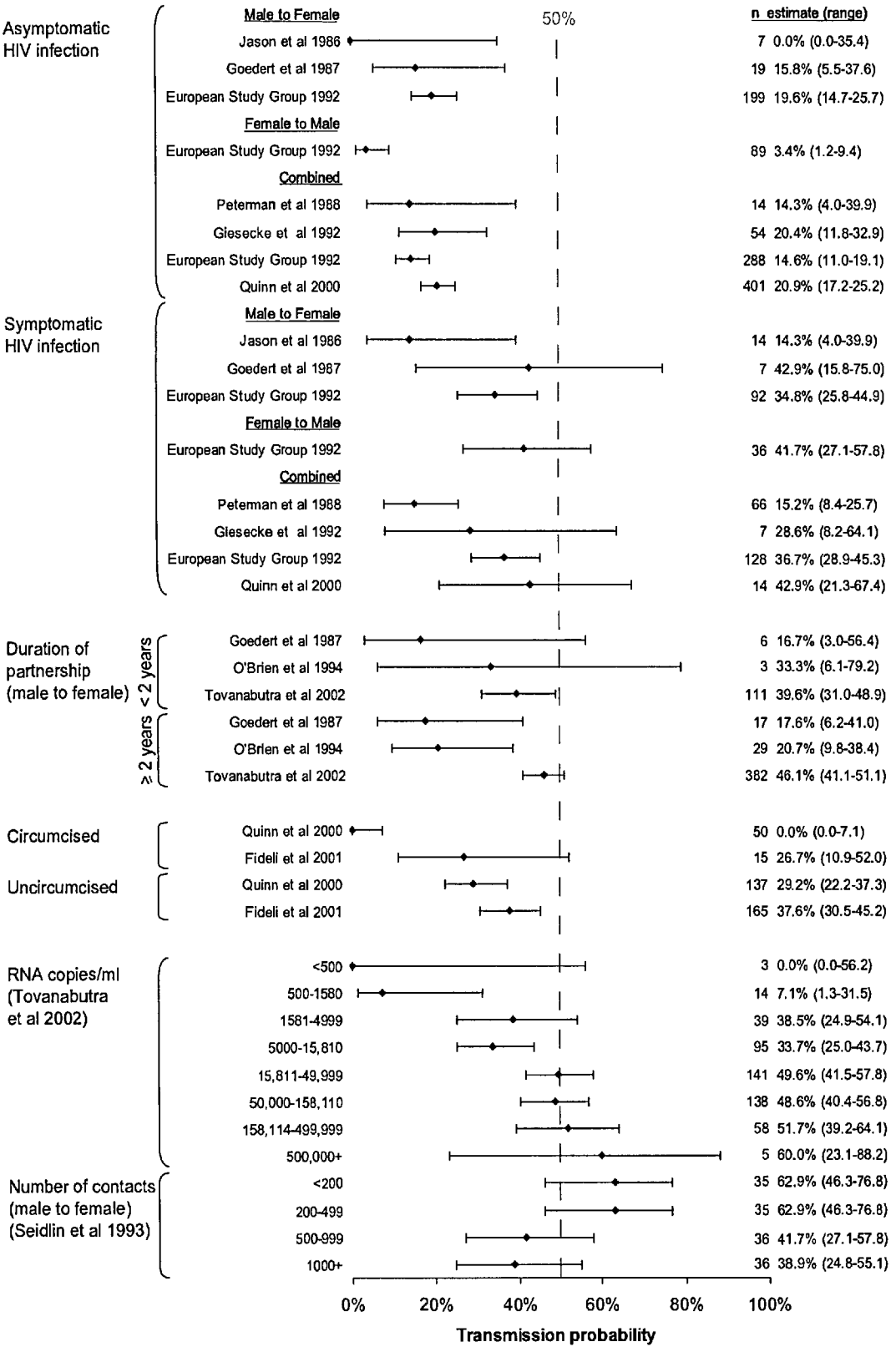


Figure 3.5 Summary of studies estimating HIV transmission probability per heterosexual partnership, stratified by risk categories, with 95% confidence intervals.

Table 3.7 Per partner HIV transmission probabilities: meta-analysis results.

Setting	Pooled estimate, % (x/n, 95% CI)	Fixed effects estimate, % (95% CI)	Random effects estimate, % (95% CI)	Q[1] (p value)	Number of studies
Combined M→F and F→M transmission					
All	23.4 (724/3099, 21.9-24.9)	20.5 (19.1-21.9)	25.2 (20.2-30.2)	237 (p<0.001)	23
Industrialised	22.7 (548/2413, 21.1-24.4)	19.5 (18.0-21.1)	23.1 (17.3-28.9)	195 (p<0.001)	18
Resource-poor	25.7 (176/686, 22.5-29.1)	24.7 (21.5-27.8)	34.4 (22.3-46.5)	34 (p<0.001)	5
M→F transmission					
All	28.4 (1434/5044, 27.2-29.7)	21.8 (20.8-22.9)	26.5 (20.9-32.0)	781 (p<0.001)	35
Industrialised	19.4 (593/3054, 18.1-20.9)	15.4 (14.1-16.6)	20.3 (15.6-25.1)	267 (p<0.001)	25
Resource-poor	42.3 (841/1990, 40.1-44.4)	40.9 (38.8-43.0)	40.2 (32.7-47.7)	94 (p<0.001)	10
F→M transmission					
All	17.2 (140/818, 14.8-20.0)	8.8 (7.0-10.7)	17.7 (10.4-24.9)	126 (p<0.001)	13
Industrialised	12.6 (65/515, 10.0-15.8)	6.3 (4.3-8.3)	15.5 (7.9-23.0)	74 (p<0.001)	10
Resource-poor	24.8 (75/303, 20.2-29.9)	22.5 (17.9-27.1)	22.1 (9.3-35.0)	13 (p=0.002)	3

[1]Test for heterogeneity

Table 3.8 Difference in per partner transmission probabilities by stage of infection and research setting: meta-regression results.

	Regression coefficient (%)	P value
By stage of infection of index case[1]		
Combined	10.3 (0.0-22.8)	0.109
M→F	12.1 (2.3-22.0)	0.016
By research setting[2]		
Combined	12.9 (0.0-30.9)	0.164
M→F	19.8 (9.0-30.7)	<0.001
F→M	3.8 (0.0-29.2)	0.767

The regression coefficient represents the absolute increase in transmission probability (%) compared to baseline.

[1]Baseline is asymptomatic infection

[2]Baseline is industrialised settings

3.5.2 Per contact transmission

The summaries of studies estimating transmission probability per heterosexual contact are shown in Tables 3.9 to 3.12 (excluded studies are listed in Table 3.6). Risk categories relate to stage of infection (such as symptomatic versus asymptomatic) [304-307], pVL [308, 309], STI [310] or circumcision status [304, 310].

As can be seen in Tables 3.9 to 3.11, fewer studies estimating per contact than per partner transmission probability were identified (21 versus 40 fitting inclusion criteria, respectively). In fact, most papers are based on a reanalysis of a restricted number of original datasets, using different assumptions and different statistical models [311-313], some of which provide point estimates and 95% CI, while others do not. As it requires more information, the estimation of HIV transmission per single sexual contact from cross-sectional or prospective studies is more difficult than estimating per partner transmission, but can be achieved in some studies [314], for example, when individuals are known to have become infected after a precise and known number of contacts with one or more infected partners [254]. This has been possible when the index partner has been infected by transfusion, for which the actual date (and thus the date of infection) is known. Other situations where the exact time of infection is known have been rare (especially since occurrence of transfusion-transmitted infection became negligible). Furthermore, self-reported data on the number of sexual contacts over a period of time is susceptible to substantial misreporting due to recall and social desirability biases, even if collected prospectively.

Table 3.10 shows that overall estimates of per contact M→F transmission probability based on different data sources and estimation procedures range between 0.03% [315] and 0.32% [316] (median = 0.10%), with a high value of 20% being classified as an outlier, for reasons explained in the next paragraph [313]. The next highest estimate (0.32%, Hayes et al [316]) was obtained from a sample of CSW in Kenya, where STI status in clients had not been controlled for, and where HIV status was inferred from HIV prevalence. Only seven studies looking at F→M transmission per contact were identified (Table 3.11). In these studies, per contact transmission probability estimates vary from 0.03% [317] to 8.22% [310] (median = 0.07%), with the higher estimates coming from studies in resource-poor settings (Table 3.11). The range of transmission probability estimates from resource-poor settings, (M→F 0.03% [315] to 0.32% [316] (median = 0.13%); F→M 3.1% [318, 319] to 8.2% [310]) (median = 5.6%)), tends to be larger than for industrialised settings (M→F 0.04% [320, 321] to 0.19% [311] (median = 0.09%), excluding the 20% outlier [313]; F→M 0.03% [317] to 0.09% [317] (median = 0.05%). Interestingly, differences in per contact transmission probability between industrialised and resource-poor settings are more marked for F→M than M→F transmission. This is most probably due to the noticeable difference in risk factor distribution within the sampled population. In the study by Cameron et al [310] (Table 3.11), all men enrolled in the study had an STI, and the transmission probability was estimated following a contact with a CSW whose serostatus was inferred from prevalence data. A similar technique was adopted by Baeten et al [322], in which the prevalence of HIV for various partnerships (long term, casual and CSW) was inferred. In the study by Cameron et

al [310], the authors suggest that the presence of an ulcerative STI is a more important cofactor of HIV infectiousness than other STIs, since none of the 36 men without GUD seroconverted, compared to six out of 37 (16.2%) of those with GUD, after one contact-exposure to HIV.

The highest transmission probability estimate was obtained from a sample of mainly uncircumcised Thai men who frequented CSW of unknown STI status [243, 319]. For this estimate, an effort was made to take into account the variability of self-reported sexual behaviour data. As will be seen, however, some studies from resource-poor settings have found transmission probabilities combining gender comparable to those from industrialised countries [308, 323] (Tables 3.9 and 3.12 and Figure 3.6) with estimates varying between 0.05% [278] to 0.14% [324] (Table 3.9).

Figure 3.6 shows that there is relatively good agreement between studies re-examining the same data. However, many authors concede that models assuming constant per contact infectiousness over the incubation period do not fit the data well [312]. In two papers, Eisenberg et al [313] and Gilbert et al [315] (Table 3.10) each used two different statistical models and obtained very different estimates for infectiousness using the same data. Eisenberg et al [313] used two models of infectiousness, one assuming homogeneous transmission probabilities across individuals, while the other heterogeneous model assumed that only 20% of those infected are infectious, thus resulting in much higher transmission probability estimates per contact per infectious individual. This assumption was investigated by Eisenberg et al because, at the time of publication (1991), there was much speculation as to why some individuals contracted HIV after very few exposures, while other individuals experienced thousands of exposures but were never infected. The speculation led to two main hypotheses; that infectiousness varies with stage of infection and that it is heterogeneous between individuals. Even though both explanations have since been shown to play a part in infectiousness, the heterogeneity in infectiousness between index cases postulated by Eisenberg et al [313] is far larger than what is currently understood based on the concept of infected individuals being either 'transmitters' or 'non-transmitters'. The high estimate by Donnelly et al [325] (0.60%) was based on a 'low risk' model, where the cofactor effect of STIs was assumed to be low and thus HIV infectiousness in the absence of STIs would be relatively high. Furthermore, returning to the per partner transmission probabilities discussed in section 3.4.2, the studies summarised in Table 3.5 indicate that infectiousness varies with stage of infection, being lower during the long incubation period than during primary infection and ARC/AIDS [304-306].

Few studies were identified which presented per contact transmission probability estimates by risk categories. Only four studies from industrialised countries [305-307, 309] and four from resource poor settings [304, 308, 310, 322] were found. Table 3.12 displays the influence of stage of infection, circumcision status, pVL and STIs on per contact transmission probability estimates, often combining gender. Estimates in this table support the hypothesis that infectiousness increases with increasing pVL [308, 309] and that circumcised males have a lower probability of acquiring infection [310, 322]. For Cameron et al, this difference did not reach statistical significance [310], but for the Baeten et al study, it was significant ($p = 0.04$) [322].

The range of per contact transmission probability estimates varies between 0.23% [308] to 5.67% [306] when index cases had developed AIDS or had a pVL more than 38,499 copies/mL, which is clearly higher than the range when index cases were in the incubating, pre-ART or asymptomatic phases, or with pVLs between 1,700-38,498 copies/mL (0.00% [305] to 0.16% [323]). Precise comparisons of transmission probability estimates by pVL cannot be made between industrialised and resource-poor settings because adequate data from industrialised countries is lacking. Chakraborty et al [309] estimated per contact transmission probability by pVL per ejaculate rather than per mL. Comparisons are made difficult because this study used biological and epidemiological data to develop the mathematical model to make inferences on infectiousness and pVL.

Estimates of the transmission probability during primary infection are extremely difficult to obtain because of the difficulty in identifying index cases at this stage of infection, while those who know that they are at risk of seroconverting (such as following accidental percutaneous exposure) may cease risky activities as a result. The only study available is by Wawer et al [304], who produced an estimate of 0.82% (95% CI 0.39-1.50%) per contact at the earliest identifiable stage of infection (within around 2.5 months of seroconversion) and 0.15% (95% CI 0.02-0.55%) per contact for index cases six to 15 months after seroconversion. It is perceived that the highest levels of infectiousness will be *before* seroconversion – before the immune system starts controlling the infection to some extent, and so per contact transmission probability from infection rather than seroconversion are likely to be even higher than these estimates. The authors' estimates are also useful in demonstrating that the period of increased infectiousness may last well beyond seroconversion, and show a quadrupling of transmission risk for individuals at late stage infection.

As with the per partnership transmission probability estimates, it is difficult to determine whether there is a difference in per contact infectiousness between industrialised and resource-poor settings, or between M→F and F→M transmission (Figure 3.6). Estimates by Mastro et al [243] and Cameron et al [310], which describe infectiousness in resource-poor settings (Kenya and Thailand respectively), stand out as being significantly higher than the others. Unlike the study by Gray et al [308], the estimate by Cameron et al includes the STI cofactor effect. The Thai study by Mastro et al is from the period of early epidemic growth, where many people were undergoing primary infection, which may explain the high infectiousness observed by this study, despite the lack of STI cofactor effect.

It is important to bear in mind that the quality of per contact transmission probability estimates inherently relies on the accuracy of self-reported frequency of sexual intercourse, which may be subject to bias, notably recall bias. However, Gray et al [308] assessed intra-couple reliability by comparing reports from both members of sexual couples, and found "relatively good agreement", with no significant difference in reported sexual frequency between men and women within a couple. However, such agreement does not reveal any consistent under- or over-estimation of sexual

frequency which is reported by both partners. Different methods have been proposed to improve self-reporting sexual behaviour [326] and the reduction of recall biases [290, 327, 328].

As illustrated by these results, a lot of uncertainty remains regarding the transmission probability of HIV by sexual contact and partnership. Given the importance of understanding the reproductive potential of HIV between hosts, it would be useful to acquire per contact transmission probability estimates stratified by both pVL and gender in the absence of other cofactors, because of the potential interaction between these two factors [329-331]. However, in the future it may prove difficult to produce transmission probability estimates by pVL which are not confounded by ARV use.

Table 3.9 Transmission probabilities per contact for heterosexual intercourse – combined M→F and F→M transmission.

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission probability, %	
INDUSTRIALISED SETTINGS				
Berglund et al 1988 [278]	Sweden (sexual partners of surviving transfusion recipients) 1979-1985	Not specified (results are presented as an aside in a paper concentrating on infectiousness of blood transfusions)	**0.05-0.10**	
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, 80 spouses of transfusion recipients, no date No other risk factors	AIDS and asymptomatic One seroconverter reported two other partners since 1978 (both "low risk") and a history of STI	**0.10**	
Wiley et al 1989 [332]	As above		**0.139**	
Kim & Lagakos 1990 [306]	As above		**0.102**	(range: 0.072-0.132)
Kaplan 1990 [324]	As above		**0.14**	(95% CI 0.06-2.2)
Longini et al 1989 [305]	Uses data from Fischl et al 1987 [265]	AIDS No other risk factors UC: condom	**0.1**	
Downs & de Vincenzi 1996 [317]	Using data from European Study Group [241, 307, 333]	Parametric analysis based on data at study entry Parametric analysis based on follow-up data Not controlled for STI	**0.05** **0.12**	(95% CI 0.03-0.06) (95% CI 0.07-0.21)
RESOURCE-POOR SETTINGS				
Gray et al 2001 [308]	Uganda prospective, 174 monogamous discordant couples 1994-1998	No GUD, HIV subtypes A and D (no difference in infectiousness between subtypes)	**0.11**	(95% CI 0.08-0.15)

Abbreviations: CDC – Centers for Disease Control and Prevention (US); condom – condom use; GUD – genital ulcer disease; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.10 Transmission probabilities per contact for heterosexual intercourse – M→F transmission.

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission Probability, %	
INDUSTRIALISED SETTINGS				
Wiley et al 1989 [332]	US CPS (prospective), recruited 1985-1986	AIDS and asymptomatic One seroconverter reported two other partners since 1978 (both low risk) and a history of STI	**0.08-0.10**	
Brookmeyer & Gail 1994 [311]	As above	Simplest model (assumes uniform infectiousness per contact) [1] Generalised linear model (assumes uniform infectiousness per contact and per partnership)[2]	**0.19** **0.10**	
Padian et al 1997 [334]	As above, 302 couples	Adjusted for condom use, history of STI and AI	**0.09**	(95% CI 0.05-0.1)
Shiboski & Padian 1998 [312]	As above, 302 couples	Adjusted for AI and condom use	**0.055**	(95% CI 0.03-0.09)
Halperin et al 2002 (abstract) [335] plus Shiboski 2003 (personal communication)	As above (mean DE 47.3 months for transmitters, 45.0 months for non-transmitters)	Unadjusted Adjusted for condom use, history of STI, AI and IDU in males	**0.04** **0.04**	(95% CI 0.03-0.06) (95% CI 0.02-0.07)
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, 51 wives of transfusion recipients, no date	No other risk factors, 2 seronegative partners reported history of STI	**0.13**	(10/7840 95% CI 0.07-0.23)
Kim & Lagakos 1990 [306]	As above		**0.134**	
Eisenberg 1991 [313]	As above	Homogeneity model (homogeneous infectiousness[3]) Discrete model (heterogeneous infectiousness[3])	**0.1** **3-20**	
Shiboski & Padian 1998 [312]	As above		**0.08**	(95% CI 0.04 - 0.2)
Downs & de Vincenzi 1996 [317]	Using data from European Study Group [241, 307, 333]	AIDS and asymptomatic, no other risk factors, UC: STI Data at study entry Follow-up data	**0.05** **0.15**	(95% CI 0.03-0.07)
Leynaert et al 1998 [336]	As above	As above	**0.07**	
Saracco et al 1997 [337]	Italy prospective cohort, 627 regular partners (DP > 6 months) of index cases attending health clinics 1987-1996	No other risk factors Cox's Proportional Hazard Model used to control for condom use, AI, ART. AIDS and asymptomatic; some partners exposed during primary infection of index, No other risk factors, UC: condom, STI	**0.06**	(range: 0.04-0.09)
Shiboski & Padian 1998 [312]	Uses data from CDC Heterosexual AIDS Transmission Study (O'Brien et al 1994 [254]) US prospective, 31 sexual partners of transfusion recipients, enrolment 1987-1992	AIDS and asymptomatic; some partners exposed during primary infection of index No other risk factors UC: condom, STI	**0.09**	(95% CI 0.04 - 0.2)
Duerr et al 2000 (abstract) [338]	Italy cross-sectional, 51 partners, no date	HIV stage not specified, no other risk factors, controlled for consistent condom use	**0.11**	(range: 0.05-0.17)

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission Probability, %	
RESOURCE-POOR SETTINGS				
Donnelly et al 1993 [325]	Senegal retrospective cohort of initially seronegative CSW 1985-1989	Assumes number of partners per week has not changed over time. Infers prevalence of HIV among partners using data from a high-risk population (CSW) and a low-risk population (antenatal clinic data) from Senegal. UC: STI	**0.0393** **0.595**	High risk model Low risk model
Duerr et al 1994 (abstract) [339]	Thailand cross-sectional, newly married couples 1992-1993	HIV stage not specified, no other risk factors, UC: STI, very little condom use reported, no effect of AI. All HIV-1 CRF_01AE*	**0.16**	(95% CI 0.06-0.26)
Hayes et al 1995 [316]	Kenya prospective, 124 female CSW without GUD 1985-1987 (reanalysis of data from Plummer et al 1991 investigating HIV cofactors, without actually calculating transmission probability [340])	Nonsexual risk factors e.g. injections were not associated with seroconversion, no AI, not controlled for STI in clients; infection status of clients inferred from prevalence data	**0.32**	
Duerr et al 2000 (abstract) [338]	Thailand cross-sectional, 78 partners of male blood donors, no date 94% HIV-1 CRF_01AE*	HIV stage not specified, no other risk factors, controlled for consistent condom use	**0.24**	(range: 0.15-0.32)
Gilbert et al 2003 [315]	Senegal retrospective cohort, initially seronegative CSWs 1985-1999	HIV status not specified (assumed to be asymptomatic). Not controlled for STI in clients; infection status of clients inferred from prevalence data. Method 1[4] Method 2[5]	 **0.0311** **0.0563**	

*Formerly subtype E.
[1] Infectiousness estimate only uses a fraction of the data from the dataset
[2] Infectiousness estimate is based on all the data in the dataset
[3] Homogeneous model assumes uniform infectiousness for all infected individuals, whereas heterogeneous model assumes that only 20% of the infected population are infectious.
[4] Only data complete for each CSW is included in the analysis.
[5] Missing data from CSW not providing mean partners-per-week data is imputed.
Abbreviations: AI – anal intercourse; CDC – Centers for Disease Control and Prevention (US); CPS – California Partners' Study; CSW – commercial sex worker; GUD – genital ulcer disease; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.11 Transmission probabilities per contact for heterosexual intercourse – F→M transmission.

Study	Setting/Study design/Population/Date	Stage of HIV infection/Other risk factors, uncontrolled cofactors	Transmission Probability, %	
INDUSTRIALISED SETTINGS				
Peterman et al 1988 [262]	US CDC Transfusion Partner Study, cross-sectional, 25 husbands of transfusion recipients, no date	AIDS and asymptomatic One seroconverter reported two other partners since 1978 (both low risk) and a history of STI	**0.05**	(2/4274 95% CI 0.01-0.17)
Kim & Lagakos 1990 [306]	As above	As above	**0.05**	
Downs & de Vincenzi 1996 [317]	Using data from European Study Group [241, 307, 333]	Parametric analysis based on data at study entry Parametric analysis based on follow-up data Not controlled for STI	**0.03** **0.09**	(95% CI 0.02-0.05)
Leynaert et al 1998 [336]	As above	As above	**0.05**	
RESOURCE-POOR SETTINGS				
Cameron et al 1989 [310]	Kenya cross-sectional, 73 men attending an STI clinic following a single exposure to a cohort of CSW 1986-1988.	All men initially seronegative and seroconverted over following 12 weeks. All had STI, serostatus of CSW inferred from prevalence data (85% prevalence). No other risk factors, not controlled for circumcision.	**8.22**	(6/73 95% CI 3.82-16.79)
Mastro et al 1994 [243]	Thailand cross-sectional, military conscripts with CSW 1991 (reanalysis of Nopkesorn et al 1993 [341]). Sample size for conscripts without history of STI not stated. Estimates also reported in Satten et al 1994 [319].	Model A (maximum likelihood method) Model B (as for Model A, allowing for random error in the self-reported frequency of contacts) No history of STI among partner (NB not known for index case), circumcision very uncommon HIV-1 CRF_01AE*	**3.1** **5.6**	(95% CI 2.5-4.0) (95% CI 4.1-7.5)
Baeten et al 2005 [322]	Kenya prospective, truck drivers and their wives, casual partners and CSW	Multiple sexual partners, HIV prevalence inferred from prevalence data for different types of partnership. UC: STI	**0.63**	(95% CI 0.35-0.91)

*Formerly subtype E.
Abbreviations: CDC – Centers for Disease Control and Prevention (US); CSW – commercial sex worker; STI – sexually transmitted infection; UC – uncontrolled cofactors

Table 3.12 Transmission probabilities per contact for heterosexual intercourse – stratified by risk categories.

Study	Setting/Study design/Population/Date/Stage of HIV infection/Other risk factors, uncontrolled cofactors (UC)	Risk categories	Transmission Probability, %	
INDUSTRIALISED SETTINGS				
Longini et al 1989 [305]	Uses data from Fischl et al 1987 [265] AIDS No other risk factors UC: condom	Combined M→F F→M: Incubation Pre-AIDS AIDS	 "close to zero" **0.07** **0.57**	 (range: 0.05 – 0.09) (range: 0.41 – 0.73)
Kim & Lagakos 1990 [306][1]	US CDC study (sexual partners of transfusion recipients); no date	Combined M→F F→M: 2-stage Model: Asymptomatic AIDS 3-stage Model: Primary Incubation AIDS	 **0.0927** **5.67** - **0.0977** **0.688**	
De Vincenzi 1994 [307]	European multi-centre study 1987-1992	Combined M→F F→M: Asymptomatic AIDS	 **0.07** **0.5**	 (range: 0.03 – 1.4) (range: 0.14 – 1.31)
Chakraborty et al 2001 [309]	US, Switzerland 1994-1997 Model linking biological and epidemiological data No men were receiving ART, not other cofactors or risk factors specified.	M→F: >100,000 HIV virions per ejaculate <1,000 HIV virions per ejaculate	 **0.39 – 0.96** **0.01 – 0.03**	
RESOURCE-POOR SETTINGS				
Cameron et al 1989 [310]	Kenya cross-sectional, 73 men attending an STI clinic following a single exposure to a cohort of CSW 1986-1988. All men initially seronegative and seroconverted over following 12 weeks. Serostatus of CSW inferred from prevalence data (85% prevalence). No other risk factors specified.	F→M: Circumcised Uncircumcised F→M: Urethritis GUD	 **2.2** **18.5** **0.0** **16.2**	 (1/46 95% CI 0.4-11.3) (5/27 95% CI 8.2-36.7) (0/36 95% CI 0.0-9.6) (6/37 95% CI 7.7-31.1)
Gray 2001 [308]	Uganda prospective, 174 monogamous discordant couples 1994-1998 No GUD, HIV subtypes A and D (no difference in infectiousness between subtypes)	Combined M→F F→M: pVL (copies/mL) <1700 1700 – 12,499 12,500 – 38,500 ≥38,500	 **0.01** **0.12** **0.14** **0.23**	
Wawer et al 2005 [304]	Uganda retrospective cohort 1995-1999	Combined M→F F→M: Primary (within ~2.5 months since index seroconversion) Early (within 6-15 months since index seroconversion) Incubation "Late-stage" (6-25 months before death of index)	 **0.82** **0.15** **0.07** **0.28**	 (range: 0.39-1.50) (range: 0.02-0.55) (range: 0.05-0.10) (range: 0.15-0.41)
Baeten et al 2005 [322]	Kenya prospective, truck drivers and their wives, casual partners and CSW	F→M: Circumcised Uncircumcised	 **0.51** **1.28**	

[1] Using data from Peterman et al 1988 [262]. Abbreviations: CDC – Centers for Disease Control and Prevention (US); condom – condom use; CSW – Commercial sex worker; GUD – genital ulcer disease; pVL – plasma viral load; STI – sexually transmitted infection; UC – uncontrolled cofactors

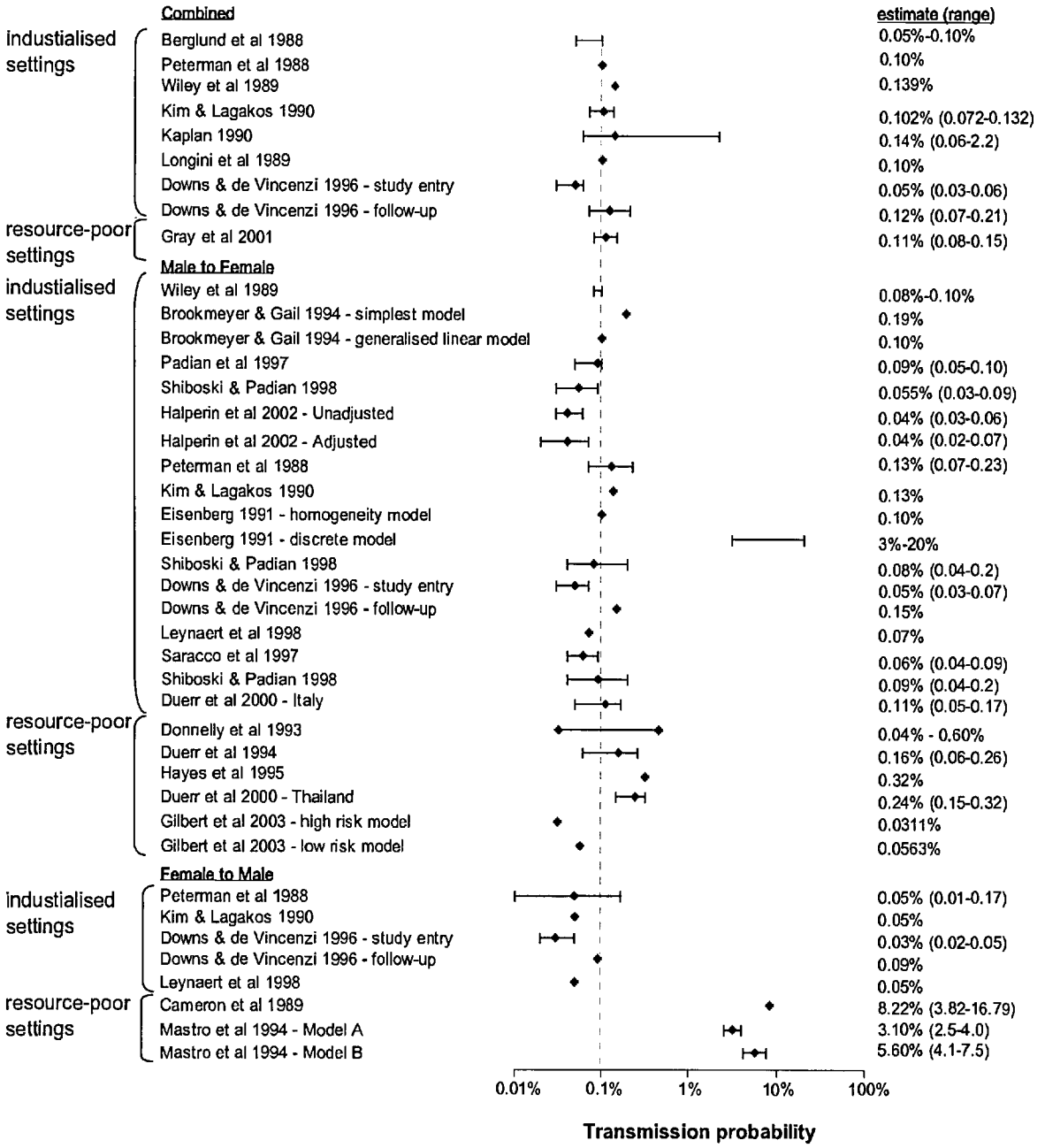


Figure 3.6 Summary of studies estimating transmission probability per heterosexual contact – logarithmic scale.

3.6 Anal intercourse

Most studies of heterosexual couples found an increase in risk for M→F transmission among couples who practiced penile-anal sex, even if only occasionally [240, 241, 266, 342, 343]. Compared to the mucosa of the mature vagina or cervix, it has been suggested that the rectal mucosa is more susceptible to traumatic abrasions which may facilitate HIV infection and to direct HIV infection of rectal mucosal cells [344]. In addition, the rectal mucosa lacks the protective humoral immune barrier present in cervicovaginal secretions [345]. The proportion of heterosexually acquired HIV infection attributable to anal sex depends largely on the frequency of this practice, which varies greatly among populations. For example, one-quarter of couples in the European study [241], 15% and 37% in two California studies [245, 346] and <1% in Africa [347] and Thailand [243] reported this practice. The summaries of studies estimating the infectiousness of AI are shown in Tables 3.13 to 3.15 (note that estimates for both heterosexual couples and MSM have been included, distinguishing between receptive and insertive intercourse). A priori, it would seem reasonable to assume that infectivities per AI contact for heterosexual and homosexual relations would be comparable, as they are biologically similar practices. However, per partner infectivities are probably not comparable due to differing frequencies of this practice between heterosexual and homosexual relationships.

Surprisingly few studies have investigated HIV transmission probabilities for homosexual intercourse (see Tables 3.13 and 3.14); only seven fitting the inclusion criteria were found [261, 324, 348-352]. It may be that relatively little attention has been given to quantifying transmission risk because it was identified early on in the epidemic that it was high. Per partner transmission probability estimates vary from 0.015% [351] to 37% (symptomatic index case) [261] for unprotected insertive anal intercourse (UIAI), from 10% [348] to 50% (symptomatic index case) [261] for unprotected receptive anal intercourse (URAI), and from 5% [324] to 10% [350] for combined or unspecified types of AI (Table 3.13). The per partner transmission probability estimates vary widely, which may at least partly be explained by differences in the distribution of risk factors in sampled populations and different study designs. For example, duration of exposure to an infected partner, frequency of sexual contact per partnership and the presence of various cofactors for transmission, such as presence of STIs or factors potentially inhibiting transmission such as condom use, will differ. Therefore information on factors potentially affecting the probability of transmission has been included in the summary tables. The per partner transmission probability estimates for these MSM populations are in surprisingly good agreement with estimates for heterosexual transmission, despite AI being perceived as a more risky act than vaginal intercourse. However, the studies of MSM are generally of more casual types of partnerships, with far lower durations of partnership, durations of exposure and numbers of contacts than for heterosexual partner studies.

Of more relevance to heterosexual transmission are estimates of per contact transmission probability for AI, which can complement estimates of vaginal-only intercourse for couples engaging in both practices. Per contact estimates vary from 0.4% (adjusted for STI, condom use) [321, 335] to 18.3% (index case with AIDS) [336] for URAI, and 0.06% [352] (one study only) for UIAI (Table 3.14).

Although the number of studies of per contact transmission probability for AI is small (only four), the estimates appear to be larger than for vaginal intercourse (range 0.04% to 0.32%, outlier 20%).

Table 3.13 Transmission probabilities per partner for anal intercourse.

Study	Setting/Study design/Population/Date	Stage of HIV infection/other risk factors, uncontrolled cofactors	Transmission probability, %	
Combined URAI AND UIAI				
Samuel et al 1992 (abstract) [350]	Using data from Grant et al 1987 [348] (see below)		**~10**	
Kaplan 1990 [324]	Using data from Grant et al 1987 [348] (see below)		**5.1**	(95% CI 2.2-8)
URAI				
Grant et al 1987 [348]	US SFMHS – prospective, MSM 1984-1985		**10.2**	(95% CI 4.3-16.0)
Giesecke et al 1992 [261][1]	Sweden cross-sectional, partner notification of all patients diagnosed in Sweden (heterosexuals and MSM), 1989-1990	Asymptomatic Symptomatic UC: condom	**35** **50**	
Samuel et al 1994 [351]	Using data from Grant et al 1987 [348] (see above)		**10**	(range: 4-12)
UIAI				
Giesecke et al 1992 [261][1]	Sweden cross-sectional, partner notification of all patients diagnosed in Sweden (heterosexuals and MSM), 1989-1990	Asymptomatic Symptomatic UC: condom	**13** **37**	
Samuel et al 1994 [351]	Using data from Grant et al 1987 [348] (see above)		**0.015-0.15**	

[1] Probabilities were independent of duration of relationship. Abbreviations: condom – condom; SFMHS – San Francisco Men's Health Study; UC – uncontrolled cofactors; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse

Table 3.14 Transmission probabilities per contact for anal intercourse.

Study	Setting/Study design/Population/Date	Stage of HIV infection/other risk factors, uncontrolled cofactors	Transmission probability, %	
URAI				
DeGruttola et al 1989 [349]	US cross-sectional (132 index MSM and 155 sexual partners)		**0.5-3.0**	
Leynaert et al 1998 [336]	European multi-centre study (525 heterosexual discordant couples) 1987-1992	Primary Infection Incubation AIDS	**18.3** **1.4** **18.3**	
Vittinghoff et al 1999 [352]	US prospective (2,189 high risk homosexual and bisexual men) 1992-1994		**0.82**	(95% CI 0.24-2.76)
Halperin et al 2002 (abstract) [335] plus Shiboski 2003 (personal communication)	US CPS, prospective (described in Padian et al 1987 [342] 59 male index cases and their female partners) Recruited 1985-1986	Unadjusted Adjusted for condom use, history of STI, IDU in males	**0.6** **0.4**	(95% CI 0.1-2) (95% CI 0.08-2)
UIAI				
Vittinghoff et al 1999 [352]	US prospective (2,189 high risk homosexual and bisexual men)		**0.06**	(95% CI 0.02-0.19)

Abbreviations: CPS – California Partners' Study; UIAI – unprotected insertive anal intercourse; URAI – unprotected receptive anal intercourse

Table 3.15 Transmission probabilities for anal intercourse – excluded studies.

Study	Setting	Transmission probability, %	Reason for exclusion
PER PARTNER			
Weller et al 1987 [353]	UK cross-sectional (regular sexual partners of AIDS patients), no date	**60.0** (21/35 95% CI 43.6-74.4)	Partners of index cases were not monogamous
Osmond et al 1988 [354]	US case-control 1983-1984	**72.6** (85/117 95% CI 63.9-79.9)	Partners of index cases were not monogamous
Seage et al 1993 [355]	US cross-sectional (index cases were MSM with AIDS or ARC) 1985-1990	**31.1** (19/61 95% CI 20.9-43.6)	Cross-sectional – direction of transmission not proved and no monogamy
Porco et al 2004 [356]	US SFMHS – prospective 1994-1999	**12.0**	Calculated using population-level trends. Study participants had multiple partners and serostatus of partners was inferred using prevalence data.
PER CONTACT			
May & Anderson 1987 [357]	-	**~5**	Inferred from data on doubling times of the HIV epidemic in various countries, duration of infection and sexual activity.
DeGruttola et al (abstract) 1988 [358]	33 couples	**2.01 – 5.37**	Abstract pre-1990

Abbreviations: ARC – AIDS-related complex; SFMHS – San Francisco Men's Health Study

3.7 Relationship between per contact and per partnership risk

The transmission probability estimates reported in this chapter were used to calculate the expected number of contacts per partnership. The transmission probability per partnership should be a function of the transmission probability per act and the number of sexual acts. If the values are consistent then the one should be a simple function of the other, with the relationship defined by equation 3.1 [359]. This is explored by calculating the number of acts required to translate estimates of the per act transmission probability from studies into those per partnership (Figure 3.8).

$$\Lambda = 1-(1-\theta)^n \qquad (3.1)$$

where Λ is transmission probability per partnership, θ is transmission probability per contact and n is number of contacts per partnership. This equation is similar to the Reed-Frost epidemic model [360], because $1-(1-\theta)^n$ represents the probability that at least one of the n sexual contacts results in HIV transmission. The probability that the susceptible member of the partnership experiences no sexual acts that result in transmission is $(1-\theta)^n$, so the chance of transmission occurring is the remainder of the probability space.

The ART models used in this thesis are not stratified by gender. Therefore the combined M→F and F→M transmission probabilities per partnership (Table 3.2) and per contact (Table 3.7) are compared. Figure 3.7 shows the average number of sexual contacts per partnership deduced for each per partnership study in Table 3.2 with 95% CI, using three different values of per contact transmission probability (the minimum (0.05%), median (0.10%) and maximum (0.14%) per contact estimates from Table 3.9). The 0.05% value taken from the lower estimate for both Berglund et al [278] and Downs and de Vincenzi [317] is likely to be an underestimate. Berglund et al's report lacks detail, concentrating on estimating the infectiousness by blood product exposure, while Downs & de Vincenzi's 0.05% estimate is based on data at study entry. All other estimates of per contact transmission in Table 3.9 range from 0.10-0.14%, but are based on limited empirical data. It is remarkable that the estimates are so similar, considering the poor relationship between transmission probability per partnership and the number of sexual contacts described in some of these publications, as well as many others. For example, Seidlin et al reports per partnership infectiousness for M→F HIV transmission by number of contacts per partnership [266]. Calculating the per contact transmission probability inferred by their results demonstrates that it is per partnership infectiousness that remains more constant than per contact infectiousness for various numbers of sex acts (Table 3.16). Furthermore, the wide variability in calculated estimates for per contact infectiousness in Table 3.16 reflects that of empirical data which ranges, for example, from 0.04% to 0.60% for M→F transmission (Table 3.10). Such findings are supported by other evidence [324, 332, 361]. Suggested reasons for this include measurement errors in number of sex acts, time dependency in

infectiousness, missing covariates, heterogeneity in viral infectiousness and/or heterogeneity in host susceptibility, and the complexity in the relationship between number of sex acts and number of partners [362, 363]. Both a constant per contact and per partnership transmission probability provide unsatisfactory models of the observed relationship between the number of sex acts and the likelihood of transmission [359]. A constant per contact transmission probability will underestimate transmission in partnerships with few sex acts and overestimate it in those with many acts. Conversely, a constant per partnership transmission probability overestimates transmission in partnerships with few acts and underestimates it in partnerships with many acts. However, the problems in collecting appropriate empirical information make it difficult to validate different transmission models. The wide heterogeneity in per contact estimates means that transmission probabilities per partnership are used in the models in this thesis.

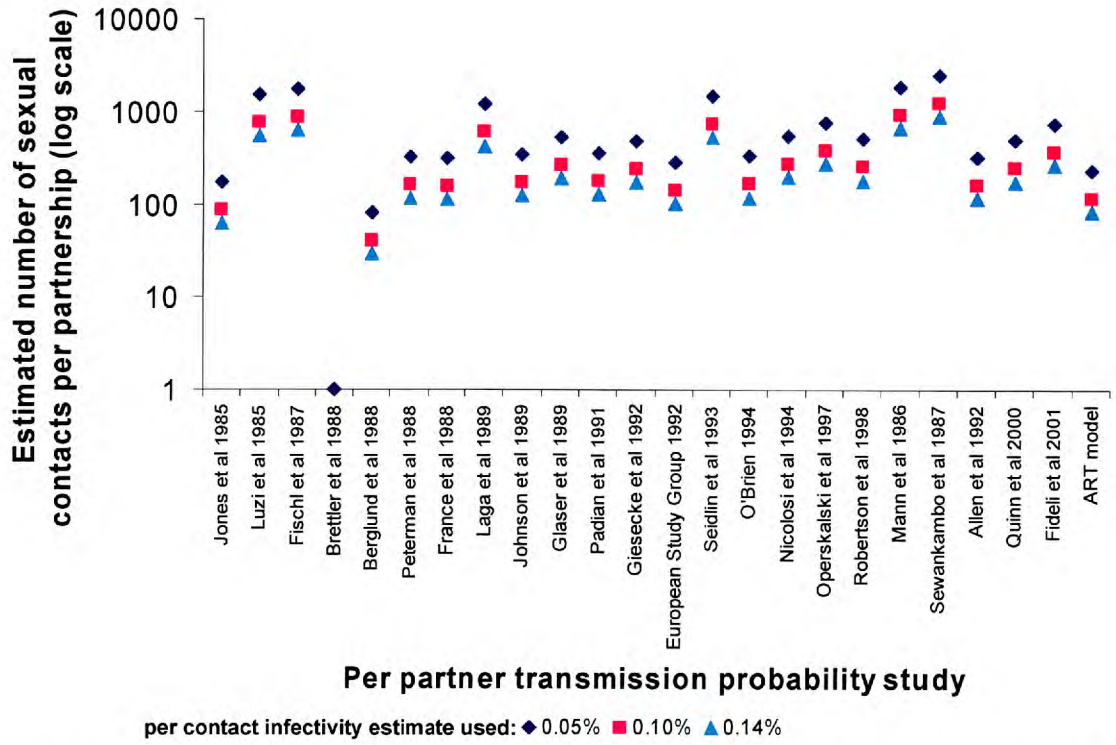


Figure 3.7 Average number of sexual contacts per partnership for each per partnership study, calculated using per sexual partnership and per sexual contact HIV transmission probability data.

Table 3.16 Per contact transmission probability for M→F HIV transmission derived using data from Seidlin et al 1993 [266].

Sexual activity group (by number of contacts)	Average number of contacts	Transmission probability per partnership, % (x/n, 95% CI)	Per contact infectiousness (%)
<200	100	62.9 (22/35, 46.3-76.8)	0.99 (0.62-1.45)
200-499	350	62.9 (22/35, 46.3-76.8)	0.28 (0.18-0.42)
500-999	750	41.7 (15/36, 27.1-57.8)	0.07 (0.04-0.12)
≥1000	1250	38.9 (14/36, 24.8-55.1)	0.04 (0.03-0.06)

3.7.1 Sexual activity with stage of infection

It is assumed that individuals' sexual activity, both partner change rate and number of contacts per partnership, will decrease as they develop HIV-related symptoms and progress to AIDS. A crude comparison between some of the data included in this chapter illustrates a decreasing trend in numbers of sexual contacts per partnership as individuals' HIV infections progress. A comparison between per partnership and per contact transmission probabilities stratified by stage of infection of the index case, as summarised in Table 3.17, was used to calculate number of contacts per partnership. The results are shown in Figure 3.8. Per contact transmission probability estimates were more specific regarding infection stage, and so were collapsed into symptomatic or asymptomatic groups. For Longini et al, the "close to zero" estimate for the HIV incubation period is ignored, while the mean of the pre-AIDS and AIDS estimates (0.32%) is taken for the symptomatic transmission probability, which assumes pre-AIDS and AIDS periods are of equal duration [305]. The two-stage model of Kim & Lagakos is used [306]. In the case of Wawer et al [304], "late stage" is assumed to encompass AIDS and pre-AIDS, primary infection as covering the first three months of infection (rather than seroconversion), "early infection" covering the next nine months, with incubation lasting for the rest of the eight year, six week asymptomatic period which is assumed in the ART models. This produces an average per contact estimate through the asymptomatic period of 0.10%.

Table 3.17 Summary of studies providing per partnership and per contact transmission probability estimates stratified by stage of HIV infection (combined M→F and F→M transmission only).

Per partnership infectiousness estimates			Per contact infectiousness estimates		
Study	**Stage of infection**	**Estimate, % (x/n 95% CI)**	**Study**	**Stage of infection**	**Estimate (range)**
Peterman et al 1988 [262]	Asymptomatic AIDS	14.3 (2/14 4.0-39.9) 15.2 (10/66 8.4-25.7)	Longini et al 1989 [305]	Incubation Pre-AIDS AIDS	"close to zero" 0.07 (0.05-0.09) 0.57 (0.41-0.73)
Giesecke et al 1992 [261]	Asymptomatic Symptomatic	20.4 (11/54 11.8-32.9) 28.6 (2/7 8.2-64.1)	Kim & Lagakos 1990 [306]	2-stage model Asymptomatic AIDS 3-stage model Primary Incubation AIDS	 0.0927 5.67 - 0.0977 0.688
European Study Group 1992 [241]	Asymptomatic AIDS	14.6 (42/288 11.0-19.1) 36.7 (47/128 28.9-45.3)	De Vincenzi 1994 [307]	Asymptomatic AIDS	0.07 (0.03-1.4) 0.5 (0.14-1.31)
Quinn et al 2000 [230]	Asymptomatic AIDS	20.9 (84/401 17.2-25.2) 42.9 (6/14 21.3-67.4)	Wawer et al 2005 [304]	Primary Early Incubation Symptomatic	0.82 (0.39-1.50) 0.15 (0.02-0.55) 0.07 (0.05-0.10) 0.28 (0.15-0.41)
ART model	Asymptomatic Symptomatic	3.7 40.5			

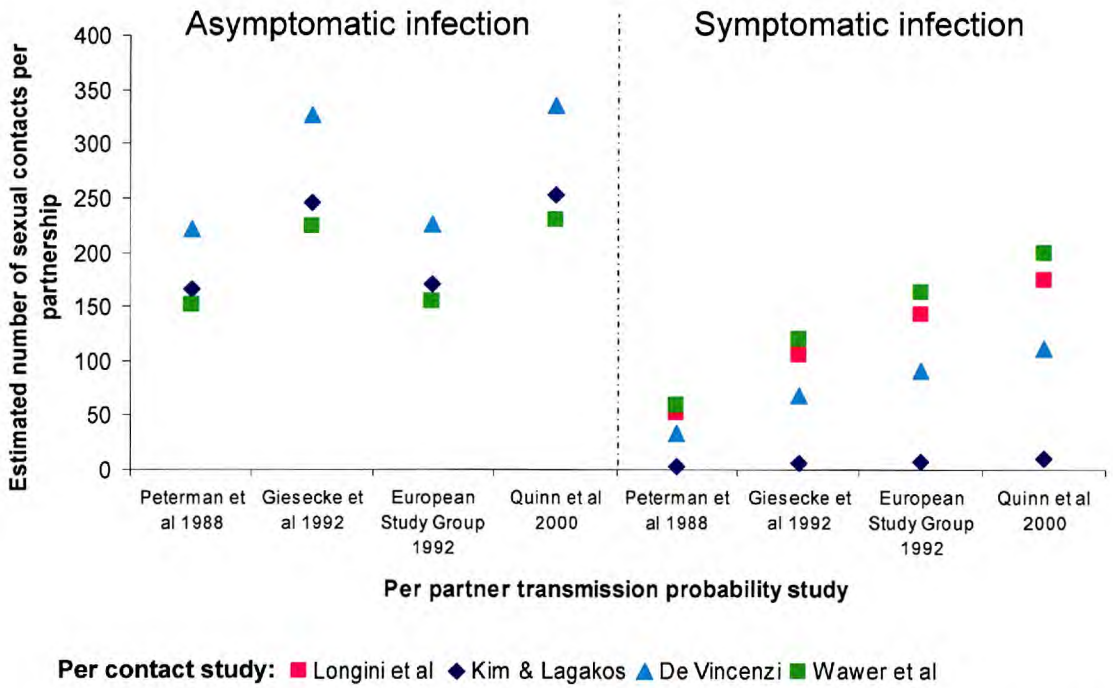


Figure 3.8 Average number of sexual contacts per partnership calculated using per sexual partnership and per sexual contact HIV transmission probability data, stratified by stage of infection of the index partner.

3.7.2 Transmission probability estimates used in the ART models

Differential infectiousness according to stage of infection has long been posited because of trends in pVL with time since infection [364], with pVL high during primary (acute) infection, then lower during incubation, followed by a resurgence as the immune system deteriorates during "pre-AIDS" and AIDS [365, 366]. Mathematical models have also examined the changes in infectiousness with stages [16, 367].

HIV can be detected in semen during primary infection [368], indicating that the male genital tract is an early site of viral dissemination and replication. During the time when HIV replication is unchecked by host immune responses, newly infected patients may transmit a viral population which is well adapted for sexual transfer. After this acute stage, the immune system gains control of HIV replication to a certain degree, and pVL is reduced [366]. However, it may still be above virus detection limits during this "incubation" period [7], and so individuals are still infectious during this time. With advanced disease, larger amounts of HIV are shed in semen [7], reflecting higher pVL and indicating higher infectiousness.

An average transmission probability per partnership is difficult to measure. There is up to a 100-fold decrease in pVL after the peak reached during primary infection [16, 364], followed by a gradual increase during the periods of pre-AIDS and AIDS [318] up to a level comparable to that during primary infection again [364, 369], or slightly lower [16]. The average value for pVL during this period will be lower because there is a very large rise and fall in pVL. Wawer et al found that infectiousness per sexual contact was approximately 12-fold higher during primary infection than incubation (0.82% compared to 0.07%) [304]. However, the period of primary infection is defined as within 2.5 months of seroconversion. The period before seroconversion, when viral replication is occurring unchecked, may be substantially higher. Therefore the models in Chapters 5 and 6 incorporate differential infectiousness with stage of infection, where infectiousness during primary infection and AIDS is a factor a higher than that during incubation, and that for the pre-AIDS stage is a factor $a/2$ higher. A first estimate for a is 50, which assumes that the 12-fold increase for primary infection estimated by Wawer et al is an underestimate because it misses the earliest period of primary infection [304], and the change in pVL is substantially larger [16, 364].

There are problems with using the empirical data presented here to parameterise these models, because the structure of the models means that HIV transmission is assumed to occur instantaneously upon partnership formation. One problem in using per partnership data in this chapter to parameterise the models is that sexual partnerships will very often traverse more than one stage of infection of the index case. Table 3.17 summarises data on per contact and per partnership HIV transmission probability by stage of infection. Estimates per sexual contact, despite their limitations, are generally more specific concerning stage of infection than estimates per partnership, which typically involve long durations of partnerships, spanning more than one stage of HIV infection with different intrinsic transmission probabilities.

In exploring the infectiousness by stage, an average transmission probability can be derived using the transmission probability by stage and the average length of time within each stage. The average transmission probability per partnership for HIV infections is defined by equation 3.2:

$$\overline{\beta}_S^U = \frac{\sum_{j=1}^{10} \beta_{Sj}^U / \left(\phi_{Sj}^U + \mu\right) + \beta_{S11}^U / \left(\nu + \mu\right)}{\sum_{j=1}^{10} 1/\left(\phi_{Sj}^U + \mu\right) + 1/\left(\nu + \mu\right)} \qquad (3.2)$$

where $\overline{\beta}_S^U$ is the average transmission probability across all infection stages, β_{Sj}^U is the transmission probability for stage j, ν is the AIDS death rate, μ is the background death rate and ϕ_{Sj}^U is the progression rate to the next HIV stage (the incubation stage is divided into eight separate stages, each with ϕ_{Sj}^U =1). Stage $j = 11$ represents AIDS.

The average durations in each infection stage are assumed to be approximately six weeks, eight years, one year and one year each for primary infection, incubation, pre-AIDS and AIDS, respectively (ignoring the effect of the background death rate μ). By assuming an average HIV transmission probability per partnership of 30.6% (the median value for estimates from resource-poor settings for combined M→F and F→M transmission, Table 3.2) and that a is 50, the transmission probability per partnership at each stage can be calculated. However, in estimating particular infectiousness values, the relative magnitude of the infectiousness by stage must be constrained so that it does not exceed 100%. Therefore this combination of parameters cannot be used because it produces infection probabilities of more than 100% for primary infection and AIDS. Even constraining parameter a so that the maximum transmission probability is 100% (equation 3.3) does not produce ideal results: β_{Sinc}^U = 21% and a= 5.5. These values produce the correct average transmission probability, but do not reflect the difference in infectiousness between HIV infection stages.

$$a\beta_{Sinc}^U = 1 \qquad (3.3)$$

where β_{Sinc}^U is the transmission probability per partnership during the incubation stage.

For models investigating the impact of ART, treatment is only initiated at late stage infection, and so infectiousness at this stage is important to parameterise well. In order to model transmission probability per partnership at late stage infection (pre-AIDS and AIDS), the values chosen are β_{Sinc}^U = 3% and a= 18. This ensures a large enough difference in infectiousness between the stages, which is consistent with Wawer et al [304], yet ensures some transmission per partnership during the incubation period, and an average transmission probability for the symptomatic periods (40.5%) that is comparable to empirical data, particularly for Quinn et al [230], which uses data from resource-poor settings (Table 3.17, Figure 3.9). The fit to estimates of infectiousness for asymptomatic HIV infection is poor; the underestimate is due to the short duration of primary infection, when the majority of

partners will probably have become infected in the empirical datasets. However, the parameters denoting sexual activity are also not known with certainty, and so the fitting of the model to prevalence data from resource-poor settings corrects for this. (An alternative solution would have been to remove the primary infection stages from the structure of the model and have one asymptomatic stage with an average per partnership transmission probability.)

This analysis helps in defining stage-specific transmission probabilities but is fundamentally undermined by the lack of an explicit partnership duration in the model structure. Such an explicit partnership would allow explicit calculations for transmission by sex act and by stage of infectiousness. However, despite the problems of realism, the rate of partner change has been used for the models in Chapters 4 to 6 because it was initially more tractable. It would be sensible in future work to extend the analysis to partnership models, allowing explicit empirical estimates to be used.

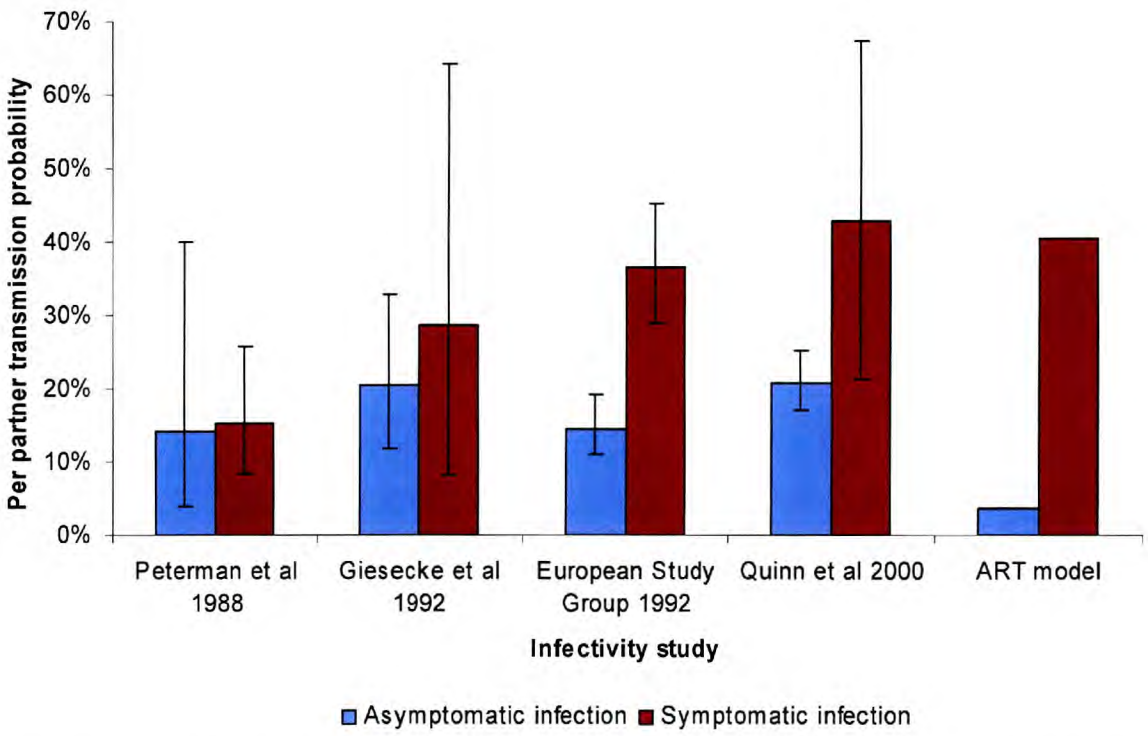


Figure 3.9 Per partnership transmission probability estimates by stage of infection of index case (asymptomatic or symptomatic) – comparison with ART model parameters.

3.8 Discussion

Estimates of both per partner and per contact sexual HIV transmission probabilities show considerable heterogeneity. While a meta-analysis for per partner infectiousness is presented, it is not appropriate to use summary estimates from such heterogeneous data and from studies with such different patterns of risk factors present as concrete evidence. While a random effects model can moderate the effect of heterogeneity for some analyses, in the case of HIV transmission, the influence of risk factors is so great that only analyses on subsets of similar studies may be reliable. However, such stratification restricts the number of studies used in each analysis. Nonetheless, the meta-analysis presented here is informative, but at a more qualitative level, identifying trends in estimates between risk groups, such as between research settings or by direction of transmission, M→F or F→M. The results suggest that per partner transmission probabilities are higher in resource-poor than industrialised research settings, higher for M→F than F→M transmission and higher for symptomatic rather than asymptomatic infection of the index case, yet these patterns generally were not statistically significant because of the high degree of heterogeneity and small numbers of studies. However, the rigorous methods used for meta-analysis of intervention studies, typically randomised control trials with large numbers of study participants, have to be compromised when attempting to estimate outcomes such as pathogen transmission probabilities, where the data available tend to be of limited quantity and quality and are usually collected retrospectively. For a variety of practical and ethical reasons, directly measuring the risk that an individual will infect a susceptible individual is extremely difficult [370].

This review of sexual HIV transmission probabilities has highlighted the difficulties in estimating many of the key parameters required for mathematical modelling of STIs and other infectious diseases. Despite the effort required to gather sufficient data, often these are of limited quality. The choice of which studies to cite and use for parameterisation may drastically alter model output. A sensitivity analysis may be useful if it examines parameter values within the range of possibilities predicted by data (or even beyond), but sometimes very little support for a given range is given. On the other hand, a wide degree of uncertainty may lead to uninformative results. While results from this review have aided parameterisation of infectiousness for the models described in the following chapters, future models incorporating an explicit partnership duration (pair or individual based models) will be able to make more direct use of these empirical estimates.

Chapter 4 Model definition and parameter assignment

Summary

A deterministic model of HIV transmission incorporating ART and stratifying infection progression into stages is presented. The model population is divided into four sexual activity groups, and is calibrated to the fast-growing, mature HIV epidemic observed in urban Malawi. The model provides the framework for investigating the impact of various treatment scenarios, the results of which are presented in Chapter 5.

In order to simulate ART provision with a sufficient degree of realism, the model requires estimation of a large number of parameters. Estimating many of these values involves a substantial degree of uncertainty, which can to some extent be compensated by uncertainty or sensitivity analyses. However, such measures cannot replace evidence-based estimation of key parameters. While there may be limitations in accuracy and reliability of many data sources, all evidence can be informative in determining what range of parameter values is sensible. A review of the literature and previous ART modelling studies provided the evidence to parameterise the model as accurately as possible, with ranges for key parameters also used for sensitivity analyses in cases of uncertainty.

4.1 Model description

A compartmental deterministic mathematical model describing HIV transmission and ART use was constructed. The basic structure of the model is illustrated in Figure 4.1. The model tracks two HIV strains, one resistant to ART and one sensitive. Each compartment of infected individuals has a defined infectiousness determined by treatment status and viral resistance type. Superinfection is only incorporated for individuals undergoing successful treatment for an ART-sensitive infection, where superinfection with an ART-resistant strain can occur. It is assumed that treatment failure (defined as viral rebound or failure to achieve viral suppression) precedes resistance evolution.

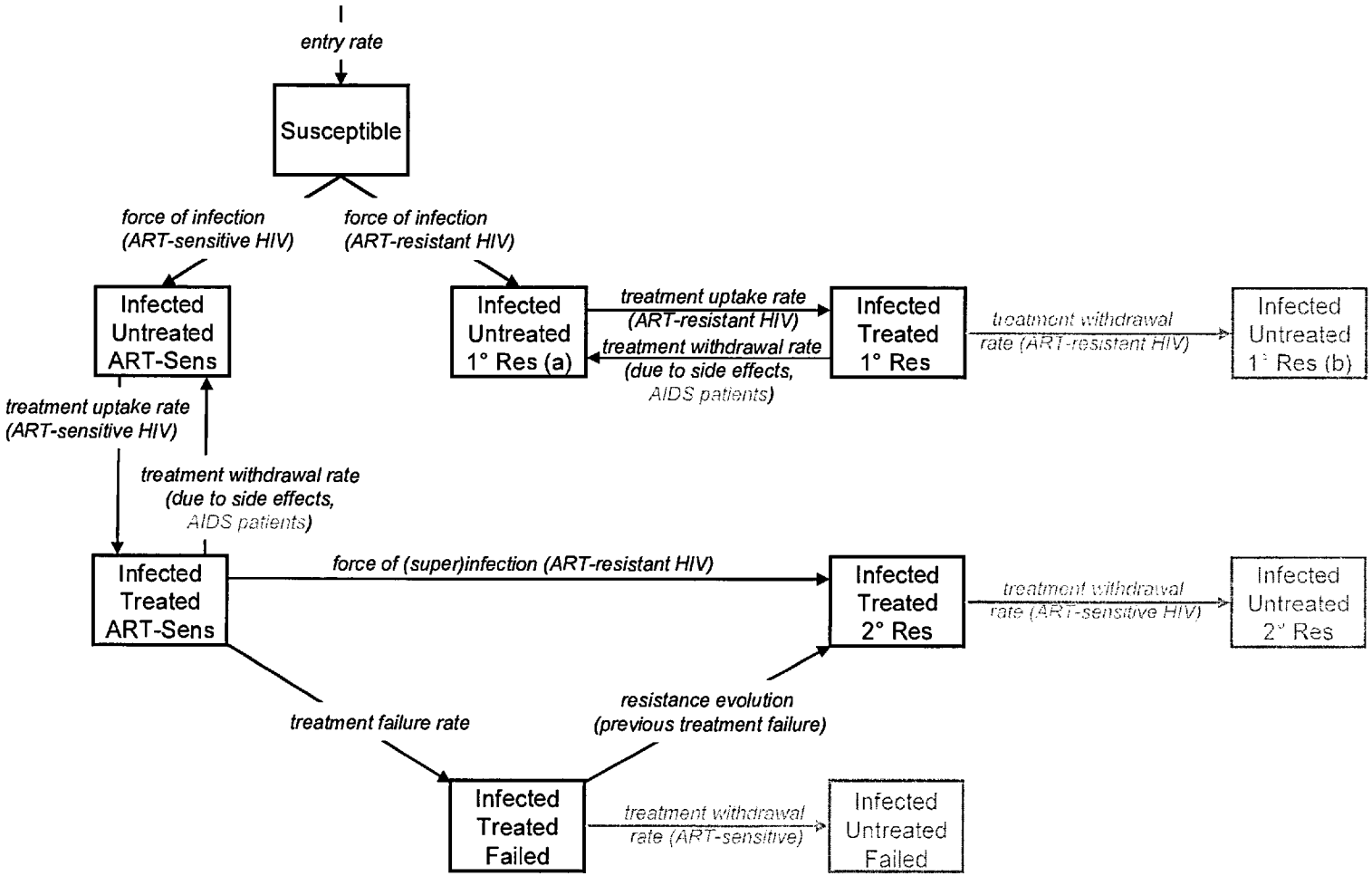


Figure 4.1 Schematic illustration of the structure of the HIV transmission model.
For clarity, stages of infection (primary infection, incubation, pre-AIDS and AIDS) and death rates are not shown. "1° Res" denotes those with primary (transmitted) resistance, while "2° Res" denotes those with secondary (acquired) resistance. "ART-Sens" denotes people infected with ART-sensitive virus. Treatment withdrawal, used in some scenarios, is shown in grey.

The state variables and transmission equations for the model are shown in section 4.1.1. The model assumes that there is a single, standard triple combination therapy regimen, with no second line or salvage therapy available for those who experience treatment failure. The WHO guidelines for ART use in resource-poor settings recommend at least one combination salvage therapy option [108]. However, it may not be realistic in all regions, especially where access to first-line therapy must be rationed, and the assumption of one ART regimen only is an appropriate starting point for analysis. The provision of second-line therapy and issues such as when to switch to a salvage regimen are explored in Chapter 6. In the model, an ART-resistant strain refers to strains resistant to the triple regimen rather than to individual drugs within that regimen. It is assumed that there is no pre-existing background level of resistance in the population generated by ART drug use outside the modelled ART programme. The model was solved numerically using the Runge-Kutte four algorithm in Berkeley Madonna version 8.0.1, but programmed concurrently using C for validation.

Superinfection with an ART-resistant strain is possible for treated individuals with viral suppression only, because these are the only individuals without viral outgrowth, and thus will have a pool of target cells which renders them susceptible to re-infection. Rates of treatment failure are determined by parameter f. All drug resistance evolves as a consequence of treatment failure, because of viral replication in the presence of continued drug pressure, and is determined by parameter κ. Parameter assignment is discussed in sections 4.2 to 4.13. Life years gained for each scenario were calculated by summation of the total number alive over time and comparing with the no treatment scenario. Person years of treatment were calculated by summation of the total number on treatment over time.

The model is stratified into four distinct HIV infection stages with different associated infectiousness: primary infection, incubation, pre-AIDS and AIDS. The HIV infection stages are 11 groups $j = 1..11$, where $j = 1$ is primary infection, $j = 10$ is pre-AIDS, $j = 11$ is AIDS and the eight groups $j = 2...9$, each of mean duration one year before progression to the next group, represent the incubation period. The incubation period is divided into eight compartments, with an average duration in each of one year, in order to approximate the average time spent in this stage more accurately than by using a negative exponential distribution.

Partnerships in this type of model occur instantaneously. The model includes four sexual activity classes, but it does not distinguish between genders because this is not required for the research questions being investigated. The sexual activity classes are defined in the model equations by four groups $i = 1..4$, with group one having the highest activity and group four the lowest. A small proportion of the population (0.1%) is in the highest activity class; 26%, 59% and 15% make up the lower classes, respectively. Upon developing AIDS, all individuals move to the lowest activity class $i = 4$, reflecting decreased sexual activity with increasing severity of disease.

Patients starting ART spend an average of six months in an 'initial' compartment (see schematic, Figure 4.2). For AIDS patients in the 'initial' period, the assumed effects of ART on sexual activity are not yet imposed – they are still too ill to increase their sexual activity. For pre-AIDS patients, with milder disease, the decrease in sexual activity (dropping to the next lowest sexual activity class) assumed to follow diagnosis and effective counselling occurs straight away. It is assumed that they are still well enough to be maintaining the same sexual activity as during the incubation period.

The incorporation of these 'initial' compartments allows for different treatment outcomes for AIDS and pre-AIDS patients initiating ART. On leaving this phase, a fraction of patients drops out (due to tolerability problems) and returns to the untreated compartment at the same infection stage (pre-AIDS or AIDS). The fraction which drops out is higher for AIDS patients than for pre-AIDS patients due to IRIS. A substantial proportion of treated AIDS patients die after leaving this stage, reflecting the high mortality observed in the first few months of treatment for those at late stage infection [25]. All other patients move to "successfully" or "unsuccessfully" treated compartments, from which point patients initiating ART at AIDS and pre-AIDS have the same progression rates through the treatment stages $m = 1..9$ where stage 9 defines a resurgence of ADCs, as illustrated in Figure 4.2. A fraction $1-\theta_4$ of AIDS patients increase their sexual activity by moving to sexual activity group $i = 3$. This reflects patients feeling well enough to increase their sexual activity, but also having been counselled on risk reduction as part of the treatment programme. For simplicity, this effect does not wane with time. These are the baseline assumptions regarding risk behaviour change of HIV patients upon initiating ART. Resurgence of clinical symptoms is modelled as progression through eight treatment stages without symptoms before development of a new ADC upon entering the ninth compartment, when all patients revert back to the lowest sexual activity group because of disease progression. "Successful" treatment is defined as long-term viral suppression, while "unsuccessful" treatment is viral outgrowth (treatment failure). A fraction of patients fail treatment each year, from which point their progression through the stages to AIDS is faster. Patients may also develop resistance as a result of treatment failure, or become superinfected with ART-resistant virus. In the case of primary resistance, there is also staged progression back to AIDS upon treatment initiation, but for simplicity, there is no 'initial' period (this is group is relatively small).

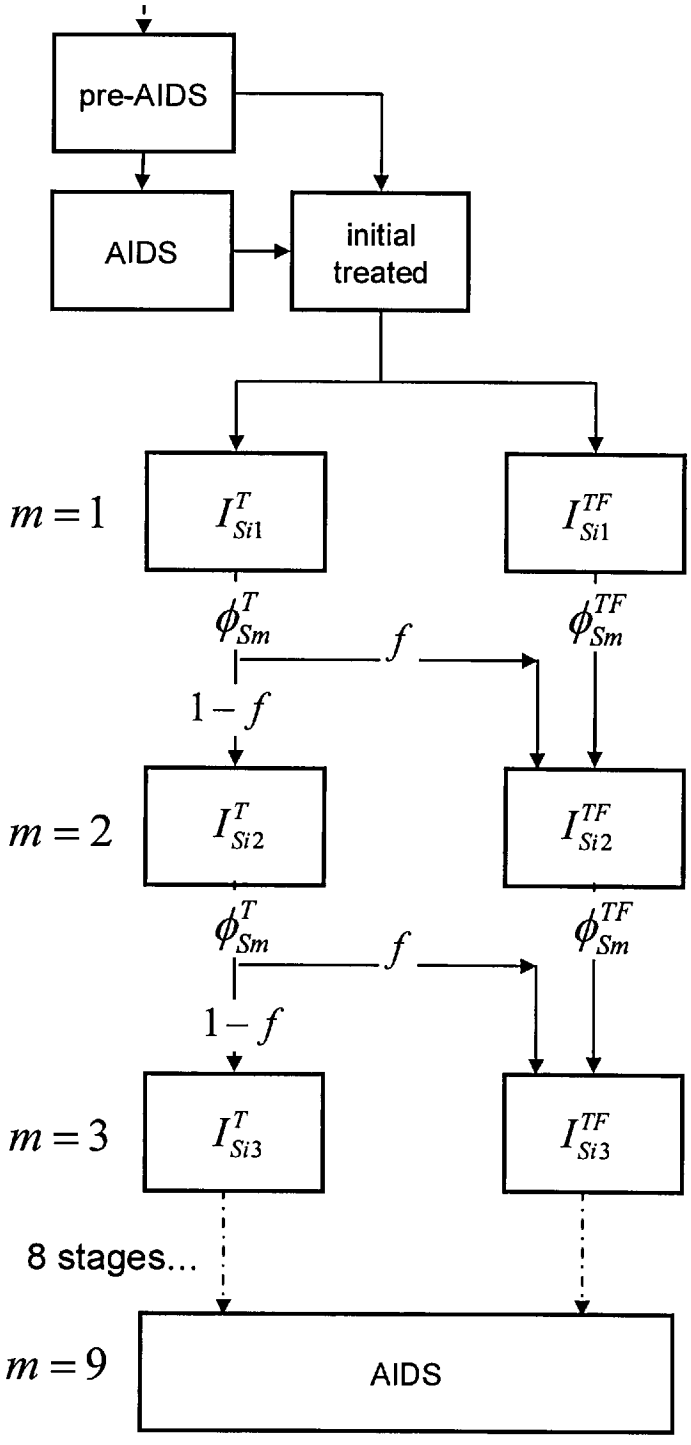


Figure 4.2 Schematic illustration of the structure of the treatment stages of the HIV transmission model.

i refers to sexual activity group while m refers to treatment stage. T is successfully treated (no viral rebound), F is viral rebound. A proportion of those successfully treated leaving each treatment stage move to next treatment failure compartment. For simplicity, ART resistance has been omitted.

4.1.1 State variables

For individuals in sexual activity class i, HIV infection stage j and treatment stage m (where applicable):

S_i = susceptible individuals $\{i = 1..4\}$

I_{Sij}^{U} = ART-sensitive HIV infected individuals, untreated $\{i = 1..4, j = 1..11\}$

I_{Sim}^{T} = ART-sensitive HIV infected individuals, treated $\{i = 1..4, m = 1..9\}$

I_{SPi}^{Temp} = ART-sensitive HIV infected individuals in the 'initial' phase (pre-AIDS patients) $\{i = 1..4\}$

I_{SA}^{Temp} = ART-sensitive HIV infected individuals in the 'initial' phase (AIDS patients)

I_{Sim}^{TF} = ART-sensitive HIV infected individuals, treated but viral rebound $\{i = 1..4, m = 1..9\}$

I_{Sim}^{UF} = ART-sensitive HIV infected individuals withdrawn from treatment $\{i = 1..4, m = 1..9\}$

I_{R2im}^{T} = ART-resistant HIV infected individuals, treated (secondary resistance) $\{i = 1..4, m = 1..9\}$

I_{R2im}^{U} = ART-resistant HIV infected individuals, untreated (secondary resistance) $\{i = 1..4, m = 1..9\}$

I_{R1aij}^{U} = ART-resistant HIV infected individuals (primary resistance), untreated $\{i = 1..4, j = 1..11\}$

I_{R1im}^{T} = ART-resistant HIV infected individuals (primary resistance), treated $\{i = 1..4, m = 1..9\}$

I_{R1bim}^{U} = ART-resistant HIV infected individuals (primary resistance), withdrawn from treatment $\{i = 1..4, m = 1..9\}$

N_i = total in sexual activity group i $\{i = 1..4\}$

4.1.2 Other terms

λ_{Si} = force of infection for ART-sensitive virus phenotype

λ_{Ri} = force of infection for ART-resistant virus phenotype

4.1.3 Transmission equations

The ordinary differential equations which define the model are shown below. A description and values for all parameters used in the following equations are given provided in sections 4.2 to 4.13.

(4.1) $S_i' = \theta_i \chi N_0 - S_i\left(\lambda_{Si} + \lambda_{Ri} + \mu\right)$ $\{i = 1..4\}$

(4.2) $I_{Sij}^{U\prime} = \lambda_{Si} S_i - I_{Sij}^{U}\left(\phi_{Sj}^{U} + \mu + \gamma_{Sj}\right)$ $\{i = 1..4, j = 1\}$

(4.3) $I_{Sij}^{U\prime} = \phi_{Sj-1}^{U} I_{Sij-1}^{U} - I_{Sij}^{U}\left(\phi_{Sj}^{U} + \mu + \gamma_{Sj}\right)$ $\{i = 1..4, j = 2..9\}$

(4.4) $I_{Sij}^{U\prime} = \phi_{Sj-1}^{U} I_{Sij-1}^{U} + PZI_{SPi}^{Temp} - I_{Sij}^{U}\left(\phi_{Sj}^{U} + \mu + \gamma_{Sj}\right)$ $\{i = 1..4, j = 10\}$

(4.5) $I_{Sij}^{U\prime} = \Theta_i + \phi_{Sj-1}^{U} \mathrm{H}_{Sij}^{U} - I_{Sij}^{U}\left(\nu + \mu + \gamma_{Sj}\right)$ $\{i = 1..4, j = 11\}$

(4.6) $I_{SPi}^{Temp\prime} = \Lambda_i - I_{SPi}^{Temp}\left(P + \mu\right)$ $\{i = 1..4\}$

(4.7) $I_{SA}^{Temp\prime} = \gamma_{Sj} I_{Sij}^{U} - I_{SA}^{Temp}\left(P + \mu\right)$ $\{i = 4, j = 11\}$

(4.8) $I_{Sim}^{T\prime} = P\left(1 - Z - f\right) I_{SPi}^{Temp} + P\left(1 - Z_P - f_P - \nu_{ST}^{P}\right)\mathrm{K}_i I_{SA}^{Temp} - I_{Sim}^{T}\left(\phi_{Sm}^{T} + \mu + \alpha_{Sm}^{T}\right)$ $\{i = 1..4, m = 1\}$

(4.9) $I_{Sim}^{T\prime} = \left(1 - f - \lambda_{Ri} - Z\right)\phi_{Sm-1}^{T} I_{Sim-1}^{T} - I_{Sim}^{T}\left(\phi_{Sm}^{T} + \mu + \alpha_{Sm}^{T}\right)$ $\{i = 1..4, m = 2..8\}$

(4.10) $I_{Sim}^{T\prime} = \left(1 - f - \lambda_{Ri} - Z\right)\phi_{Sm-1}^{T} \mathrm{H}_{Sim}^{T} - I_{Sim}^{T}\left(\nu + \mu + f + \lambda_{Ri} + Z + \alpha_{Sm}^{T}\right)$ $\{i = 1..4, m = 9\}$

(4.11) $I_{Sim}^{TF\prime} = Pf I_{SPi}^{Temp} + Pf_P \mathrm{K}_i I_{SA}^{Temp} - I_{Sim}^{TF}\left(\phi_{Sm}^{TF} + \mu + \alpha_{Sm}^{TF}\right)$ $\{i = 1..4, m = 1\}$

(4.12) $I_{Sim}^{TF\prime} = f\phi_{Sm-1}^{T} I_{Sim-1}^{T} + \left(1 - \kappa - Z\right)\phi_{Sm-1}^{TF} I_{Sim-1}^{TF} - I_{Sim}^{TF}\left(\phi_{Sm}^{TF} + \mu + \alpha_{Sm}^{TF}\right)$ $\{i = 1..4, m = 2..8\}$

(4.13) $I_{Sim}^{TF\prime} = f\left(I_{Sim}^{T} + \phi_{Sm-1}^{T} \mathrm{H}_{Sim}^{T}\right) + \left(1 - \kappa - Z\right)\phi_{Sm-1}^{TF} \mathrm{H}_{Sim}^{TF} - I_{Sim}^{TF}\left(\nu + \mu + \kappa + Z + \alpha_{Sm}^{TF}\right)$ $\{i = 1..4, m = 9\}$

(4.14) $I_{R2im}^{T\prime} = \lambda_{Ri}\phi_{Sm-1}^{T} I_{Sim-1}^{T} + \kappa\phi_{Sm-1}^{TF} I_{Sim-1}^{TF} + \left(1 - Z\right)\phi_{Rm-1}^{T} I_{R2im-1}^{T} - I_{R2im}^{T}\left(\phi_{Rm}^{T2} + \mu + \alpha_{Rm}^{T2}\right)$ $\{i = 1..4, m = 1..8\}$

(4.15) $I_{R2im}^{T\prime} = \lambda_{Ri}\left(I_{Sim}^{T} + \phi_{Sm-1}^{T} \mathrm{H}_{Sim}^{T}\right) + \kappa\left(I_{Sim}^{TF} + \phi_{Sm-1}^{TF} \mathrm{H}_{Sim}^{TF}\right) + \left(1 - Z\right)\phi_{Rm-1}^{T} \mathrm{H}_{R2im}^{T} - I_{R2im}^{T}\left(\nu + \mu + \alpha_{Rm}^{T2}\right)$ $\{i = 1..4, m = 9\}$

(4.16) $I_{Sim}^{UF\prime} = \left(Z\phi_{Sm-1}^{T} + \alpha_{Sm-1}^{T}\right) I_{Sim-1}^{T} + \left(Z\phi_{Sm-1}^{TF} + \alpha_{Sm-1}^{TF}\right) I_{Sim-1}^{TF} + \phi_{Sm-1}^{UF} I_{Sim-1}^{UF} - I_{Sim}^{UF}\left(\phi_{Sm}^{U} + \mu\right)$ $\{i = 1..4, m = 1..8\}$

$$(4.17)\quad I_{Sim}^{UF\prime} = \left(Z+\alpha_{Sm}^{T}\right)I_{Sim}^{T} + \left(Z\phi_{Sm-1}^{T}+\alpha_{Sm-1}^{T}\right)\mathrm{H}_{Sim}^{T} + \left(Z+\alpha_{Sm}^{TF}\right)I_{Sim}^{TF} + \left(Z\phi_{Sm-1}^{TF}+\alpha_{Sm-1}^{TF}\right)\mathrm{H}_{Sim}^{TF} + \phi_{Sm-1}^{UF}\mathrm{H}_{Sim}^{UF} - I_{Sim}^{UF}\left(\nu+\mu\right) \quad \{i=1..4, m=9\}$$

$$(4.18)\quad I_{R2im}^{U\prime} = \left(Z\phi_{Rm-1}^{T}+\alpha_{Rm-1}^{T2}\right)I_{R2im-1}^{T} + \phi_{Rm-1}^{U2}I_{R2im-1}^{U} - I_{R2im}^{U}\left(\phi_{Rm}^{U2}+\mu\right) \quad \{i=1..4, m=1..8\}$$

$$(4.19)\quad I_{R2im}^{U\prime} = \left(Z+\alpha_{Rm}^{T2}\right)I_{R2im}^{T} + \left(Z\phi_{Rm-1}^{T}+\alpha_{Rm-1}^{T2}\right)\mathrm{H}_{R2im}^{T} + \phi_{Rm-1}^{U2}\mathrm{H}_{R2im}^{U} - I_{R2im}^{U}\left(\nu+\mu\right) \quad \{i=1..4, m=9\}$$

$$(4.20)\quad I_{R1aij}^{U\prime} = \lambda_{Ri}S_i - I_{R1aij}^{U}\left(\phi_{Rj}^{U1}+\mu+\gamma_{Rj}\right) \quad \{i=1..4, j=1\}$$

$$(4.21)\quad I_{R1aij}^{U\prime} = \phi_{Rj-1}^{U1}I_{R1aij-1}^{U} - I_{R1aij}^{U}\left(\phi_{Rj}^{U1}+\mu+\gamma_{Rj}\left(1-Z\right)\right) \quad \{i=1..4, j=2..10\}$$

$$(4.22)\quad I_{R1aij}^{U\prime} = \phi_{Rj-1}^{U1}\mathrm{H}_{R1aij}^{U} - I_{R1aij}^{U}\left(\nu+\mu+\gamma_{Rj}\left(1-Z_P\right)\right) \quad \{i=1..4, j=11\}$$

$$(4.23)\quad I_{R1im}^{T\prime} = \left(1-Z\right)\tau_i + \left(1-\nu_{ST}^{P}-Z_P\right)\mathrm{K}_i\gamma_{R11}I_{R1ai11}^{U} - I_{R1im}^{T}\left(\phi_{Rm}^{T1}+\mu+\alpha_{Rm}^{T1}\right) \quad \{i=1..4, m=1\}$$

$$(4.24)\quad I_{R1im}^{T\prime} = \left(1-Z\right)\phi_{Rm-1}^{T}I_{R1im-1}^{T} - I_{R1im}^{T}\left(\phi_{Rm}^{T1}+\mu+\alpha_{Rm}^{T1}\right) \quad \{i=1..4, m=2..8\}$$

$$(4.25)\quad I_{R1im}^{T\prime} = \left(1-Z\right)\phi_{Rm-1}^{T}\mathrm{H}_{R1im}^{T} - I_{R1im}^{T}\left(\nu+\mu+Z+\alpha_{Rm}^{T1}\right) \quad \{i=1..4, m=9\}$$

$$(4.26)\quad I_{R1bim}^{U\prime} = \left(Z\phi_{Rm-1}^{T}+\alpha_{Rm-1}^{T1}\right)I_{R1im-1}^{T} + \phi_{Rm-1}^{U2}I_{R1bim-1}^{U} - I_{R1bim}^{U}\left(\phi_{Rm}^{U2}+\mu\right) \quad \{i=1..4, m=1..8\}$$

$$(4.27)\quad I_{R1bim}^{U\prime} = \left(Z\phi_{Rm-1}^{T}+\alpha_{Rm-1}^{T1}\right)\mathrm{H}_{R1im}^{T} + \left(Z+\alpha_{Rm}^{T1}\right)I_{R1im}^{T} + \phi_{Rm-1}^{U2}\mathrm{H}_{R1bim}^{U} - I_{R1bim}^{U}\left(\nu+\mu\right) \quad \{i=1..4, m=9\}$$

where:

$$\phi_{Sj}^{U} = \phi_{Rj}^{U1} = 0 \quad \{j=0\}$$

$$\phi_{Sm}^{T} = \phi_{Sm}^{TF} = \phi_{Rm}^{T} = \phi_{Rm}^{U2} = 0 \quad \{m=0\}$$

$$\Theta_i = 0\ \{i=1..3\}\quad \Theta_i = PZ_P I_{SA}^{Temp}\ \{i=4\} \quad \{j=11\}$$

$$\Lambda_i = 0\ \{i=1\}\quad \Lambda_i = \gamma_{Sj}I_{Si-1,j}^{U}\ \{i=2..3\}\quad \Lambda_i = \gamma_{Sj}\left(I_{Si-1,j}^{U}+I_{Sij}^{U}\right)\{i=4\} \quad \{j=10\}$$

$$\mathrm{K}_i = 0\ \{i=1..2\}\quad \mathrm{K}_i = 1-\theta_4\ \{i=3\}\quad \mathrm{K}_i = \theta_4\ \{i=4\}$$

$$\tau_i = 0\ \{i=1\}\quad \tau_i = \gamma_{Rj}I_{R1ai-1j}^{U}\ \{i=2..3\}\quad \tau_i = \gamma_{Rj}\left(I_{R1ai-1j}^{U}+I_{R1aij}^{U}\right)\{i=4\} \quad \{j=10\}$$

$$\mathrm{H}_{xin}^{y} = 0\ \{i=1..3\}\quad \mathrm{H}_{xin}^{y} = \sum_{i=1}^{4} I_{xin-1}^{y}\ \{i=4\} \quad \{n=1..11\}$$

where

$x = S, R1, R1a, R1b, R2$

$y = U, T, TF, UF$

The forces of infection for ART-sensitive (λ_{Si}) and ART-resistant (λ_{Ri}) HIV are given below. They are determined by the infectiousness of individuals in each compartment (β), the probability that

ART-resistant rather than ART-sensitive virus is transmitted in the case of mixed infections (ω), the rate of sexual partner change for individuals in sexual activity group i (c_i) and the proportion of the total population infected with each strain. The probability that a partnership made by an individual in sexual activity group i is made with an individual in sexual activity group k is determined by the mixing matrix ρ_{ik}. The probability that such an individual is infected is the total number from all infected compartments in group k, divided by the total size of group k in the population (N_k). The infected compartments include the 11 stages of untreated infection, denoted by j, the nine treatment stages, denoted by m, and individuals in the 'initial' phases of treatment. The force of infection is equivalent to the incidence rate per susceptible individual.

$$(4.28)\quad \lambda_{Si} = c_i \sum_{k=1}^{4} \frac{\rho_{ik}}{N_k} \left(\begin{array}{l} \sum_{j=1}^{11} \left(\beta_{Sj}^{U} I_{Sij}^{U} + \left(1-\omega_{Uj}^{1}\right) \beta_{Rj}^{U1} I_{R1aij}^{U} \right) + \beta_{S1}^{T} I_{SPi}^{Temp} + \beta_{S9}^{T} I_{SA}^{Temp} + \\ \sum_{m=1}^{9} \left(\begin{array}{l} \beta_{Sm}^{UF} I_{Sim}^{UF} + \beta_{Sm}^{TF} I_{Sim}^{TF} + \beta_{Rm}^{U2} \left[\left(1-\omega_{U}^{2}\right) I_{R2im}^{U} + \left(1-\omega_{Um}^{1}\right) I_{R1bim}^{U} \right] \\ + \beta_{Rm}^{T} \left[\left(1-\omega_{T}^{2}\right) I_{R2im}^{T} + \left(1-\omega_{T}^{1}\right) I_{R1im}^{T} \right] + \beta_{Sm}^{T} I_{Sim}^{T} \end{array} \right) \end{array} \right)$$

(4.29)

$$\lambda_{Ri} = c_i \sum_{k=1}^{4} \frac{\rho_{ik}}{N_k} \left(\sum_{j=1}^{11} \beta_{Rj}^{U1} \omega_{Uj}^{1} I_{R1aij}^{U} + \sum_{m=1}^{9} \left(\beta_{Rm}^{U2} \left(\omega_{U}^{2} I_{R2im}^{U} + \omega_{Um}^{1} I_{R1bim}^{U} \right) + \beta_{Rm}^{T} \left(\omega_{T}^{2} I_{R2im}^{T} + \omega_{T}^{1} I_{R1im}^{T} \right) \right) \right)$$

where

(4.30)

$$N_i = S_i + I_{SPi}^{Temp} + \mathrm{B}_i I_{SA}^{Temp} + \sum_{j=1}^{11} \left(I_{Sij}^{U} + I_{R1aij}^{U} \right) + \sum_{m=1}^{9} \left(I_{Sim}^{T} + I_{Sim}^{TF} + I_{Sim}^{UF} + I_{R2im}^{T} + I_{R2im}^{U} + I_{R1im}^{T} + I_{R1bim}^{U} \right)$$

where $\mathrm{B}_i = 0 \ \{i = 1..3\}$ $\mathrm{B}_i = 1 \ \{i = 4\}$

4.1.4 Mixing matrix definition

ρ_{ik} denotes the probability that, given an individual in sexual activity class i forms a sexual partnership, the partnership is with a member of sexual activity class k. The value of ρ_{ik} depends on the pattern of mixing which could vary from fully assortative, where partnerships only form within the same activity class, to random, where partnerships form randomly between different activity classes.

$$(4.31)\quad \rho_{ik} = \varepsilon \delta_{lm} + \left(1-\varepsilon\right) c_k \frac{N_k}{\sum_{i=1}^{4} c_i N_i}$$

where $\delta_{lm} = 1$ when $l = m$ and $\delta_{lm} = 0$ when $l \neq m$. ε describes the pattern of mixing between individuals by sexual activity class (0 = fully assortative, 1 = random).

Infectiousness of individuals varies with stage of infection. The model assumes that individuals with primary infection and AIDS (stages one and 11) have a higher degree of infectiousness than individuals in the incubation period (stages two to nine) by factor a. For individuals with pre-AIDS (stage 10), it is by factor $a/2$:

(4.32) $\beta_{Sj}^{U} = a\beta_{S}^{U} \quad \{j = 1,11\}$

(4.33) $\beta_{Sj}^{U} = \beta_{S}^{U} \quad \{j = 2..9\}$

(4.34) $\beta_{Sj}^{U} = \frac{a}{2}\beta_{S}^{U} \quad \{j = 10\}$

4.1.5 Treatment

ART introduction is delayed until the start time by switching γ_{Sj} and γ_{Rj} from 0 to their experimental values at time = start time. For scenarios where a limited number of individuals can receive treatment at one time, the following algorithm was used in order to ensure that numbers treated did not exceed programme capacity:

(4.35) $\gamma_{Sj} = T_{Sj}\left(1 - (\zeta / \Omega)^{5}\right)$

where:

T_{Sj} is the experimental treatment uptake value for those infected with ART-sensitive HIV and at infection stage j and Ω is the maximum number allowed on treatment at any time.

(4.36) $\zeta = \sum_{m}\left(I_{Sm}^{T} + I_{Sm}^{TF} + I_{R2m}^{T} + I_{R1m}^{T}\right)$, the total number currently receiving ART.

The exponent in equation (4.35) is set to five in order to maintain γ_{Sj} as high as possible when the total number on treated ζ drops below the total number that can be treated, Ω. This ensures that the number on treatment at any time is maintained as close to capacity as possible (when demand outstrips supply) by ensuring γ_{Sj} is as close to the value of T_{Sj} as possible when the number treated falls below capacity. (However, the difference in numbers on treatment, ζ, between this value of the exponent and smaller values is not actually that great. Running the model with treatment of AIDS and pre-AIDS patients using baseline parameters from Table 4.1, best case scenario and initiating treatment in 2010, 10 years after ART introduction the number on treatment using an exponent value of five in equation (4.35) is 4996, compared to a value of 4982 when the exponent is set to one.) A

sufficiently small time step size is required in order to ensure that this algorithm works correctly (0.005 years).

4.1.6 Pessimistic sexual behaviour assumptions

For the pessimistic behaviour change scenario for AIDS patients, K_i used in equations (8) and (23) above, is changed to:

$$\mathrm{K}_i = 0 \{i=1\} \ \mathrm{K}_i = 1-\theta_3-\theta_4 \{i=2\} \ \mathrm{K}_i = \theta_3 \{i=3\} \ \mathrm{K}_i = \theta_4 \{i=4\}$$

Therefore AIDS patients can move to sexual activity group 2 as well as groups 3 and 4 (the baseline assumption is that AIDS patients move to group 3 or remain in group 4 upon initiating ART).

For the pessimistic behaviour change scenario for pre-AIDS and AIDS patients, Λ_i and τ_i used in equations (4.6) and (4.23) respectively, are changed to:

$$\Lambda_i = \gamma_{Sj} I^U_{Sij} \qquad \{i=1..4, j=10\}$$

$$\tau_i = \gamma_{Rj} I^U_{R1aij} \qquad \{i=1..4, j=10\}$$

i.e. there is no behaviour change upon initiating treatment for pre-AIDS patients – their sexual activity class does not change (the baseline assumption is that each pre-AIDS patient moves to the next less active sexual activity group).

4.2 Parameter assignment

The model described in this chapter requires the estimation of a large number of parameters, many of which are not easy to quantify. All behavioural, demographic and biological parameters with baseline values, ranges for Latin Hypercube Sampling (LHS) sampling and values for best and worst case scenarios, where applicable, are shown in Table 4.1, along with sources justifying the estimates for each parameter, and with more detailed discussion provided in the text. While some information has been taken from previous modelling studies, the majority of parameter values have been arrived at after review of the literature. Detailed reviews for each parameter were impracticable due to time restraints, but the systematic review of HIV infectiousness for sexual HIV transmission described in Chapter 3 demonstrates the usefulness of thorough research in estimating key parameters used in HIV mathematical models. Rather than the citation of one or two sources, the publication of reviews such as Chapter 3 and Appendix D and more informal sharing of literature searches and summaries, such as the work presented in this chapter, may encourage more reliable parameterisation of such models. Such summaries would inform new researchers of a range of data and sources, allowing them to arrive at their own estimates and ranges, rather than adopting the values used in other models, in the most time-efficient manner.

Table 4.1 Summary of parameters used in the ART model

Symbol	Parameter Description	Baseline value (range)	Sources
Behavioural parameters			
c_i	Rate of partner change per year for individuals in sexual activity class i	152.8,13.6,0.5,0.2 partners per year (i = 1,2,3,4 respectively)	Estimated using the curve fit function in Berkeley Madonna in order to broadly represent the HIV epidemic in Malawi, using antenatal clinic prevalence data [371].
θ_i	Proportion recruited into sexual activity class i	0.1%,26%,59%,15% (i = 1,2,3,4 respectively)	
ε	Pattern of mixing (0= fully assortative, 1= random)	0.37	
Biological parameters			
β_S^U	Transmission probability per partnership from an untreated individual with ART-sensitive virus during the incubation period	3%	Baggaley et al 2004 [372] Chapter 3
a	Relative transmission probabilities per partnership for an untreated individual with ART-sensitive virus at infection stage j, $j = 1..11$	$a = 18$ $\beta_{S1}^U = 54\%, \beta_{S2..9}^U = 3\%$ $\beta_{S10}^U = 27\%, \beta_{S11}^U = 54\%$	Jacquez et al 1994 [16] Daar et al 1991 [364] Piatek et al 2003 [373] Quinn 1997 [374] Chapter 3
$1/\phi_{S1}^U$	Duration of primary infection stage for an untreated individual with ART-sensitive virus	1.5 months	Vanhems et al 2000 [375] Niu et al 1998 [376] Daar et al 1991 [364] Clark et al 1991 [377] Horsburgh et al 1989 [378]
$1/\phi_{S2..9}^U$	Duration of incubation stage (8 years in total, from stages 2 to 9) for an untreated individual with ART-sensitive virus	1 year	Crampin et al 2002 [379] Morgan & Whitworth 2001 [380] Sewankambo et al 2000 [107]
$1/\phi_{S10}^U$	Duration of pre-AIDS stage for an untreated individual with ART-sensitive virus	1 year	Fauci et al 1996 [366] Connor et al 1993 [381] Models: [200, 382]
ν	Duration before death with AIDS (all infection categories)	9 months	Kitayapom et al 1996 [383] Mulder et al 1994 [142] Sewankambo et al 2000 [107] Morgan et al 2000 [141] Gail et al 1997 [384] Chequer et al 1992 [385] Models: [199, 229, 382, 386]
Treatment parameters			
$\gamma_{S1..9}$, $\gamma_{R1..9}$	Rate of treatment uptake for untreated individuals (ART-sensitive and ART-resistant virus) during primary infection and incubation	0 year^{-1}	Experimental values. Changed in treatment scenarios, Chapter 5.
γ_{S10}, γ_{R10}	Rate of treatment uptake for untreated individuals (ART-sensitive and ART-resistant virus) during pre-AIDS	12 year^{-1}	Experimental values. Changed in treatment scenarios, Chapter 5.
γ_{S11}, γ_{R11}	Rate of treatment uptake for untreated individuals (ART-sensitive and ART-resistant virus) during AIDS	12 year^{-1}	Experimental values. Changed in treatment scenarios, Chapter 5.
κ	Fraction of treated patients with viral rebound developing resistance at each treatment stage	40% LHS range: 20-60%	Gallego et al 2002 [75] Weidle et al 2002 [132]

Symbol	Parameter Description	Baseline value (range)	Sources
Z	Fraction of treated patients who drop out after each treatment stage due to side effects	2% LHS range: 1-5%	Kumarasamy et al 2003 [97]
Z_P	Fraction of AIDS patients initiating ART who drop out due to side effects during the 'initial' phase	5% - best case scenario 15% - worst case scenario	Kumarasamy et al 2003 [97]
f	Fraction of treated patients who suffer viral rebound at each treatment stage	10% - best case scenario 30% - worst case scenario	Ledergerber et al 1999 [27] Lucas et al 2003 [41] Models: [188, 229]
f_P	Fraction of AIDS patients initiating ART who develop viral rebound or failure to suppress during the 'initial' phase	30% - best case scenario 50% - worst case scenario	Lucas et al 2003 [41] Rastegar et al 2003 [387] Deeks et al 1999 [42] Moore & Chaisson 1999 [46]
P	Exit rate from 'initial' phase for patients first starting ART	2 $year^{-1}$ (average duration: 6 months)	Moore & Chaisson 1999 [46] Tassie et al 2003 [121] Models: [228]
ν_{SP}^{T}	Fraction of AIDS patients initiating ART who die during the 'initial' phase	10% - best case scenario 20% - worst case scenario	Tassie et al 2003 [121] Lee et al 2001 [388]
$\phi_{S1..8}^{T}$	Rate of transfer to next treatment stage, successful viral suppression	1 $year^{-1}$ (average duration before progression to AIDS: 8 years)	Lucas et al 2003 [41]
ϕ_{S9}^{T}, ϕ_{S9}^{TF}, ϕ_{R9}^{T1}, ϕ_{R9}^{T2}, ϕ_{S9}^{UF}, ϕ_{R9}^{U2}	Rate of transfer to next treatment stage, stage 9	0 $year^{-1}$	All patients die of AIDS at rate ν
$\phi_{S1..8}^{TF}$, $\phi_{R1..8}^{T1}$, $\phi_{R1..8}^{T2}$	Rate of transfer to next treatment stage, treatment failure (duration before AIDS 80% of that for successful treatment)	1.25 $year^{-1}$ ($x\phi_{Sj}^{T}$ where x =1.25)	Lucas et al 2003 [41] Ledergerber et al 1999 [27]
$\phi_{S1..8}^{UF}$, $\phi_{R1..8}^{U2}$	Rate of transfer to next treatment stage after removal of ART (duration before AIDS 20% of that for successful treatment)	5 $year^{-1}$ ($y\phi_{Sj}^{T}$ where y =5)	Miller et al 2000 [145] Deeks et al 2001 [389]
$\phi_{R1..11}^{U1}$	Infection progression rate for ART-naive individuals with ART resistance (=$\phi_{S1..11}^{U}$)	$\phi_{R1}^{U1}=8$, $\phi_{R2..10}^{U1}=1$, $\phi_{R11}^{U1}=0$ $year^{-1}$	Miller et al 2000 [145] Deeks et al 2001 [389]
$\beta_{S1..8}^{T}$	Transmission probability per partnership from a treated individual with ART-sensitive virus, treatment stages 1 to 8 $\beta_{S1..8}^{T}=w\beta_{S10}^{U}$ where w = 2% (LHS range: 1-10%)	0.54% LHS range: 0.27-2.7%	Musicco et al 1994 [390] Perelson et al 1997 [3]
β_{S9}^{T}	Transmission probability per partnership from a treated individual with ART-sensitive virus, treatment stage 9 $\beta_{S9}^{T}=w\beta_{S11}^{U}$ where w = 2% (LHS range: 1-10%)	1.08% LHS range: 0.54-5.4%	Musicco et al 1994 [390] Perelson et al 1997 [3]
$\beta_{S1..8}^{TF}$, $\beta_{R1..8}^{T}$	Transmission probability per partnership from a treated individual with treatment failure and/or resistance, treatment stages 1 to 8 $\beta_{S1..8}^{TF}$, $\beta_{R1..8}^{T}=z\beta_{S10}^{U}$ where z = 75% (LHS range: 50-100%)	20.3% LHS range: 13.5-27%	Leigh Brown et al 2003 [83] Deeks et al 1999 [42]

Symbol	Parameter Description	Baseline value (range)	Sources
β_{S9}^{TF}, β_{R9}^{T}	Transmission probability per partnership from a treated individual with treatment failure and/or resistance, treatment stage 9 β_{S9}^{TF}, $\beta_{R9}^{T} = z\beta_{S11}^{U}$ where z = 75% (LHS range: 50-100%)	40.5% LHS range: 27-54%	Leigh Brown et al 2003 [83] Deeks et al 1999 [42]
$\beta_{R1..11}^{U1}$	Transmission probability per partnership from untreated, treatment-naïve individuals with primary (transmitted) resistance, infection stage j (= β_{Sj}^{U})	$\beta_{R1}^{U1} = 54\%, \beta_{R2..9}^{U1} = 3\%$ $\beta_{R10}^{U1} = 27\%, \beta_{R11}^{U1} = 54\%$	Assumes all untreated infections have equal infectiousness.
$\beta_{S1..8}^{UF}$, $\beta_{R1..8}^{U2}$	Transmission probability per partnership from untreated individuals withdrawn from treatment, stages 1 to 8 (= β_{S10}^{U})	27%	Assumes all untreated infections have equal infectiousness.
β_{S9}^{UF}, β_{R9}^{U2}	Transmission probability per partnership from untreated individuals withdrawn from treatment, stage 9 (= β_{S11}^{U})	54%	Assumes all untreated infections have equal infectiousness.
ω_U^2	Probability that an untreated individual with secondary (acquired) resistance transmits resistant rather than sensitive virus	5% LHS range: 0-10%	Little et al 1999 [391] Wainberg & Friedland 1998 [56]
ω_T^2	Probability that a treated individual with secondary (acquired) resistance transmits resistant virus rather than sensitive virus	30% LHS range: 20-40%	Leigh Brown et al 2003 [83]
ω_{U1}^1	Probability that an untreated individual with primary (transmitted) resistance and primary (acute) infection transmits resistant rather than sensitive virus	100% LHS range: 75-100%	Hance et al 2003 [392] Yerly et al 2002 [393]
$\omega_{U2..11}^1$	Probability that an untreated individual with primary (transmitted) resistance transmits resistant virus, all other stages of infection	5% LHS range: 0-10%	Hance et al 2001 [394] Nicastri et al 2003 [89]
ω_T^1	Probability that a treated individual with primary (transmitted) resistance transmits resistant rather than sensitive virus	100%	Model assumption.
$\alpha_{S1..9}^{T}$, $\alpha_{S1..9}^{TF}$ $\alpha_{R1..9}^{T1}$, $\alpha_{R1..9}^{T2}$	Baseline rate of withdrawal of failing therapy (due to primary or secondary resistance or other viral rebound)	0 year^{-1}	Experimental values. Changed in treatment scenarios, Chapter 5.
Ω	Programme capacity (i.e. maximum number that can be treated at any point in time)	5,000 individuals	Experimental values. Changed in treatment scenarios, Chapter 5.
Demographic parameters			
χ	Entry rate into susceptible population	0.03 year^{-1}	Set to produce a growing population in the absence of the HIV epidemic
$1/\mu$	Duration of time individuals stay in model population	35 years	Models adults aged 15-49 years
N_0	Population size at $t = 0$	1,000,000 individuals	Experimental value.

i represents sexual activity classes 1..4, j represents stages of HIV infection 1..11, LHS – Latin hypercube sampling

Parameters with LHS ranges, where used, are varied independently of one another. "Best" and "worst" case scenarios refer to the effectiveness of ART provision in terms of mortality and drop-out rates of AIDS patients in the 'initial' treatment period and treatment failure for all ART recipients. This is to reflect the success of the programme in promoting adherence, ensuring adequate drug supplies, managing complications and providing other medications and nutritional supplements where necessary, so a best case would have low rates of treatment failure because patient adherence is high and drop-out low.

4.3 Infectiousness

$\beta_S^U = 3\%$, $a = 18$

The systematic review of HIV transmission probabilities described in Chapter 3 has been used to parameterise the infectiousness parameters used in the models in this thesis. A description detailing how these parameters were estimated is provided in section 3.2.9.

4.4 Effect of ART on infectiousness

$\beta_{S1..8}^T = 0.02\beta_{S10}^U$, $\beta_{S9}^T = 0.02\beta_{S11}^U$

i.e. for asymptomatic treatment stages (one to eight), infectiousness is 2% of that for untreated pre-AIDS patients, while for the symptomatic treatment stage with development of new ADCs (stage nine), infectiousness is 2% of that for untreated AIDS patients.

As infectiousness is related to pVL [309, 395] and ART regimens have been shown to decrease pVL, it is reasonable to predict that ART would decrease the infectiousness of a patient receiving such treatment. The effect on infectiousness will depend on how it affects viral shedding in the genital tract, which is a separate tissue compartment from the blood, from which pVL is measured. Therefore there may be localised replication of the virus, if certain ARV drugs penetrate such compartments poorly, and so a decrease in pVL does not necessarily correlate with a decrease of viral load in semen or the female genital tract, although several studies have suggested that this may occur in the case of semen [396, 397]. Such decreases in concentration or detection of seminal HIV in men taking ARV drugs have been observed in some [7, 396] but not all [398, 399] studies, although studies with more pessimistic outcomes tended to have been reported before the triple therapy era. ART does not seem to affect the detection of HIV in cervicovaginal specimens [400]. However, ART has been demonstrated to reduce infectiousness directly by one study. Musicco et al in 1994 found that the rate of transmission from ZDV-treated men was lower than from untreated men (relative risk 0.5; 95% CI 0.1-0.9) [390]. ZDV monotherapy will have a limited effect compared with current triple ART regimens. It is unlikely that there will be further opportunities to measure this reduction at the individual level in future studies because of methodological limitations.

Previous models of ART and HIV transmission have assumed between two- and 100-fold reductions in infectiousness due to treatment [186, 188, 214, 231], and Law et al used a median value of a 10-fold decrease, with a zero- to 100-fold range [192]. As virological treatment failure is typically defined as the presence of detectable virus (at least to the limits of sensitivity of early pVL assays), then treatment success should be defined as pVL maintained below this level, which is typically more than a magnitude below average pVL for untreated individuals, especially of those at more advanced infection stages, when pVL rises [366]. Another study found that at least 99% of virions in plasma were removed when the patient was treated with ART [3]. Therefore an average 10-fold reduction in infectiousness while undergoing successful treatment would be quite pessimistic. The value chosen for w where $\beta^T_{S1..8} = w\beta^U_{S10}$ ("pre-AIDS") and $\beta^T_{S9} = w\beta^U_{S11}$ (AIDS) is 2% and represents a 50-fold reduction in infectiousness compared to an untreated, treatment-naïve individual at the equivalent stage of HIV infection. This value is for a strict definition of treatment success for I^T_S patients; individuals will fail treatment, after which their probability of transmission is higher, and there is considerable risk of resistance evolution.

4.5 Sexual activity

c_i = 152.8, 13.6, 0.5, 0.2 partners per year (for i = 1 to 4 respectively)

θ_i = 0.1%, 26%, 59%, 15% (for i = 1 to 4 respectively)

ε = 0.37

Reliable estimates for partner change rates and HIV infectiousness are difficult to obtain [401, 402]. Parameter values have been chosen to represent the HIV epidemic in Malawi as closely as possible, using data on HIV prevalence from antenatal clinics in major urban areas [371]. Malawi was chosen as an example of a country with a mature, high prevalence HIV epidemic, with limited resources with which to provide ART for all those in need. These values also reflect the situation in resource-poor settings more generally. There are large differences in HIV prevalence between major urban and non-urban areas in Malawi [371]. The model was parameterised to reflect urban prevalence because it is likely that ART will be introduced in urban areas before gradual roll-out to other regions. Partner change rates, distributions of individuals between classes and degree of assortative mixing between classes were parameterised by fitting the model to the prevalence data using the Curve Fit function in Berkeley Madonna version 8.0.1, having seeded the population with five infecteds with primary infection in the highest sexual activity class (in a model population of one million). The Curve Fit function automatically fits the values of these parameters to minimise the deviation between model-derived prevalence and the Malawi prevalence data. The deviation is the root mean square of the differences between individual data points in the dataset and the corresponding points in the model run. Input into the function is outlined in Table 4.2; calculated values are shown in summary Table 4.1. The partner change rate for individuals in the highest risk

group is set very high, at 153 partners per year, while that of the lowest risk group is just 0.23 partners per year, in order to mimic the timing and scale of the Malawi epidemic as closely as possible, with a peak prevalence of 27%. A comparison of the model simulation run using the parameters in Table 4.1, with the antenatal clinic prevalence data from urban centres in Malawi, is shown in Figure 4.3. The simulated epidemic is not a close fit to the data, but produces levels of HIV prevalence and rates of epidemic growth that are representative of many high prevalence countries in sub-Saharan Africa, such as Malawi. Many combinations of values for the parameters used to calibrate the model could produce an adequate fit to the data. Therefore the sensitivity of results to changes in these values was tested by refitting to produce a different set of parameter values. Model results using these alternative values were very similar to those using the original parameter values, suggesting that they are not particularly sensitive to this (Chapter 5 section 5.3.4).

Table 4.2 Input values for curve fit to Malawi prevalence data

Parameter	Minimum	Maximum	Guess #1	Guess #2
c_1	2	500	35	100
c_2	1	50	5	15
c_3	0.4	10	0.5	0.8
c_4	0.05	10	0.1	0.3
θ_1	0.001	0.05	0.01	0.03
θ_2	0.01	0.3	0.1	0.25
θ_3	0.1	0.8	0.15	0.50
ε	0.01	0.99	0.3	0.6

where $\theta_4 = 1-(\theta_1+\theta_2+\theta_3)$

Certain assumptions regarding sexual activity and HIV/AIDS are required, such as how sexual activity is affected by AIDS and by successful treatment with ART. In the models in this thesis, upon developing AIDS, all individuals are placed in the lowest activity class. In scenarios where ART is initiated before reaching AIDS (pre-AIDS), individuals move to the next sexual activity class with a lower partner change rate, to represent the effect of counselling and testing (however, more pessimistic assumptions regarding behaviour change are also investigated in Chapter 5). For simplicity, this effect does not wane with time. For patients starting ART after reaching AIDS, they spend an 'initial' period averaging six months where their sexual activity remain very low, and the risks of drop-out (due to side effects and IRIS), treatment failure and mortality are relatively high (see Table 4.1), as suggested by the literature [25]. Those who respond well to ART then move to a more stable phase, and θ_4 remain in the lowest sexual activity class, while the remaining fraction move to the next highest class.

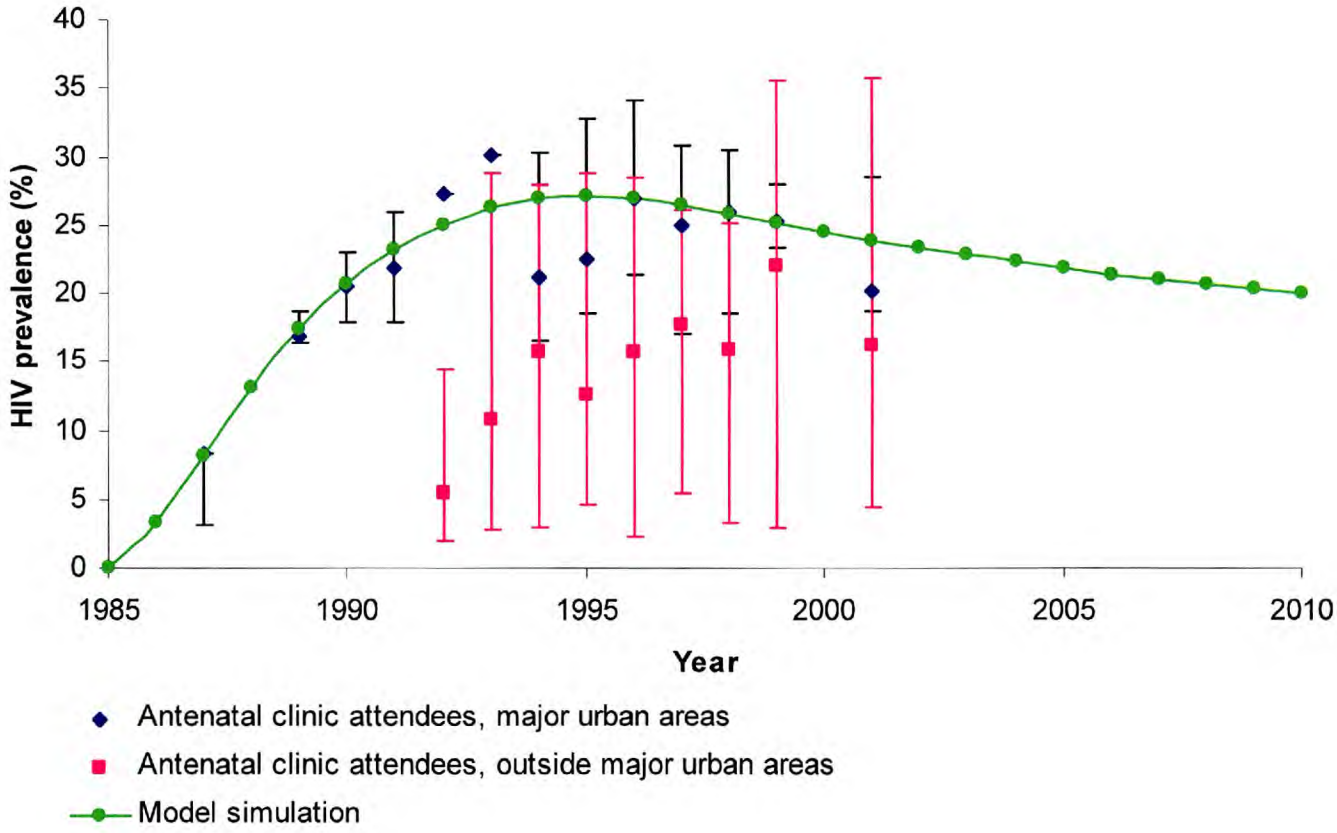


Figure 4.3 Comparison of the projected epidemic using baseline parameter values, with UNAIDS prevalence estimates from antenatal clinics in Malawi [371].

4.5.1 Sexual activity of AIDS patients

In the UNAIDS-DAI in Côte d'Ivoire, Moatti et al found that, as in developed countries [403], absence of sexual activity in patients was related to physical impairment associated with HIV disease and, in the case of male patients, with more advanced immunodepression [152]. Mathematical modelling papers often assume that sexual activity ceases once an individual progresses to AIDS [404, 405], or incorporate an arbitrary reduction in infectiousness of the compound parameter that is a product of infectiousness and sexual activity (typically referred to as βc) to reflect a decrease in sexual contact after symptoms appear. Gray et al examined whether the health status of male partners of HIV-1-infected women (in concordant partnerships) in Uganda might affect sexual activity, and found that the proportion of HIV-1-positive men reporting sexual intercourse during the month preceding interview was 91.6% and 96.2% in individuals with and without symptoms, respectively [406]. However, these symptoms may not have been ADCs. In contrast, a quality of life survey by the WHO found that symptomatic interviewees self-reported a lower scoring for sexual activity [407]. Although it seems intuitive that sexual activity will decrease with onset of symptoms, the magnitude of this decrease may differ between industrialised and developing countries. This may especially be the case for women, who may not be in a position to negotiate their own sex lives. However, the diagnosis of AIDS is typically made later for individuals in resource-poor settings [30, 31, 121], when their symptoms are more severe and they are closer to death, at which point their sexual activity will be lower. Therefore in our model scenarios, we have assumed that all individuals with AIDS move to the lowest sexual activity class, with a partner change rate of just 0.2 partners/year.

4.5.2 Changes in sexual activity in the ART era

Data from cohort studies in industrialised countries remain unclear about whether or not HIV positive individuals receiving ART effectively tend to adopt risky sexual behaviours more frequently than those who are not on treatment [149, 408, 409]. Concerns about increase in risky behaviour in the ART era may be even more justified in the context of resource-poor settings [152, 410], as condom use in Africa is low [411, 412], and only a minority of Western African women disclose a positive serostatus to their main partners and find it difficult to avoid unprotected sexual relations [153, 154]. However, Moatti et al claim that in the DAI in Côte d'Ivoire, sexual abstinence is, "the preventive strategy of choice for a majority of HIV-infected patients aware of their serostatus and consulting for care in Côte d'Ivoire" [152]. Access to ART was not associated with an increase in HIV-related risky sexual behaviours. However such effects may wane with time, the quality of counselling may decrease with scale-up and over time, and the data may be affected by social desirability bias. Furthermore, while the majority reported abstinence, more than 45% had remained sexually active (albeit at a lower frequency), and of these more than 40% declared HIV-related risky sexual behaviours and a third did not use condoms during their last intercourse. While data regarding sexual behaviour of HIV positive people in resource-poor settings are relatively scarce, these data are

supported by a cross-sectional study from Brazil where 60% of female partners of HIV infected men reported safe sexual behaviour after they had been informed of their partner's serostatus [413]. In Tanzania, access to care has been associated with increased adoption of preventive behaviours among recently diagnosed patients [414]. While the findings of Moatti et al are encouraging, this effect was reported from a small scale programme after a short follow-up and may not be reproducible elsewhere. There are specific difficulties in negotiating condom use in the context of monogamous relationships that have already been documented in Africa [415, 416].

Chapter 1 section 1.3.8 discusses some of the relevant issues regarding sexual behaviour change at the population and individual level in the ART era. The relationship between ART provision and general availability with risk-taking behaviours is likely to be very complex. Boily et al 2005 suggested that an increase in risk-taking behaviour was due to re-pooling of the highest risk-taking groups of MSM, who previously would have become infected and died of AIDS at a relatively young age, leaving other MSM with fewer choices of partner and perhaps having to decrease their risk-taking due to a lack of potential partners [10]. Whether this effect could occur in high ART coverage resource-poor settings will depend on whether there is replenishment of high risk taking groups already, even before scale-up, which appears to be the case in Zimbabwe. Unlike MSM, where duration in high risk groups can be decades, individuals dying from HIV/AIDS in Zimbabwe have typically already left the high risk groups, which tend to be in the youngest age groups, especially for women (Timothy Hallett, personal communication).

In the context of resource-poor settings, changes in sexual behaviour at both of these levels are difficult to predict, with competing effects. Increasing ART coverage may reduce the stigma surrounding HIV/AIDS, leading to more people coming forward for VCT, which may decrease the risk behaviour not only of those found to be positive, but also those who test negative. However, such scale-up, if successful, may lead to a disinhibition effect because HIV is no longer perceived as fatal. Regardless, many people will not be in a position to change their levels of sexual behaviour through lack of empowerment and/or competing interests, regardless of counselling provision [415, 416].

The model in Chapter 5 assumes that individuals put on ART at pre-AIDS rather than AIDS attenuate their sexual behaviour to a certain extent to reflect the effect of counselling – each individual moves to the next lowest sexual activity class. AIDS patients who are successfully treated (i.e. have passed the six month 'initial' phase, when they are at higher risk of treatment failure and death), feel better enough to resume sexual activity to a certain degree, but not to pre-sickness levels or to the levels of pre-AIDS patients. This is to reflect the impact of ADCs and counselling. The model does not incorporate VCT provision but there is investigation of more pessimistic assumptions regarding behaviour change of HIV patients initiating treatment.

4.6 Entry and exit rates

χ = 0.03 year^{-1}, μ = 1/35 year^{-1}

The models are investigating the impact of ART on sexual transmission rather than perinatal transmission; therefore the model population represents the sexually active section of society at greatest risk of HIV transmission and acquisition, generally assumed to be those aged 15 to 49 years. Therefore an average duration within the subgroup of 35 years and thus an exit rate of 1/35 year^{-1} is assumed. Entry rate into the model population should then be set to produce a population growth rate comparable to those projected for Malawi. However, projections of population growth have been greatly distorted by the AIDS epidemic, and so an arbitrary value of 0.03 is used, which is slightly larger than the background exit rate (1/35 = 0.0286) to reflect population growth, had the HIV epidemic not occurred. Therefore some of the results in Chapter 5 are presented as total number of infections rather than prevalence because of the uncertainties regarding population growth rates.

4.7 Survival times of AIDS patients and duration of HIV infection

4.7.1 Duration of primary infection

$1/\phi_{S1}^{U}$ = 1.5 months

Mathematical models assume a range of durations of primary infection, from one month or less [367, 386], three months [231, 417], up to six months or more [382, 418]. However empirical studies appear to suggest a duration of around one to two months [364, 375-378] from infection to seroconversion. Daar et al reported that pVL declined at least 100-fold from its peak in "as little as 10 days" [364]. Vanhems et al reported a median incubation period between exposure and detectable virus of 21.5 days, followed by a median duration of primary infection of 15.5 days (range: 3-67 days) [375], while Horsburgh et al reported a median of 2.1 months from exposure to seroconversion [378]. Therefore the average duration of primary infection is set at 1.5 months.

4.7.2 Duration of HIV infection and incubation

$1/\phi_{Sj}^{U}$ = 1 year $\{j = 2..9\}$

There has been considerable debate as to whether HIV infected individuals in resource-poor settings have a lower life expectancy that those in industrialised countries in the pre-ART era. It has been postulated that poorer nutritional status, helminth infections and poor management of OIs may lead to shorter progression times to AIDS [419]. Although some studies have suggested that HIV-1 infection develops more rapidly in patients in Africa [420, 421], most have reported disease progression similar to that in industrialised countries [379, 380, 422, 423]. Anzala et al reported a median time from seroconversion to AIDS in Africa of 4.4 years [424], but this estimate was based on simulation modelling rather than direct prospective observation, with a high loss to follow-up. The women in the cohort had faster declines in CD4 counts than HIV-infected women from the general

population, and in a later report the authors stated that the rapid progression of HIV-1 infection was specific to this group of women [425]. They speculated that infection with multiple HIV-1 strains and a heavy burden of STIs could account for this observation. The findings should therefore not be extrapolated to the general African population. As Crampin et al point out [379], new long-term natural history cohorts are unlikely because interventions of proven efficacy are now available.

Sewankambo et al measured mortality as 132.6 per 1000 person-years (py) in HIV-infected versus 6.7 per 1000py in uninfected subjects in Uganda [107], giving an HIV-specific death rate of 0.126 and thus an average life expectancy of approximately eight years for these subjects. Similar results were obtained by Mulder et al (also in Uganda) who calculated the mortality as 116 and 7.7 per 1000py in HIV-infected and uninfected subjects, respectively [142], giving an HIV-specific death rate of 0.108 and thus an average life expectancy of approximately nine years for those infected. A retrospective cohort study in Malawi measured mortality as 93.3 per 1000py in HIV-infected versus 11.3 per 1000py in uninfected subjects, giving an HIV-specific death rate of 0.082, and a life expectancy of approximately 12 years [379]. Ten year survival was 36% in the HIV-positive cohort and median survival was eight years. Given that the dates of infection of the subjects in these studies were not known, they are likely to underestimate survival, and so it appears that life expectancy in this population is comparable to that of untreated individuals in industrialised countries. Morgan & Whitworth estimated that the median survival in their Ugandan cohort was likely to be around 10 years [380]. Therefore a mean duration of HIV infection of around 10 years (from transmission to death) is assumed, in the absence of treatment. The incubation period is taken as 10 years less the assumed average duration of pre-AIDS and AIDS only, as the duration of primary infection is negligible. Therefore the mean duration of the incubation period of HIV infection is taken to be eight years.

4.7.3 Duration of pre-AIDS

$1/\phi_{S10}^{U}$ = 1 year

Models often distinguish between three phases of HIV infection: primary infection, incubation and AIDS, but sometimes incorporate a "pre-AIDS" stage, during which pVL increases, CD4 count decreases and the patient may experience clinical symptoms (excepting ADCs). While pre-AIDS and AIDS patients may all qualify for treatment, where rationing of ART must take place, a distinction to determine those with AIDS, at a more advanced stage of disease and closest to death, is required. The timing of treatment initiation is examined in Chapter 5.

Patients with symptoms which are not classified as ADCs may rapidly progress and die, especially in resource-poor settings where many conditions are non-specific and common in the general population. The definition of pre-AIDS used here and in Chapter 5 refers to patients in immunological decline with CD4 lower than 200 cells/mm^3, but without overt, classic ADCs identifying these patients clinically as priorities for treatment. A cut off point often used to distinguish different

probabilities of survival for patients initiating ART is a CD4 count less than 50 cells/mm^3, which is akin to the AIDS (rather than pre-AIDS) stage used in the model described in this chapter. The WHO recommends that ART should be initiated at WHO Stage IV HIV disease, WHO Stage III disease with a CD4 count less than 350 cells/mm^3 (at the doctor's discretion), or WHO Stage I or II disease with a CD4 count less than 200 cells/mm^3 [29]. Therefore the definition of AIDS used in Chapter 5 is analogous to WHO Stage IV, with the pre-AIDS stage referring to those at WHO Stage III but at greatest risk of progression to Stage IV (those with a CD4 count less than 200 cells/mm^3).

Empirical studies have demonstrated the appearance of "constitutional symptoms" one or two years before the development of ADCs [365, 366]. Mathematical models have typically assigned the pre-AIDS stage a duration of one year [200, 382, 426], which is the value assumed in the ART models here.

4.7.4 Survival times of AIDS patients

$1/\nu$ = 9 months

It is inappropriate to use data on survival times of AIDS patients from industrialised countries to estimate the survival of patients in resource-poor settings, as patients from industrialised countries enjoy substantially better nutritional status, access to healthcare services and management of OIs, and the prevalence of other endemic diseases may contribute to shorter survival times in developing countries. Furthermore, non-specific signs and symptoms associated with HIV may be common in the general population, which may delay AIDS diagnoses [383]. There does not appear to be a difference in survival by race, because disease progression amongst black Africans in industrialised countries before the era of triple therapy was no different from that of the white population [427].

Survival of patients once diagnosed with AIDS varies. Although there have been few reports of survival with AIDS from less developed countries, those that have been published suggest a much shorter survival time than for patients in industrialised countries. A summary of a selection of studies estimating the duration of AIDS is presented in Table 4.3. The estimates are more similar to the survival times of AIDS patients in industrialised countries very early in the epidemic, being around 10 or 11 months, before diagnosis and management of HIV infection and OIs became established [388, 428].

It appears that while survival time for most patients with an ADC is shorter in resource-poor settings, the median CD4 count at which such ADCs develop is higher [141]. It has been observed that the ADC predicts survival [428, 429] and estimates of median survival after a single ADC have been found to range from three to 31 months depending on the disease [384]. Differences in survival are also partly due to the definition of AIDS used by studies, and delays in such diagnoses, often because of the non-specific nature of many ADCs in resource-poor settings with high prevalences of many infectious diseases.

Several mathematical models estimate AIDS survival as one year [186, 199, 229, 382], many modelling HIV transmission in resource-poor settings, while other models set in these areas assume an even shorter duration of six months [386, 417]. If we speculate that provision of treatment for OIs for AIDS patients will improve as ART rolls out across sub-Saharan Africa, a mid-way estimate of nine months seems reasonable.

Table 4.3 Selection of studies estimating AIDS survival time in resource-poor settings

Study	Country	AIDS survival time (months)[1]
Chequer et al 1992 [385]	Brazil	5.1
Mulder et al 1994 [142]	Uganda	6.0[2]
Kitayaporn et al 1996 [383]	Thailand	7.0
Sewankambo et al 2000 [107]	Uganda	40.5% subjects reported no illness <10 months preceding death
Morgan et al 2000 [141]	Uganda	9.3

[1]Median survival time, unless otherwise stated.
[2]A "substantial proportion" of study participants progressed from asymptomatic infection or mild disease to death within six months.

4.8 Effect of ART on survival

$\phi^{T}_{S1..8}$ = 1 year^{-1}

i.e. eight treatment stages, each compartment being occupied on average for one year.

Mathematical models have assumed various increases in life expectancy due to ART, with estimates from four [229] to seven years [224]. For patients undergoing successful treatment, their disease progression is slow but there remains a substantial degree of mortality. Lucas et al found that five years after initiation of ART, the estimated proportion surviving in the durable suppression group of the cohort was 89%, compared to 76% in the rebound group and 56% in the failure to suppress group [41]. In resource-poor settings, where nutritional status and access to other medication and healthcare services may be compromised, excess mortality despite viral suppression is likely. Therefore, under circumstances of poorer nutrition and patient management in resource-poor settings, rate of progression to a new ADC for patients with successful viral suppression is assumed to be one year^{-1} for each of eight successive treatment stages, designed to produce a more realistic progression time (following a gamma function rather than an exponential distribution), with average. duration before progressing to AIDS (with a new ADC) of eight years.

It is often unclear to what extent ART has improved survival of AIDS patients, as management of OIs has greatly improved and has also contributed to the overall improvement in

prognosis. Better management of OIs was shown to double the median survival time after an AIDS diagnosis in Europe prior to the introduction of triple therapy [430, 431].

The ART Cohort Collaboration, an international collaboration between the investigators of 13 cohort studies in Europe and North America, found that a lower CD4 count and a previous AIDS diagnosis were both predictors of poorer outcomes on treatment [25]. Patients starting ART with a CD4 count <200 cells/mm^3 have a poorer prognosis [25, 432]; therefore a syndromic management initiative, where treatment is only initiated once an individual has reached AIDS, will not be as effective in extending the life of a patient compared to a programme initiating treatment before clinical symptoms have developed. This is incorporated by the fraction of AIDS patients dying during the 'initial' phase of ART (ν_{SP}^{T}), while all pre-AIDS patients initiating therapy survive to progress through the treatment stages.

4.9 Effect of ART in resource-poor settings

There is a large body of evidence that ART can be successful in Africa [30, 125, 131, 132, 433], with virological and immunological outcomes similar to those from industrialised countries. Table 4.4 summarises a selection of studies reporting the performance of ART projects in resource-poor settings. While ART provision is now being scaled up, these reports typically cover performance over a short time and describe smaller scale initiatives, where levels of care, including availability of health care professionals, are high. A recent review by Akileswaran et al reported that of the 28 articles and abstracts involving studies from 14 African countries, monitoring of CD4 count and pVL at a minimum of six month intervals was completed by all studies [65], and most exceeded WHO recommendations [29]. Twenty six of the 28 cohorts included less than 500 patients, and many of these studies took place under controlled research conditions. The high rates of adherence reported by such studies (the majority reported that a high proportion of their subjects had adherence rates of 95% or more) may be due to high levels of support and counselling, and selection bias. Therefore the rates of mortality and treatment failure, and improvements in CD4 count, must be regarded as the optimum performance of an ART programme. A scaled-up programme is likely to have considerably poorer outcomes, and these may further deteriorate over time.

More encouragingly, these results suggest that there is no intrinsic differential response to ART by setting, as results are similar to those in industrialised countries. Furthermore, the Swiss Cohort Study found that the prognosis of patients from sub-Saharan Africa on triple therapy was equivalent to that of Northwest European patients, despite lower baseline CD4 counts in sub-Saharan Africa patients [27]. However, Wood et al found that the prognosis is dependent upon the experience of the physician. Among patients with a baseline CD4 count <50 cells/mm^3, the adjusted relative hazard of mortality was 5.07 (95% CI 2.50-10.26) for patients with experienced physicians and 11.99 (95% CI 6.33-22.74) for patients with inexperienced physicians compared to patients with a CD4 count ≥200 cells/mm^3 treated by experienced physicians [63]. Areas such as sub-Saharan

Africa are suffering chronic shortages in health care personnel [434], a problem which may worsen in the future, so it is unlikely that large scale ART programmes will enjoy expert patient management, with the duty of care being delegated to nurses, community workers and volunteers. While patients will still benefit from treatment delivered in this way, they will not receive the same levels of care as patients enrolled in current ART pilot projects. For example, Akileswaren et al's review reports low incidence of drug resistance in the studies which report resistance testing, yet outside of carefully controlled ART use, Vergne et al reported that around 60% of patients with a mean 17.7 months of ART (including dual as well as triple therapy) had major mutations associated with drug resistance in Gabon [109], with comparable results reported from Côte d'Ivoire [66].

This highlights the concern that less developed health systems will not be able to manage such complex treatment; there is a wide range of side effects and toxicities to manage, as well as treatment failure, meaning changes to more appropriate regimens are required. However, the WHO have recommended standardised first and second regimens so that management of therapies is easier, both for the physician and the patient [29].

Table 4.4 Summary of a selection of studies reporting performance of ART in resource-poor settings

Study	Setting	Study population (n)	Duration of treatment	Mortality (%)	Viral load (copies/mm^3)
Idoko et al 2002*	Nigeria	40 (ART-naïve)	24 weeks	0	Undetectable HIV-1 RNA for 8% (week 24)
Kebba et al 2002 [435]	Uganda	11 (ART-naïve)	No data	0	<400 for 88.9% (12 weeks), 71.4% (31 weeks)
Djomand et al 2003 [124]	Côte d'Ivoire	276 (ART-naïve)	No data	16 (probability at 1 year)**	<200 for approximately 50% (1 year)
Kumarasamy et al 2003 [97]	India	333 (265 ART-naïve)	≥3 months	2.1	No data
Landman et al 2003 [64]	Senegal	40 (ART-naïve)	15 months	0	<500 for 95% (month 6) <50 for 78% (month 6), 70% (month 9), 77% (month 12), 69% (month 15)
Sungkanuparph et al 2003 [31]	Thailand	60 (ART-naïve)	48 weeks	3.4	<400 for 96.4% (12 weeks), 88.5% (24 weeks), 92.0% (36 weeks), 87.8% (48 weeks)
Tassie et al 2003 [121]	MSF initiatives in Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand, Guatemala	743 (339 ART-naïve)	Median 4 months	Estimate for 6 months: 10.5	<500: 89.8% (6 months)
Jeannin et al 2003 (abstract)*	Malawi	1266 (96.8% ART-naïve)	≥6 months	12.9	<400 for 84.1%
Macharia et al 2003 [126]	Kenya	300 (217 on triple therapy)	24 months	11	<400 for 59% (month 6), 47% (month 12), 49% (month 18), 32% (month 24)
Ndwapi et al 2003 (abstract)*	Botswana	306 (ART-naïve)	Median 283 days	10.8	<400 for 84.5% (month 6)
Emberti Gialloreti et al 2003 (abstract)*	Mozambique	82	2 months	Adjusted mean reduction of death hazard: 87	<500 for 71% (month 2)
Mougnutou et al 2003 (abstract)*	Cameroon	117 (116 ART-naïve)	Median 10.5 months	7.7	<400 for 85.2% (month 12)
Ekong et al 2003 (abstract)*	Nigeria	74	9 months	1.3	No data
Kibangou et al 2003 (abstract)*	Congo	49	≥6 months	2	No data
Seyler et al 2003 [436]	Côte d'Ivoire	101	Median 17 months	9.9 By initial CD4 count, mortality at 18 months: ≥50 cells/mm^3: 6 <50 cells/mm^3: 24	Undetectable for 51% (month 12)
Laurent et al 2004 [61]	Cameroon	60 (96% ART-naïve)	24 weeks	8 (absolute) 15 (estimate at 24 weeks, as-treated)	<400 for 82% (week 12), 92% (week 24) <50 for 46% (week 12), 73% (week 24)
Hosseinipour et al 2004 (abstract)*	Malawi	141	6 months	27	<400 for 79% (month 6)
Oyugi et al 2004 (abstract)*	Uganda	70	12 weeks	8.6	<400 for 78% (week 12), 78% (week 24)

Study	Setting	Study population (n)	Duration of treatment	Mortality (%)	Viral load (copies/mm^3)
Jack et al 2004 [127]	South Africa	20 (TB-positive, ART-naïve)	No data	0	<50 for 80% (week 24)
Coetzee et al 2004 [437]	South Africa	287 (ART-naïve)	Median 13.9 months	13.7 at 24 months By CD4 count: ≥50 cells/mm^3: 8.6 <50 cells/mm^3: 18.2	<400 for 89.2% (month 6), 84.2% (month 12), 69.7% (month 24)
Sow et al 2004 (abstract)*	Senegal, Côte d'Ivoire, Uganda, Kenya	207 (ART-naïve)	24 weeks	4	<400 for 68% (week 24)
Ekong et al 2004 (abstract)*	Nigeria	219	12 months	No data	No data
Torpey et al 2004 (abstract)*	Ghana	114	6 months	No data	No data
Hudspeth et al 2005 (abstract)*	South Africa	352 (2/3 ART-naïve)	10 weeks	1.4	No data
Karcher et al 2004 (abstract)*	Uganda	76	2 months (n=42), 6 months (n=23)	0	Mean 0 (months 2 and 6)
Guiard-Schmid 2004 (abstract)*	Cameroon	26 (ART-naïve)	48 weeks	7.7	<50 for 92.3% (week 48)
Mujugira et al 2004 (abstract)*	Botswana	146	Median 1.15 years	Probability of survival at one year: 70	Undetectable HIV-1 RNA for 9.5% (month 9)
Spacek et al 2004 (abstract)*	Uganda	137 (73% ART-naïve)	≥12 weeks	No data	Undetectable HIV-1 RNA for 65%
Kabugo et al 2004 (abstract)*	Uganda	171 (ART-naïve mother and their infected spouses)	6 months	2.4	No data
Marih et al 2004 (abstract)*	Morocco	479	42 months	7	<50 for 68% (month 42)
Mutuluuza et al 2005 (abstract)*	Uganda	200 (ART-naïve)	24 weeks	3	<50 for 49% (week 12), 54% (week 24) <400 for 85% (week 12), 72% (week 24)
Stringer et al 2005 (abstract)*	Zambia	1043	6 months	10.5	No data
Laurent et al 2005 [62]	Senegal	176 (92% ART-naïve)	Median 30 months	17.6 during follow-up 16 (2 years) 19 (3 years)	<1000 for 65.8% (2 years), 61.8% (3 years)
Idigbe et al 2005 [438]	Nigeria	50 (ART-naïve)	12 months	4	<400 for 71.8% (week 24)
Kabugo et al 2005 [101]	Uganda	321 (44% initiated triple therapy)	Median 512 days	21 known (another 21% lost to follow-up)	<400 for 50%-60% (1 year) <1000 for 56%-71% (1 year)
Sungkanuparph et al 2005 [439]	Thailand	159 (ART-naïve)	60 weeks	0.6	<50 for 50% (12 weeks), 71.2% (24 weeks), 79.7% (36 weeks), 79.4% (48 weeks), 80.1% (60 weeks) <400 for 88.5% (12 weeks), 92.8% (24 weeks), 92.8% (36 weeks), 91.2% (48 weeks), 88.2% (60 weeks)

Abbreviations : MSF – Médecins sans Frontière, RNA – ribonucleic acid
* Table entries adapted from Akileswaran et al 2005 [65]
**Unclear whether this refers to the 276 patients receiving triple therapy or the 480 patients receiving triple or dual therapy

4.10 Effect of ART by stage of infection upon treatment initiation

ν_{SP}^{T} = 10%, 20% (best and worst case scenarios respectively);

f_P = 30%, 50% (best and worst case scenarios respectively);

Z_P = 5%, 15% (best and worst case scenarios respectively)

It is generally accepted that initiation of ART for individuals at a more advanced disease stage may be less effective [25, 27], partly due to higher toxicity [28], IRIS [31] and higher treatment failure rates (a summary of a selection of studies reporting survival by CD4 count is presented in Table 4.5). This is important in the context of resource-poor settings, where individuals typically present at a very advanced stage of disease [124, 132]. However, studies have shown that even when treatment is initiated at very low CD4 baseline levels, dramatic improvements in CD4 count and symptoms are made by the majority of patients [31, 32]. Late stage treatment initiation is also associated with an increased risk of treatment failure [42, 432].

The six month 'initial' period in AIDS patients involves an elevated risk of mortality (ν_{SP}^{T}), viral rebound (plus failure to ever suppress) (f_P) and drop-out due to side effects (Z_P), including IRIS. Mortality for the initial period is set at 10% and 20% for the best and worst case scenarios, respectively. The Kaplan-Meier curve from Lee et al [388] for those diagnosed with an OI in 1997 (in the triple ART era) indicates that roughly 10% of patients died in the first six months after diagnosis, with a slower progression after this period (another 10% of patients had died by 24 months after diagnosis). Similar rates have been found in developing countries. Tassie et al [121] found that 10% of patients died within the first six months in MSF projects in seven low and middle income countries. Djomand et al found in Côte d'Ivoire that the probability of survival for at least a year for patients starting a triple or two-NRTI regimen was 84% (95% CI 80-89%) [131]. However, of all those initiating ART, 10% (n=73) did not return for follow-up, a proportion of whom may also have died. Seyler et al, again in Côte d'Ivoire, found that survival after six months of ART was 80% for those initiating with a CD4 count less than 50 cells/mm^3, but this remained stable at 80% and 76% for 12 and 18 months of treatment, respectively [436]. The ART models presented in this thesis aim to represent a large scale programme in resource-poor settings without the expert health care provided by institutions such as MSF. In order to reflect poorer standards of care, nutrition and availability of other medications, mortality during the 'initial' phase is therefore slightly higher than these values. The duration of the 'initial' phase is six months because many studies have reported outcomes such as survival for this period [46, 121], since outcomes during this time are markedly different from the remaining treatment time [388].

There has been considerable debate as to the optimum point at which therapy should be initiated, where a balance is achieved between unnecessary side effects and a decrease in future treatment options from early ART initiation on one side, and a worse prognosis and increased risk of

treatment failure by delaying treatment, on the other. Current guidelines have recommended treatment initiation at a CD4 count of either 200 [136] or 350 cells/mm^3 [22], and Ahdieh-Grant et al, citing data from the Multicenter AIDS Cohort Study, believe the threshold is around 275 cells/mm^3 [440]. It appears that ART confers minimal [432, 441] or no benefit [442, 443] in asymptomatic patients who initiate therapy at CD4 counts >350 cells/mm^3. Results presented in Chapter 5 do not investigate the impact of ART earlier than the pre-AIDS stage because such treatment is unwarranted clinically and unfeasible financially.

Table 4.5 Selection of studies reporting survival by CD4 count

Study	Setting	CD4 count* (cells/mm^3)	Outcome
Ahdieh-Grant et al 2003 [440]	US Multicenter AIDS Cohort Study	200-349	Probability of remaining AIDS-free after ~10 years: **~73%**
		<200	**~47%**
Weidle et al 2002 [132]	Uganda	Overall	1 year survival: **74%** (range: 67%-79%)
		≥50	**82%** (range: 65%-91%)
		<50	**67%** (range: 47%-81%)
Egger et al 2002 [25]	ART Cohort Collaboration, Europe and US	200-349	3 year survival: **~98%**
		100-199	**~95%**
		50-99	**~93%**
		0-49	**~90%**
Palella et al 2003 [432]	US	200-350	Death rate: **15.4** /1000py
		<200	**56.4** /1000py
Wood et al 2003 [63]	Canada	≥200	3 year survival: **96%**
		50-199	**85%**
		<50	**78%**
Cozzi Lepri et al 2001 [443]	UK	>200	AIDS and death rate: **30** /1000py (95% CI 5-70)
		50-199	**50** /1000py (95% CI 20-100)
		<50	**190** /1000py (95% CI 100-330)
Kaplan et al 2003 [444]	US ART-naïve patients without ADC	200-349	AIDS and death rate: **20** /1000py
		50-199	**60** /1000py
		0-49	**140** /1000py

*CD4 count upon initiating ART

4.11 Effect of treatment failure on survival and disease progression

$\phi_{S1..9}^{TF} = \phi_{R1..9}^{T1} = \phi_{R1..9}^{T2} = x\phi_{S1..9}^{T}$ x = 1.25 (LHS range: 1.11-2.00)

Although it is intuitive that after viral rebound an individual will resume progression to further ADCs and eventually death, data from several cohorts have demonstrated sustained clinical benefits [27, 145, 445] and that CD4 counts may remain stable or even continue to rise in patients continuing ART [42, 446-449]. In contrast, discontinuing treatment leads to rapid increases in pVL and declines in CD4 count [145, 389]. Generally, virological failure precedes immunological failure which precedes clinical failure, with these events often separated by months or years. Deeks et al found that immunological failure (defined in this case as a return to baseline CD4 count) occurred an average of three years following virological failure in patients remaining on the same ART regimen [38]. Lucas et al [41] point out that most studies suggesting that the risk of clinical disease progression or death is similar in patients with and without durable viral suppression have less than two years of follow-up [27, 46, 47]. However, Lucas et al found that the survival trajectories of the durable suppression group and the viral rebound group were similar for the first two years, but diverged thereafter and became significantly different over the prolonged follow up [41]. At five years, the estimated proportions surviving were 89% in the durable suppression group, 76% in the rebound group and 56% in the failure to suppress group. Ledergerber et al reported that at 30 months, 6.6% (95% CI 4.6%-8.6%) of patients who achieved and maintained undetectable pVL developed AIDS and/or died, compared to 9.0% (95% CI 5.5%-12.5%) of patients who first achieved suppression before viral rebound, and 20.1% of patients who never achieved undetectable concentrations (adjusted for CD4 count) [27]. Therefore in the model, duration before progression to AIDS for treated patients with detectable pVL is set at 80% (i.e. $1/x$) of the value for patients with viral suppression, to reflect a worse prognosis, but still a considerable beneficial effect. However, continuation of ART in the presence of detectable levels of HIV risks further viral evolution toward higher levels of resistance [450] and perhaps compensatory mutations increasing the replicative fitness and transmissibility of virus particles.

4.12 ART resistance and treatment failure

f_P = 30%, 50% (best and worst case scenarios respectively);

f = 10%, 30% (best and worst case scenarios respectively); κ = 40% (LHS range: 20-60%)

Numerous studies have documented a correlation between successful suppression of pVL and adherence to medication schedules [451, 452]. A report from the Frankfurt clinic cohort found that viral rebound was associated with treatment interruption in the vast majority of cases, leaving only a few cases attributable to genuine treatment failure [453]. This study and others suggest that non-adherence is the most important reason for initial lack of response to treatment and subsequent viral rebound [217, 454, 455]. It has consistently been found that very high daily adherence (of around 90-

95%) is required to achieve an undetectable pVL, and to prevent viral rebound and resistance evolution [50, 456-459]. Maintaining this level of adherence is difficult, regardless of the setting. Imperfect adherence is common; surveys have indicated that one third of patients missed doses within three days of the survey [54]. Therefore it is not surprising that longitudinal studies have reported that durable viral suppression occurs in only a minority of patients starting ART [42-44], although higher rates of viral suppression have been reported in some cohorts [27, 45]. Lucas et al reported that only 36% of patients started on a triple regimen achieved durable viral suppression; 26% achieved suppression followed by viral rebound and 38% never achieved viral suppression throughout the 18 month follow-up of this largely ART-naïve cohort [41]. However the study population had a high prevalence of poverty, substance abuse and psychiatric illness, which may be associated with poorer adherence. Rastegar et al showed a similar success rate at 39% for PI-based triple therapy and 47% for all regimens, including those using newly introduced NNRTI drugs [387]. Deeks et al reported that 50% of their cohort achieved an undetectable pVL at 48 weeks, but this did not include drop-outs (which would have lowered the success rate to 42%) [42]. Moore and Chaisson reported that 50% of patients achieved an undetectable pVL by six months, 65% by 12 months and 67% by 18 months [46]. However, much higher success rates have been reported elsewhere [27, 45]. Ledergerber et al found that 90.7% of treatment-naïve patients reached undetectable pVL by 12 months, while for pretreated patients, estimates ranged from 70.3% treated with one new drug to 78.7% on three new drugs [27]. Two years after reaching undetectable concentrations, an estimated 20.1% of treatment-naive patients and 35.7-40.1% of pretreated patients had viral rebound. At 30 months, an estimated 6.6% (95% CI 4.6-8.6) of patients who had maintained undetectable concentrations, 9.0% (95% CI 5.5-12.5) who had viral rebound, and 20.1% (95% CI 15.3-24.9) who had never reached undetectable concentrations developed AIDS or died. Compared with patients who maintained undetectable pVL, the adjusted relative hazard of AIDS or death was 1.00 (95% CI 0.66-1.55) for patients with viral rebound and 2.40 (95% CI 1.72-3.33) for patients who failed to reach undetectable concentrations. However, treatment was changed at least once in 52.4% of patients, who all benefited from expert care. Phillips et al found that 85% of patients achieved viral suppression by 32 weeks [45]. All of these studies reported results less favourable than from randomised trials [2, 460, 461].

It is difficult to parameterise from these results because of the high frequencies of regimen change (52.4% for Ledergerber et al [27], 14.8% for Tassie et al [121]). Previous ART models have adopted baseline values for resistance evolution of 10% per year [188] and 25% per year [229]. As education and support by healthcare providers may be less well established in resource-poor settings, optimistic rates of treatment failure from industrialised settings will be underestimates. Furthermore, irregular drug supplies and disrupted lifestyles of treated patients may also hinder adherence. Garnett et al state that in clinical practice, in contrast to clinical trials of carefully selected patients, rates of virological failure of ART approach 40% [81], and Blower et al have modelled

uncertainty in the rate of resistance evolution up to 60% of those receiving treatment per year [188]. A review of ART use in Africa found that among 21 studies reporting pVL decreases, a median of 73% of patients achieved undetectable pVL by the end of the study period (typically around six months) [65]. Many of these studies took place under controlled research conditions with expert care, and can be considered as the best possible performance of an ART programme in this setting.

In this model, large fractions of the treated population experience viral rebound (or failure to suppress) during the 'initial' period: 30% in the best case and 50% in the worst case scenario for AIDS patients, in addition to drop-out due to side effects (5% and 15% for best and worst case scenarios, respectively) and high mortality for AIDS patients (10% and 20%, respectively). Therefore the proportion of AIDS patients progressing from the 'initial' period with successful viral suppression is 55% for the best case scenario and 15% for the worst case. The subsequent fraction failing treatment after each one year treatment stage then drops to 10% and 30% per year for best and worst case scenarios respectively. Ledergerber et al found that two years after reaching undetectable virus levels, 20% of treatment-naïve patients had viral rebound [27], which is agreement with the 10% per year failure rate for the best case scenario.

Rebound may be associated with viral drug resistance to one or more of the agents used in combination therapy [36, 460]. However, Descamps et al believe that virological failure is more related to problems of adherence and ART potency than selection of resistant mutant viruses, having found very low frequencies of resistance mutations in their patients with virological failure [217]. A similar conclusion was reached by Havlir et al [78]. The Swiss cohort study reported that among ART-naïve patients, 73.9% reached undetectable levels of pVL by 12 months, but among those that did achieve suppression, the probability of viral rebound two years after reaching undetectable concentrations was 20.1% for treatment naïve patients and 35.7%-40.1% for pre-treated patients [27]. This cohort of patients benefits from very high standards of care, which demonstrates just how frequently virological failure occurs.

The definition of drug resistance used in our model is phenotypic resistance to the regimen, rather than point mutations to one particular drug. It is assumed that all initial treatment failure is with virus remaining phenotypically sensitive to the current ART regimen, but that resistance develops as a result of continued treatment pressure in the presence of substantial viral replication. κ is set at 40% per year (LHS range: 20%-60%) because continuing viral replication in the presence of ART is likely to result in evolution of resistance-conferring mutations. A study in Spain found that 78.5% of all patients with virological failure harboured HIV strains which showed genotypic resistance to two or more drug classes [75]. However, due to the cross-sectional design of the study, the timing of resistance emergence could not be determined. A report from the DAI in Uganda stated that among patients with treatment failure (>1,000 copies/mm^3) more than 90 days into therapy, phenotypic resistance to NRTIs was found for 40% (18/45) of patients receiving triple therapy [132]. The

definition of resistance used here is phenotypic resistance to the entire triple regimen, and therefore we assume a lower rate of evolution of 40% per year.

There has been considerable concern that the evolution and spread of drug resistance will be far more rapid in resource-poor settings than industrialised settings. Several studies have found that resistance rarely emerged in their pilot programmes, at rates comparable to those in industrialised countries [30, 462-465]. Laurent et al in Senegal found that only two cases of viral resistance from 58 patients (3.4%) occurred during 18 months of follow-up [30]. Moatti et al [466] claim that studies from Brazil [467], Senegal [462] and South Africa [130] show that once financial barriers to drug access have been overcome, adherence to ART can be as high in developing countries as that generally observed in industrialised countries. However, several of these publications concede that these rates are lower than for other studies from Africa [66, 109] due to strict respect of prescription and monitoring guidelines and no breakdown in drug supply. Financial barriers to drug access are not always easy to overcome. Even if drug provision is free for the patients, costs such as transport are still an issue. Furthermore, the follow-up periods for these studies tend to be short; there is the possibility during roll-out that drug resistance could quickly increase, especially if strict procedures adhered to during small-scale pilots lapse with roll-out and over time. Stevens et al [49] assert that study populations have tended to be urban with above average education and income, and are therefore probably not representative of most African patients requiring treatment [30, 130].

Large scale roll-out of ART across Africa, with compromises on quality of care and monitoring, means that patient outcomes will be worse than those reported in clinical trials and carefully designed and monitored studies [42, 44, 216], largely because of poorer adherence [387, 452, 468], due to both quality of counselling and monitoring, patient selection, and problems with drug supply.

4.12.1 Treatment failure by stage of infection

Several studies have found that patients with lower CD4 counts at initiation of ART were significantly less likely to achieve durable virological suppression [27, 42, 443, 469-471], although Wood et al recently reported that, among persons who started ART at CD4 counts <200 cells/mm^3, outcomes were dramatically improved once the analysis was adjusted for adherence [63]. However, adherence levels are likely to deteriorate with increasing burdens of symptoms unless financial support, transportation and psychosocial support measures are in place. Ledergerber et al also reported that clinical stage C was associated with a decrease in probability of reaching undetectable pVL [27]. However, in a scaled-up setting with large numbers of patients, it is likely that adherence would be less for those with more advanced disease in the absence of sufficient provision of care, such as home visits, nutritional support and counselling and support services. Palella et al in the US HIV Outpatient Study (HOPS) found that those initiating ART before their CD4 count dropped below 200

cells/mm^3 were significantly more likely to achieve an undetectable pVL during the (median) three to four years of follow-up [432]. Cozzi Lepri et al (UK) reported that by 96 weeks since starting ART, probability of virological failure was 51.0% (95% CI 46.4%-55.6%) and 43.8% (95% CI 37.6%-50.4%) for patients starting ART with a CD4 count of ≤200 and 201-350 cells/mm^3, respectively [443]. Chaisson et al reported that of patients initiating ART with CD4 counts 200-350 cells/mm^3, 62% experienced an initial viral response with 29% having a durable response, while only 56% and 19% of patients with CD4 <200 cells/mm^3 had an initial and durable response, respectively [470].

4.12.2 Replicative fitness and transmission of drug resistance

$\beta^{TF}_{S1..8} = \beta^{T}_{R1..8} = z\beta^{U}_{S10}$, $\beta^{TF}_{S9} = \beta^{T}_{R9} = z\beta^{U}_{S11}$ z = 75% (LHS range: 50-100%)

ω^{1}_{U1} = 100% (LHS range: 75-100%) $\omega^{1}_{U2..11}$ = 5% (LHS range: 0-10%) ω^{1}_{T} = 100%

ω^{2}_{U} = 5% (LHS range: 0-10%) ω^{2}_{T} = 30% (LHS range: 20-40%)

ART-resistant virus variants are generally not as fit as wild type [83, 84, 472], with lower replication capacity with increasing numbers of mutations [89], and so are not as easily transmitted. The rebound of plasma viraemia as a result of resistance evolution tends to be below baseline levels [42, 88] and drug-resistant HIV-1 has been demonstrated to have decreased replication capacity in vitro [473]. Goudsmit et al interpreted the rapid replacement of ZDV-resistant mutants in newly-infected individuals in their study as being a reflection of the lower fitness and therefore infectiousness of resistant mutants [90]. However, transmission of resistant strains is possible and the frequency of this is increasing (Chapter 1 section 1.2.2.3). Nijhuis et al have found that continuous pressure in culture with a PI led to production of virus containing compensatory mutations that actually increase fitness, and predict that after a dip in infectiousness, viral fitness will eventually increase in patients infected with ART-resistant phenotypes [91]. Quinones-Mateu and Arts believe that this continual evolution under drug pressure will eventually lead to a recovery in fitness to levels similar or even higher than that of wild type virus [474]. Nonetheless, transmission of multidrug resistance still appears to be an uncommon occurrence, despite a high prevalence among treated patients. Leigh Brown et al estimated the frequency of transmission of drug-resistant HIV from patients receiving ART using retrospective surveys of clinic data and found that resistant virus was transmitted only ~20% as frequently as expected from these patients [83]. This figure was based on a series of assumptions about parameter values, with a high proportion of all infected individuals having received ART, and no allowance for decreases in risk behaviour of those on ART and those with virological failure. Authors investigated whether transmission of drug-resistant virus could be reduced because individuals with drug-resistant virus have lower average pVL. They found no difference in mean pVL between individuals with pVL >1,000 copies/mm^3 who had never received ART and individuals with treatment failure. If it is assumed that by having similar pVLs, these patients have similar infectivities, then transmission probabilities for treated individuals with treatment failure,

with or without resistance, can be assumed to equal the transmission probability for an untreated patient at the same infection stage. However, if the control group were at an earlier stage of infection, which is likely considering that they were ART naïve, this may not be a fair comparison. Other sources have reported that rebound of pVL as a result of resistance evolution tends to be below baseline levels [42, 88]. Therefore the model samples transmission probabilities for treated patients with treatment failure as 50%-100% (baseline 75%) of the transmission probability for an untreated infection at the same stage. However, treated patients with secondary resistance transmit ART resistant virus at a low frequency (ω_T^2 = 30%, LHS range: 20-40%) to reflect the findings of Leigh Brown et al [83]. This is in contrast to other models [188] and does not change with time. ART resistance is not the focus of the findings in Chapter 5; an analysis of the sensitivity of model results to changes in the assumed fitness of resistant variants, and changes in fitness of these variants over time and/or with scale of ART coverage, is an important area to be investigated.

Rates of transmission of drug resistance are probably underreported; unless blood samples are obtained shortly after infection, resistance may no longer be detectable in circulating virus, despite persisting in proviral reservoirs. This emphasises the potential role that individuals in the primary infection stage may play in transmitting drug resistance [393]. Therefore the probability that an individual with primary, transmitted ART resistance and not undergoing treatment transmits resistant virus is set to vary with stage of infection, with a very high probability for primary infection (100%, LHS range: 75-100%), and a much lower probability for later stages (5%, LHS range: 0-10%), to represent loss of resistance-conferring mutations in the absence of treatment pressure. However, the "memory" of resistance is not lost in these individuals, with only resistant virus being transmitted if ART is initiated (ω_T^1). Some models have incorporated a loss of resistance mutations and a return to completely ART-sensitive virus when treatment pressure is removed [90, 188, 475] because of the difference in replicative fitness between resistant and wild type strains. Such resistant strains are usually only detectable within months of infection, but they can persist for years [476, 477]. While outgrowth of fitter strains which have evolved to lose some of their resistance-conferring mutations occurs, quasispecies of the original resistant strain still remain, ready to replicate once treatment pressure is applied. Hance et al detected a small proportion of drug resistant variants more than five months after ART was discontinued, and showed that conventional genotyping techniques were not sensitive enough to detect persistence of all strains [394]. Therefore the model used in Chapter 5 does not assume a permanent loss of resistance, for individuals with primary or secondary resistant infections.

4.12.3 Other treatment failure and drop-out

Z_P = 5%, 15% (best and worst case scenarios respectively); Z = 2% (LHS range: 1-5%)

Treatment failure can also occur without resistance evolution, although viral rebound in the continued presence of ART greatly increases the likelihood that resistance will eventually evolve. However, treatment failure could also be considered as including drop-out due to tolerability issues. ARVs are toxic drugs with a myriad of side effects; therefore in the context of resource-poor settings where alternative regimens and facilities to manage these conditions may often be absent, this subgroup may be substantial. In a south Indian cohort, 26% of patients developed side effects and 10% discontinued ART as a result [97]. In Thailand, 7% of ART patients had to discontinue ART while a further 7% had to change one or two ARV drugs within their regimen [439]. However data on tolerability in the African setting are limited. Laurent et al reported that 51.7% of patients enrolled in their study of the Senegalese government's ART initiative experienced adverse effects [30]. No patients died as a result, but 4.3% of effects were life-threatening, 12.8% were severe and 8.5% involved hospitalisation of the patient. All cases of diarrhoea (25.5%) were related to the intake of multiple low-dose ddI pills and stopped when this dose form was abandoned. In settings where regimen changes and expert medical case are not readily available, the rate of drop-out as a result of such a pattern of adverse effects could be considerable.

The baseline assumption in the model is that patients are not withdrawn from ART at any time, despite virological or immunological failure, because of the substantial residual benefit that ART achieves even in the presence of continued viral replication. However, there can be voluntary withdrawal of treatment, or drop-out. Migration is not incorporated into this parameter, rather it is assumed that all withdrawal is due to tolerability problems, either because of toxicity or IRIS. It is assumed that there is a higher frequency of drop-out during the 'initial' phase for AIDS patients (5% best case, 15% worst case) than subsequently (2% per year, LHS range 1%-5%), because of IRIS (Djomand reported that the probability of an adverse even occurring in Côte d'Ivoire within six months of starting ART was 20% [131]).

4.13 Monitoring and evaluation

The type of monitoring facilities and frequency with which patients are seen following treatment uptake will affect the speed with which treatment failure is detected and acted upon. Programmes established in developing countries have typically recalled participants every three months [124, 380] or six months [30, 121, 137], often with closer monitoring just after treatment initiation [124]. The WHO guidelines recommend that a reasonable frequency of CD4 count measurement (where available) in patients on ART in resource-limited settings is every six months, with a first follow-up visit one month after treatment initiation [136]. However clinical monitoring should be more frequent, at least every three to four months. Monthly visits, combined with drug dispensing, are encouraged, as this gives an opportunity to reinforce adherence and safe sex education as well as to enquire

about any new symptoms. USDHHS guidelines recommend that pVL testing should be performed more frequently than CD4 count testing, every three to four months compared to every three to six months for CD4 counts [22]. The scenarios investigated in Chapter 5 assume a patient is seen by a doctor or another individual responsible for altering the patient's treatment every six months.

4.14 Discussion

This chapter presents a complex ART model which aims to capture some of the detail regarding drug resistance, changes in infectiousness and changes in sexual behaviour with stage of infection and treatment status. The model is used to compare various treatment scenarios and different assumptions regarding ART use in Chapter 5. A modified version of this model is used in Chapter 6 to investigate the impact of provision of second-line therapy and the timing of regimen switching. The core structure involving staged progression of HIV infection, followed by a second progression through treatment stages upon initiating ART, can be adapted to incorporate any number of separate treatment classes, depending on the nature of the research question.

Despite considerable attention being paid to estimate each parameter, inevitably some values will be more reliable than others. Future models of ART use could parameterise partner change rates using empical sexual behaviour data in order to gain more realistic estimates. However, in view of the limitations in using data on HIV infectiousness by stage of infection, as discussed in Chapter 3, it may be more appropriate in the future to estimate sexual behaviour parameters using survey data, where available, and to fit a model to HIV epidemics by varying the transmission probability parameters instead. The partner change rate for the most active sexual activity class given in Table 4.1 may be too high, even though it represents the core group, primarily composed of CSWs. Despite this issue, it is unlikely that results reported in the following chapters would be substantially affected by changing sexual behaviour parameters because the majority of results investigate benefits to those already infected. The investigation of the effect on transmission of unlimited ART to pre-AIDS and AIDS patients, conducted in the next chapter, may be more influenced by different partner change rate estimates. However, even where a substantial decrease in risk behaviour is envisaged and no ART patients are in the highest sexual activity group, HIV prevalence is still predicted to increase, as it is in all scenarios where the Malawi epidemic is simulated. Therefore it is unlikely that lower partner change rates would change the conclusions drawn from these results. There is some investigation of this in Chapter 5.

While the review of the literature in this chapter cannot be described as conclusive, the detailed investigation and use of sources of empirical data increases the reliability of model output. It may also be of use to other researchers parameterising HIV transmission models. The majority of data on the long-term effects of ART have been taken from studies in industrialised countries. As the results of more ART projects in resource-poor settings with longer durations of follow-up and with larger patient numbers are published, some of these parameters may be estimated more accurately for these settings.

Chapter 5 Impact of ART – results and treatment strategies

Summary

In this chapter, the deterministic model of HIV transmission and ART use introduced in Chapter 4 is used to gain insights into the effect of treatment in resource-poor settings. The impact of ART with unlimited treatment coverage is investigated and the effects of various treatment strategies under circumstances of limited coverage are also analysed. These strategies include the provision of laboratory facilities for CD4 count and pVL testing and the stage of infection at which treatment is initiated.

The model provides the framework for investigating the impact of various treatment scenarios. It examines the impact of these strategies on various epidemiological outcomes including number of infections, infections averted and life years gained per person year of treatment, as well as examining the emergence of drug resistance.

Unlimited ART provision initiated at late stage infection (AIDS) increases HIV prevalence. The effect of additionally treating pre-AIDS patients depends on the behaviour change of treated patients. Different coverage levels for ART do not affect benefits such as life years gained per person year of treatment and have minimal effect on infections averted when treating AIDS patients only. Scaling up treatment of pre-AIDS patients results in more infections being averted per person year of treatment, but the absolute number remains small. As coverage increases, the emergence and risk of spread of drug resistance increases. The withdrawal of failing treatment (clinical, immunological or virological failure) increases the numbers who can benefit from ART, but effectiveness per person is compromised. Only withdrawal upon virological failure would have a substantial impact on drug resistance emergence.

Therefore ART cannot be seen as a direct transmission prevention measure, regardless of the degree of coverage. Counselling of patients to promote safe sexual practices is essential, and must aim to effect long-term change without behavioural disinhibition. The chief aims of an ART programme, such as maximising numbers treated or effectiveness of treatment per patient, will determine which treatment strategy is most effective.

5.1 Background

In order to maximise the benefit of ART to patients and their communities, its impact on HIV epidemics should be evaluated and different approaches to ART delivery should be investigated. The effect that ART will have on transmission relies not only on its effect on life expectancy, infectiousness and treatment failure rates, but also on the stage of infection at which treatment is initiated, levels of coverage (which rely on the availability of resources and identification of patients qualifying for ART) and the scale and stage of HIV epidemic that the community is experiencing.

Previous mathematical models have predicted that ART will have a striking effect on transmission when coverage is high. Models based on the HIV epidemic among MSM in San Francisco [19] and Australia [192] have produced optimistic outcomes, providing risk behaviour does not increase substantially. However, it is unlikely that treatment of patients in resource-poor settings will be at an earlier stage of infection than CD4 counts of 200 cells/mm^3, as many are only diagnosed when their CD4 counts have reached less than 50 cells/mm^3 [22, 108]. Models need to explore more realistic patterns of ART use in such settings, incorporating the problems of late presentation of HIV infection, rationing of finite resources, limited health care facilities and inadequate nutrition levels.

Among the issues that need addressing are inclusion and exclusion criteria for ART programmes, which may involve TB status (and with that perhaps a proven record of good adherence from a TB DOT programme), and infection stage. ART may be targeted at those most in need and closest to death (AIDS patients), or it may also be used for pre-AIDS patients (pre-AIDS being defined as the period where virus is escaping immune system control and CD4 count declines, without ADCs), who are likely to have a better prognosis due to preserved immune function, and are likely to avoid the complications associated with IRIS. Given the limited data on effectiveness of ART programmes in resource-poor settings, further investigation of which approaches may be optimal, including cost effectiveness analysis, would be valuable before programme roll-out [478].

Mukherjee et al believe that the implementation of ART cannot wait until sufficient infrastructure is in place, and discuss the problem of limited laboratory infrastructure, suggesting that a stepwise progression as more resources become available would be appropriate [479]. They recommend initially implementing an ART programme based on clinical management (or at most TLC), with sequential addition of CD4 count testing, pVL testing and resistance testing. In this chapter, the effect of sequential adoption of these laboratory facilities on key outcome measures is investigated. The adoption of CD4 count testing allows for the identification of infected individuals who present without an ADC, but are still at a relatively late stage of infection, with a CD4 count in decline (pre-AIDS patients). The adoption of pVL testing can assist with the identification of such individuals, but additionally identifies treatment failure with viral rebound, which can precede further

decline in CD4 count or reappearance of OIs by a substantial period of time [480]. However, where rationing of ART exists, the expense of such facilities will further restrict the number on treatment. Furthermore, these facilities allow the identification of individuals who are more likely (pre-AIDS patients) and less likely (those failing therapy) to benefit from ART, leading to difficult ethical considerations concerning prioritisation.

In this chapter, many of these issues are explored by predicting and comparing the epidemiological impacts of alternative strategies, which provides a clear illustration of the trade-offs involved.

5.2 Treatment scenarios

Research questions included in the analysis were:

5.2.1 Effect of ART on different HIV epidemics

In order to model different types of HIV epidemic, with different basic reproductive numbers and thus scales, the partner change rates across all activity groups were cut to a third, generating an epidemic with a peak prevalence of 14.4%. ART was introduced in 2010 and 2040 to investigate the impact by maturity of each epidemic, with unlimited treatment of eligible individuals (details are provided in Table 5.1). HIV patients are recruited into the ART programme very quickly (an average of one month after qualifying for treatment due to reaching the appropriate HIV infection stage). This represents the most optimistic scenario, where all individuals qualifying for ART are screened, identified and treated virtually straight away, in order to investigate the maximum impact of ART. Results are investigated with baseline assumptions regarding behaviour change upon initiating ART, as described above, compared with more pessimistic assumptions, as described in Table 5.2.

Table 5.1 Summary of treatment scenarios – effect of ART on various epidemics, changes in size and maturity of HIV epidemic.

Graph	*Partner change rate by sexual activity class (per year)*				*Proportion in each activity class (%)*				*Time at which ART introduced*
	1	*2*	*3*	*4*	*1*	*2*	*3*	*4*	
a)	152.8	13.6	0.5	0.2	0.1	26	59	15	2010
b)	152.8	13.6	0.5	0.2	0.1	26	59	15	2040
c)	50.9	4.5	0.2	0.1	0.1	26	59	15	2010
d)	50.9	4.5	0.2	0.1	0.1	26	59	15	2040

Other parameters: all other parameters as in Table 4.1 using best case scenario values with unlimited treatment coverage. Graph letters refer to results shown in Figures 5.1 and 5.2.

Table 5.2 Summary of treatment scenarios – effect of ART on various epidemics, changes in ART patients' risk behaviours.

	Treatment uptake rates (year^{-1})		*Risk behaviour assumptions*	
Scenario	*AIDS*	*Pre-AIDS*	*AIDS*	*Pre-AIDS*
1	12	0	Baseline – patients stay in (lowest) sexual activity group 4 or move to group 3	No change (not treated)
2	12	0	Pessimistic – patients stay in (lowest) sexual activity group 4 or move to groups 2 and 3	No change (not treated)
3	12	12	Baseline – patients stay in (lowest) sexual activity group 4 or move to group 3	Baseline – patients move to the next lowest (less active) sexual activity group
4	12	12	Baseline – patients stay in (lowest) sexual activity group 4 or move to group 3	Pessimistic – no change in sexual activity group
5	0	0	No change	No change

Other parameters: all other parameters as in Tables 4.1 and 5.1 using best case scenario values with unlimited treatment coverage.

5.2.2 Impact of ART – levels of coverage

Using baseline values for all parameters (Table 4.1) and for baseline changes in risk behaviour upon initiating ART, key outcome measures were recorded for ART programme capacities varying from 5,000 to 60,000 patients. Best and worst case scenarios as well as scenarios where AIDS patients only versus AIDS and pre-AIDS patients qualified for treatment were calculated. ART is introduced in 2010.

5.2.3 Impact of ART – treatment strategies

To represent the availability or absence of CD4 count testing and pVL monitoring, timing of treatment initiation and withdrawal of failing treatment, parameters were varied as shown in Table 5.3. The model assumes that without CD4 count or pVL testing, only AIDS patients (defined as those showing ADCs) can be identified and treated (Scenarios A and D). A programme which offers CD4 count testing can treat individuals at an earlier stage of immunological decline, during pre-AIDS (Scenarios B and C, E to G). Where drugs are rationed, two possible approaches are explored: patients treated in the order in which they present to the clinic (a 'first come first served' approach, Scenario B); alternatively those likely to benefit most from ART and least likely to suffer complications such as IRIS and treatment failure may be preferentially treated (a 'best prognosis' approach, Scenario C).

Treatment failure in this case is defined as viral rebound, which can often precede immunological treatment failure (decline in CD4 count) and clinical progression by a considerable period [480], with patients still able to respond well to ART [41, 63]. Scenario D investigates clinical management, where patients having failed ART are removed from therapy an average of three months after developing AIDS. In Scenario E, even though CD4 testing would allow earlier detection of immunological treatment failure, it is still assumed that ART is only withdrawn for those with AIDS, whereas the earlier withdrawal due to the detection of failure is used in Scenario F. Scenario F involves withdrawal of ART at this detection stage, when immunological decline is identified. Individuals are withdrawn from ART after stage 7 of treatment ($j = 7$) i.e. within a year before progression to AIDS.

Scenario G incorporates pVL testing and assumes the extreme measure of withdrawing all ART at the virological treatment failure stage, when patients are still benefiting from treatment. pVL testing is assumed to identify treatment failure and facilitate withdrawal of individuals from therapy less than a year after treatment failure.

5.2.4 Parameter assignment

The majority of parameter values have been arrived at after review of the literature, as discussed in Chapter 4. The baseline values (best case scenario) were used for model runs in Figures 5.1 and 5.2 and the LHS ranges were used for the uncertainty analyses, sampling 100 times. LHS is used to explore ranges of possible values for model parameters in an efficient way, by providing a random coverage of parameter space across the LHS range [481]. Rather than simple random sampling, the parameter range is divided into 100 segements, with estimates randomly sampled, one from each of these segments. This ensures that the sample chosen is a good representation of the real variability. The model is then run 100 times, adopting each of the 100 values for each varied parameter once and at random (without replacement). Table 4.1 in Chapter 4 illustrates the range of parameter values used for LHS and the best and worst case scenarios for ART.

Table 5.3 Summary of treatment scenarios – availability of laboratory facilities

Scenario		Entry criterion	ART uptake rates (year^{-1})	Withdrawal of ART*
A	'Clinical management' or 'most in need'	AIDS only	Pre-AIDS = 0 AIDS = 12	No withdrawal
B	CD4 testing and 'first come first served'	AIDS and pre-AIDS	Pre-AIDS = 12 AIDS = 12	No withdrawal
C	CD4 testing and 'best prognosis'	Pre-Aids only	Pre-AIDS = 12 AIDS = 0	No withdrawal
D	Treatment withdrawal, clinical management	AIDS only	Pre-AIDS = 0 AIDS = 12	Rate of ART withdrawal upon progressing to AIDS: $\alpha_{Sj}^{T} = \alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 4$ (year^{-1}) $\{j = 9\}$
E	CD4 testing and 'first come first served' with treatment withdrawal	AIDS and pre-AIDS	Pre-AIDS = 12 AIDS = 12	Rate of ART withdrawal upon progressing to AIDS: $\alpha_{Sj}^{T} = \alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 4$ (year^{-1}) $\{j = 9\}$
F	Treatment withdrawal, CD4 count testing	AIDS and pre-AIDS	Pre-AIDS = 12 AIDS = 12	Patients withdrawn from ART before progressing to AIDS for all treated compartments $\alpha_{Sj}^{T} = \alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 1$ $\{j = 7,8\}$ $\phi_{Sj}^{T} = \phi_{Sj}^{TF} = \phi_{Rj}^{T1} = \phi_{Rj}^{T2} = 0$ (year^{-1}) $\{j = 7,8\}$ $\alpha_{Sj}^{T} = \alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 4$ (year^{-1}) $\{j = 9\}$
G	Treatment withdrawal, CD4 count and pVL testing	AIDS and pre-AIDS	Pre-AIDS = 12 AIDS = 12	Patients withdrawn from ART after viral rebound $\alpha_{Sj}^{T} = 1$ $\{j = 7,8\}$ $\alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 1$ $\{j = 1..8\}$ $\phi_{Sj}^{T} = 0$ (year^{-1}) $\{j = 7,8\}$ $\phi_{Sj}^{TF} = \phi_{Rj}^{T1} = \phi_{Rj}^{T2} = 0$ (year^{-1}) $\{j = 1..8\}$ $\alpha_{Sj}^{T} = \alpha_{Sj}^{TF} = \alpha_{Rj}^{T1} = \alpha_{Rj}^{T2} = 4$ (year^{-1}) $\{j = 9\}$

*Withdrawal as a result of treatment failure (defined as viral rebound or failed viral suppression, with or without drug resistance). All parameters not referred to above are as at baseline (Table 4.2). Treatment introduced at 2010. Other parameters: maximum number on treatment = 5,000. Best and worst case scenarios refer to optimistic and pessimistic selection of parameters regarding treatment failure rates (Table 4.2). Baseline assumptions regarding behaviour change upon initiating ART are assumed.

5.3 Results

5.3.1 Effect of ART on different HIV epidemics

The scenarios in Figures 5.1 and 5.2 illustrate the various long-term impacts that ART may have on HIV prevalence when used without limited capacity. The impact of widespread ART on the HIV epidemic (Figure 5.1) and cumulative HIV infections averted per person year of treatment (Figure 5.2) are illustrated. Figure 5.1 presents the total number of HIV infections rather than percentage prevalence because population growth has only been crudely estimated, so number of infections gives a clearer picture of the effect of ART on the epidemic.

All scenarios have high treatment uptake rates, requiring a rigorous screening programme in order to identify all patients eligible for ART, and the "best case" scenarios are used. Therefore this represents the best possible outcome of ART introduction.

The impacts of treating AIDS patients and pre-AIDS patients are different, partly because, in these unlimited treatment scenarios, the numbers receiving ART differ substantially. Treating only AIDS patients increases prevalence for all modelled epidemics by increasing life expectancy, while additionally treating pre-AIDS patients initially counteracts this to some extent by averting more infections (Figure 5.2). Changing the assumptions regarding behaviour change upon initiation of ART (see Table 5.2 for details) has little effect, when ART eligibility is limited to AIDS patients. In contrast, the pessimistic assumption of an absence of behaviour change for treated pre-AIDS patients (Scenario 4) substantially increases prevalence for all scenarios, especially for the epidemic with the lower R_0 (Figure 5.1). The most optimistic impact that ART may have on an HIV epidemic when there is no limitation on numbers treated is no change in number of infections compared to the no treatment scenario, which requires treatment of all AIDS and pre-AIDS patients, accompanied by significant change in risk behaviour, and an epidemic with an intrinsically low R_0 (Figure 5.1 c) and d)). Figure 5.2 suggests that while treating pre-AIDS patients may prevent infections in the short term, over the long term the net gain is considerably reduced. This is not due to outgrowth of ART-resistant virus; the constraint that wild type is more transmissible than the resistant phenotype prevents substantial primary resistance under this choice of parameters. Rather, the immediate effect of decreased risk behaviour among treated patients is negated by their increased life expectancy.

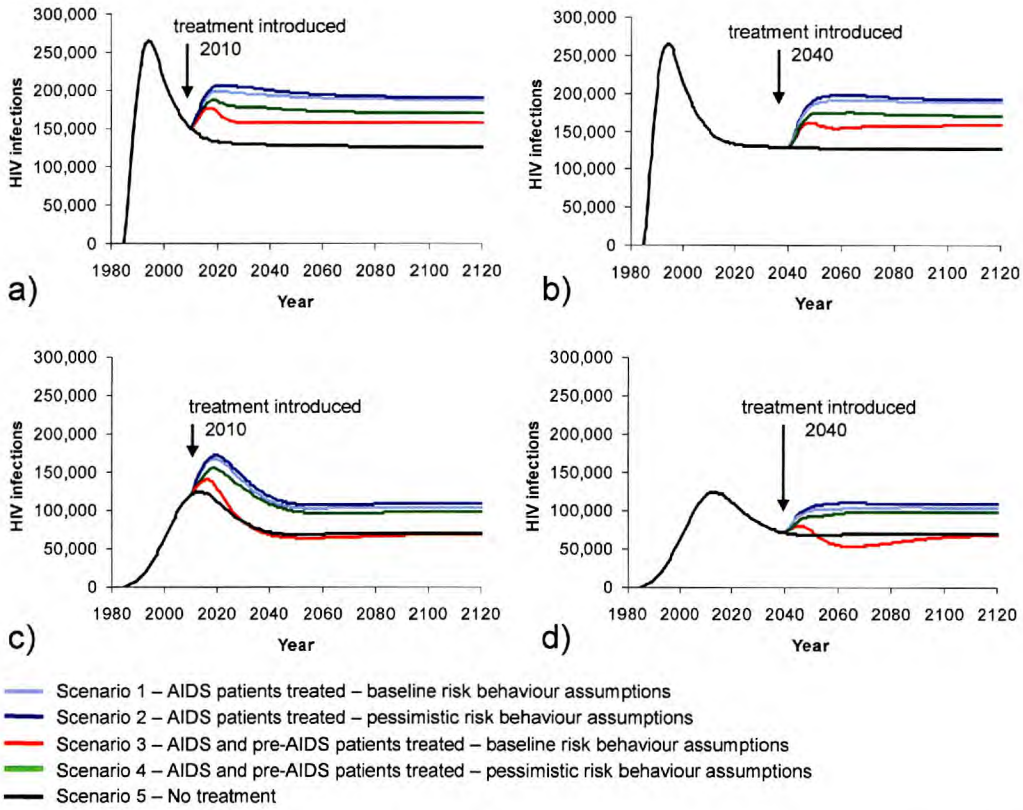


Figure 5.1 Total number of HIV infections through time for different HIV epidemics and under different assumptions regarding behaviour change of treated patients.
(a) and (b) a high prevalence, mature epidemic, similar to that of Malawi; (c) and (d) a smaller-scale epidemic (partner change rates a third of those for the Malawi simulation). (a) and (c) introduce ART in 2010, before equilibrium for (a) and early in the epidemic for (c); (b) and (d) introduce ART in 2040, once equilibrium is reached for (b) and after the peak of the epidemic for (d). For each HIV epidemic scenario graph, two treatment options and two behaviour change scenarios have been illustrated: 1) treatment of AIDS patients only, baseline behaviour change assumptions (Table 5.2); 2) treatment of AIDS patients only, pessimistic behaviour change assumptions (Table 5.2); 3) treatment of AIDS and pre-AIDS patients, baseline behaviour change assumptions; 4) treatment of AIDS and pre-AIDS patients, pessimistic behaviour change assumptions.

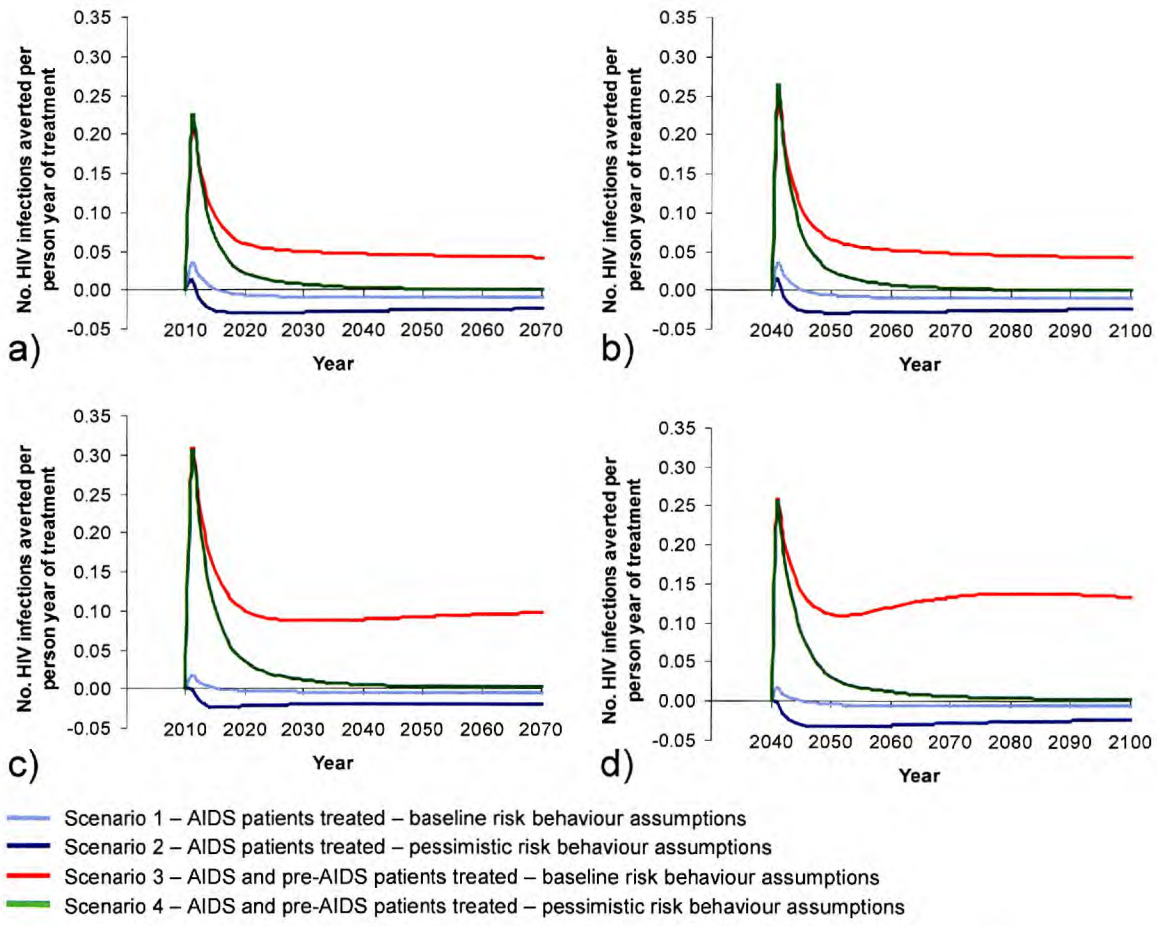


Figure 5.2 Total number of HIV infections averted per person year of treatment for various HIV epidemics and under different assumptions regarding behaviour change of treated patients. Scenarios as for Figure 5.1.

5.3.2 Impact of ART – levels of coverage

The effect when there are no constraints on the availability of ART drugs was compared with a limited number being treated at any one time, to reflect resource constraints (Figure 5.3). The implication for treatment coverage, in terms of proportion of individuals in need (AIDS and pre-AIDS patients) receiving ART for each programme capacity, is shown in Figure 5.3a.

Because of the limited effect of treatment on transmission in terms of infections averted per person year of treatment, the benefits of ART to the community per person year of treatment do not vary substantially with the capacity of a programme, as measured by life years gained (Figure 5.3b). Each additional person treated produces the same benefit in terms of life years gained and reduction in transmission and morbidity – for a mature epidemic, there will be no herd-effect producing a non-linear pattern of benefit of increasing access to ART in the short term. Paradoxically, treating both AIDS and pre-AIDS patients saves fewer life years per person year of treatment than an AIDS-only approach (Figure 5.3b), despite treating pre-AIDS averting more infections over this period (Figures 5.2a). The benefits of delaying imminent AIDS deaths are demonstrated immediately, while the prevention of future deaths by preventing infection impacts more slowly. The number of life years saved per person year of treatment for pre-AIDS and AIDS treatment overtakes that for AIDS-only treatment by 2029 for the 30,000 coverage scenario (Figure 5.4), while the results presented in Figure 5.3 represent programme performance at 2020.

A greater degree of coverage leads to a greater degree of resistance evolution and potential spread (Figure 5.3d). Furthermore, the greater the coverage of a poorly run programme where resistance evolution is frequent, the greater the opportunity for relatively fit ART-resistant mutants to evolve, which may compromise the entire programme in that area and possibly others.

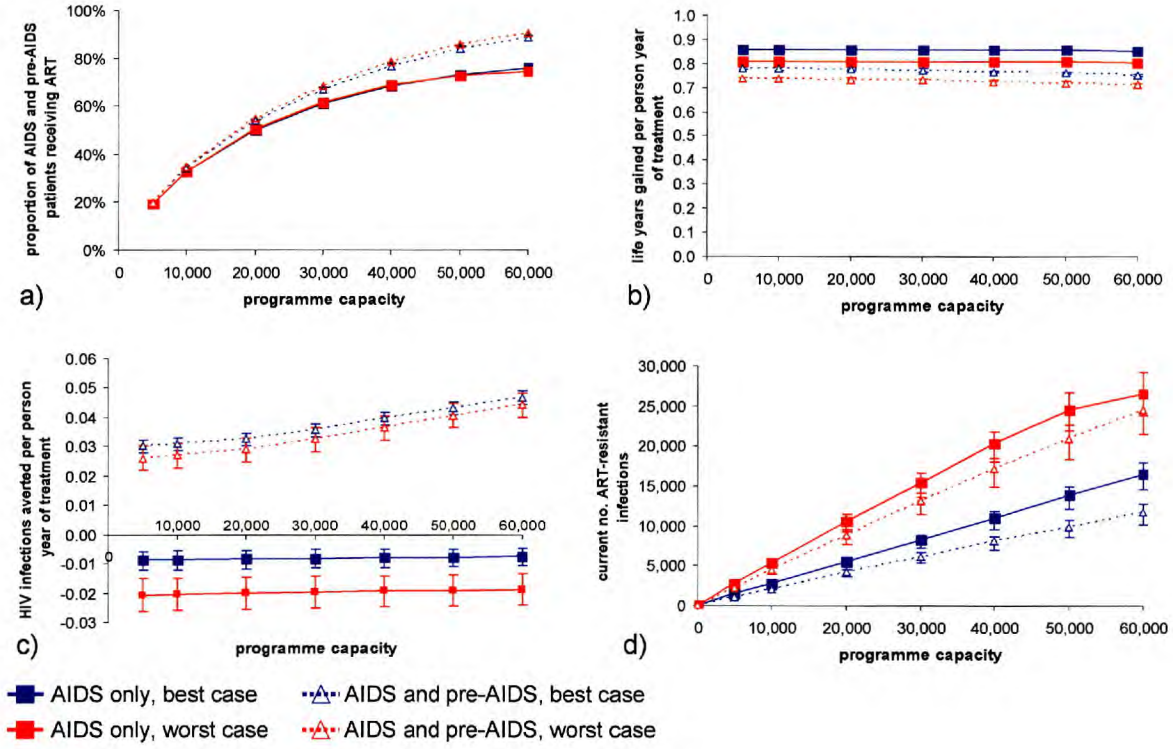


Figure 5.3 Effect of programme capacity.
Outcome measures 10 years after introduction of ART compared with no treatment, for various levels of coverage (ART programme capacities of 5,000 to 60,000) and for treating AIDS patients only or AIDS and pre-AIDS patients. Results are for the epidemic calibrated to Malawi prevalence data. Best and worst case scenarios refer to optimistic or pessimistic outcomes of ART use, respectively (see Table 4.1). (a) Coverage level, defined as proportion of individuals in need (AIDS and pre-AIDS patients) receiving ART; (b) cumulative number of life years gained over 10 years, per person year of treatment; (c) HIV infections averted per person year of treatment over 10 years; (d) current number of ART-resistant infections 10 years after ART introduction. Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range.

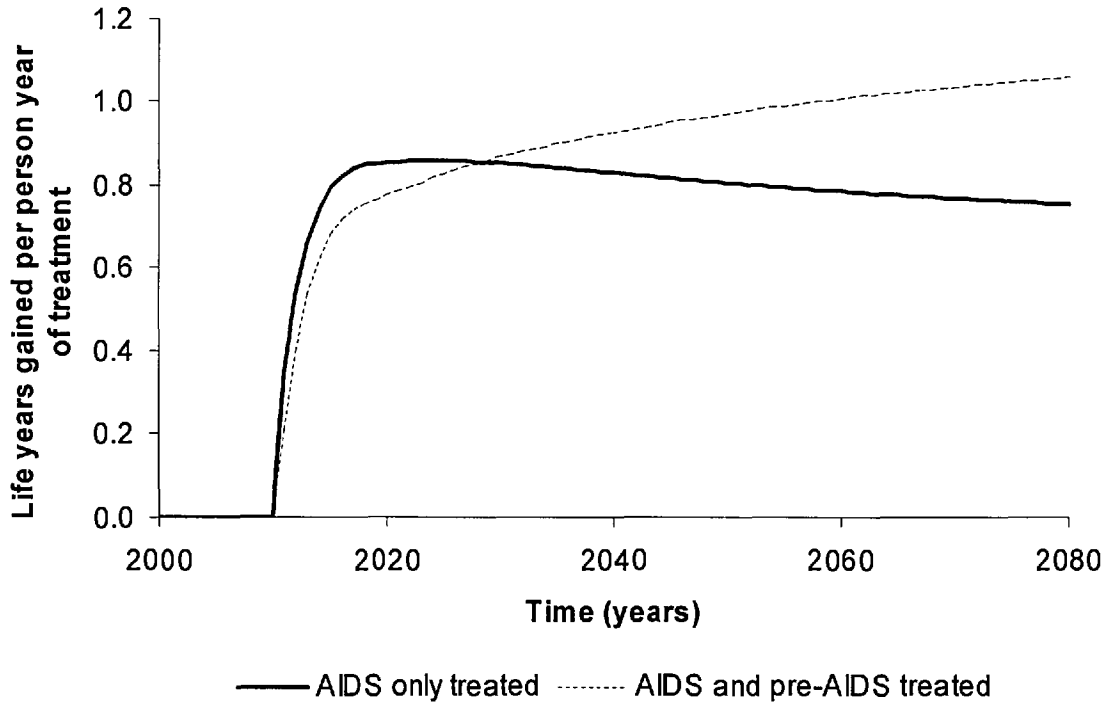


Figure 5.4 Comparison of life years gained per person year of treatment over time for AIDS only and AIDS and pre-AIDS treatment strategies.
Model run with treatment capacity of 30,000, best case scenario parameters.

5.3.3 Impact of ART – availability of laboratory facilities

Scenarios which may potentially be adopted by ART programmes in resource-constrained settings are described in Table 5.3 and Chapter 4 section 4.1, and relate not only to the availability of laboratory facilities but also to the priorities for treatment assigned by public health officials. It is assumed here that initiating treatment earlier before total destruction of the cellular immune system, at pre-AIDS rather than AIDS, leads to less risk of mortality, treatment failure and drop-out due to drug intolerability. It is also assumed that treatment failure leads to a decrease in effectiveness of treatment, but that ART still has a substantial beneficial effect in the "failed patient" (see Table 4.1).

Figure 5.5a again shows that 10 years after treatment introduction, the benefits of averting new infections by treating pre-AIDS patients have not yet been generated, so treating only AIDS patients appears to confer more benefit in terms of life years gained (Scenario A versus Scenario C). Figure 5.5b shows that without treatment withdrawal, pre-AIDS patients remain on ART substantially longer than AIDS patients, because they have a better prognosis (lower mortality and likelihood of treatment failure). The influence of rates of treatment failure on duration on ART is shown by the large differences between best and worst case scenarios. Treatment withdrawal significantly decreases the average duration on ART, by over a year in some scenarios. Figure 5.5c again shows that the earlier individuals are placed on ART, the more infections that are averted under these assumptions regarding behaviour change. Figure 5.5d shows population-level resistance prevalence, which appears relatively low, but is the result of relatively small coverage of the population (approximately 20% of all those in need at 2020).

For "clinical" treatment withdrawal, there is little impact in terms of infections averted and resistance emergence (Scenario A versus D and B versus E, Figures 5.5c and 5.5d). ART withdrawal is just a few months before death from AIDS, but in the context of rationing, this frees up previously ineffectual treatment for others. Therefore, both life years gained per person year of treatment and the number of individuals that can be reached with ART increase slightly (Figures 5.5a and 5.5b). The unrealistic strategies of removing treatment which still confers benefit (Scenarios F and G) increase access to ART but decrease the benefit per person receiving ART (Figure 5.5b). Life years gained per person year of treatment increase slightly because resources are directed in a more "efficient" way (Figure 5.5a). However, the difference in life years gained for all scenarios is small; all patients must receive ART continuously to benefit, so this is not surprising. Assumptions regarding treatment withdrawal for Scenario G mean that all patients are withdrawn from ART after treatment failure before emergence of drug resistance, which is unrealistic, but illustrates the maximum impact that such a policy could have (Figure 5.5d). The impact on HIV transmission and life years gained remains minimal (Figure 5.5c), and patients' duration on ART (a measure of life expectancy) is substantially reduced, although total numbers benefiting from therapy increases (Figure 5.5b).

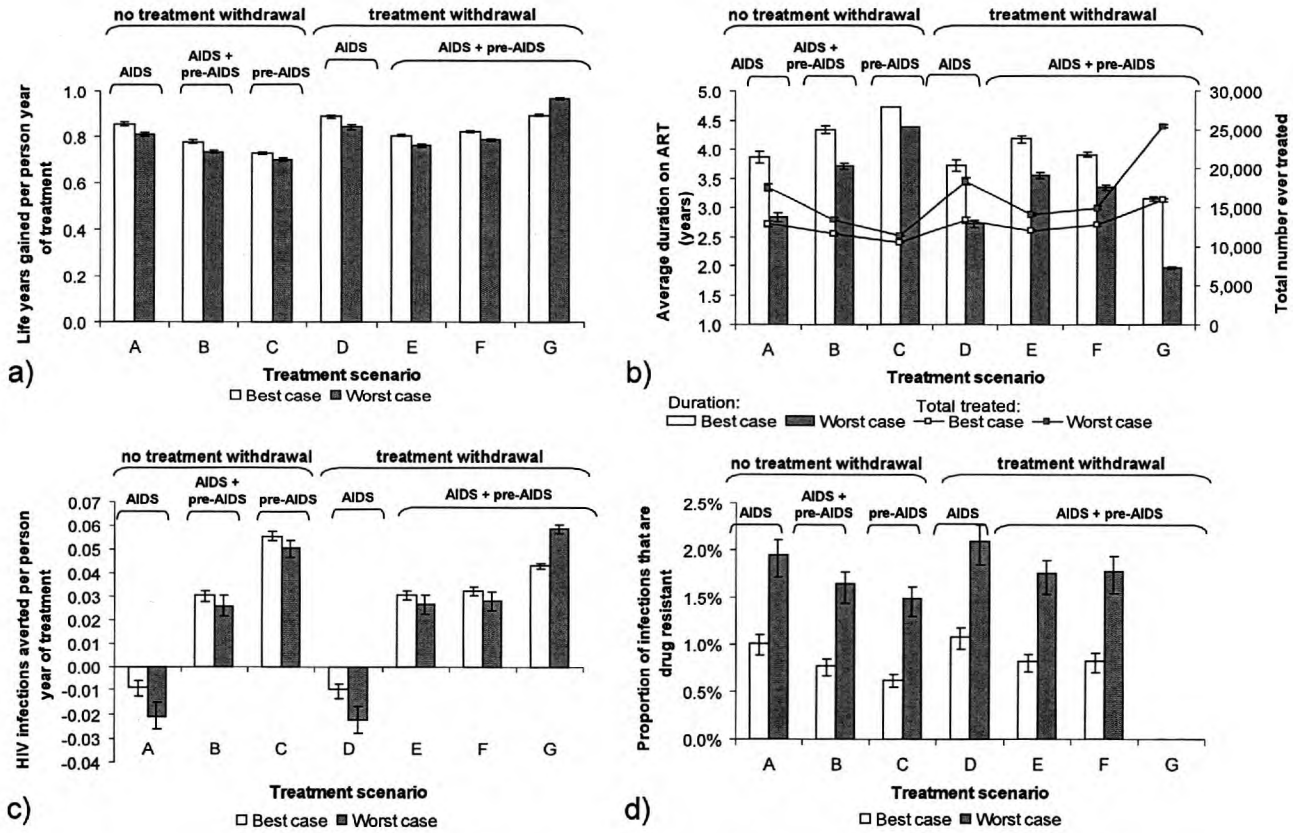


Figure 5.5 Description of potential treatment strategies for ART programmes in resource-poor settings.
The seven scenarios shown refer to different levels of use of laboratory testing and prioritisation of different groups of patients (see Table 5.3). (a) Cumulative life years gained per person year of treatment compared to no treatment; (b) average duration on ART per patient and cumulative number ever treated; (c) HIV infections averted per person year of treatment compared to no treatment; (d) proportion of all infections in the population that are ART-resistant at 10 years after ART introduction. Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range. Outcome measures are 10 years after introduction of ART compared with no treatment. Best and worst cases refer to optimistic and pessimistic parameter estimates.

5.3.4 Sensitivity of results to partner change rate estimates

The partner change rate for the most active sexual activity class given in Chapter 4 Table 4.1 may be too high, even though it represents the core group, primarily composed of CSWs. It is likely that many combinations of parameter values could fit to the Malawi prevalence data, and so the robustness of the model output to changes in these parameters was tested. A subsequent curve fit to the Malawi prevalence data using more stringent restrictions on the maximum values produced more conservative estimates for partner change rates, of 60, 13.6, 0.5 and 0.2 partners per year for sexual activity groups one to four respectively, composing 0.6%, 25%, 46% and 28% of the population, with mixing parameter ε set at 0.37. Figure 5.6 compares the model results for effect of unlimited ART on prevalence using the original partner change rates with those using the partner change rates from the second curve fit. As predicted in the Discussion section 4.14 in Chapter 4, there is not a large difference in results, which increases the validity of the conclusions drawn from this model regarding the effect of ART on transmission. Sexual behaviour data may lead to different estimates for partner change rates and distributions between the sexual activity classes, which may lead to more substantial differences in model results than shown here, but it is unlikely that they would lead to a qualitative difference or change the conclusions made.

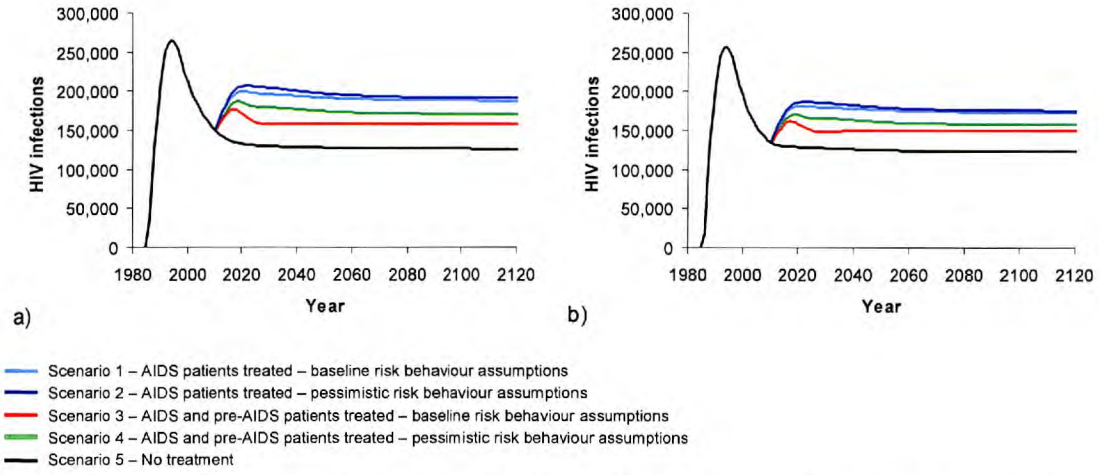


Figure 5.6 Comparison of predicted effect of ART using different partner change rate estimates.
Total number of HIV infections through time under different assumptions regarding behaviour change of treated patients, as for Figure 5.1a with treatment introduced at 2010. (a) represents baseline partner change rates from Chapter 4 Table 4.1; (b) represents the lower partner change rate for the most active sexual activity class, as defined in the text.

5.4 Discussion

HIV epidemics in sub-Saharan Africa are not likely to be amenable to control through treatment, regardless of the extent of ART roll-out. Therefore treatment must be integrated with prevention methods. In the absence of substantial behaviour change of treated patients through effective counselling, prevalence is likely to increase. Different coverage levels for ART do not affect benefits such as life years gained per person year of treatment and have minimal effect on infections averted when treating AIDS patients only. Scaling up treatment of pre-AIDS patients results in more infections being averted per person year of treatment, but the absolute number remains small. As coverage increases, the emergence and risk of spread of drug resistance increases. The withdrawal of failing treatment (clinical, immunological or virological failure) increases the numbers who can benefit from ART, but effectiveness per person is compromised. Only withdrawal upon virological failure would have a substantial impact on drug resistance emergence.

Therefore ART cannot be regarded as a direct transmission prevention measure, regardless of the degree of coverage. Counselling of patients to promote safe sexual practices is essential, and must aim to effect long-term change without behavioural disinhibition. The chief aims of an ART programme, such as maximising numbers treated or effectiveness of treatment per patient, will determine which treatment strategy is most effective.

While this model incorporates some behaviour change upon initiating ART, it does not consider the complex effects of VCT on risk behaviour. Both uptake of VCT and risk taking behaviour may vary substantially by scale of coverage and performance of ART programmes, and their impact is likely to have a large impact on prevalence. The absence of gender reduces model complexity to a certain extent, but models incorporating VCT and predicting the effects of this intervention on risk behaviour will need more realistic structure. Gender and age would need to be modelled explicitly, due to the complex mixing patterns by age and sex observed in sub-Saharan Africa and the differential impact of HIV diagnosis on risk behaviour by gender due to the social context, including women's autonomy. Including gender and age in this model would have provided the opportunity to model patterns of sexual mixing in sub-Saharan Africa more realistically, incorporating preferential mixing of older men with younger women, for example. However, the impact of ART on transmission, in terms of reducing infectiousness and increasing duration of infection, (biological rather than behavioural effects), is not likely to be significantly altered by adding this level of complexity, and the effect of ART in terms of behaviour change is unknown in this context, and so it may not be particularly informative to model a myriad of scenarios involving complex patterns of behaviour change.

CD4 count testing allows the identification of pre-AIDS patients. Additionally, the implementation of laboratory facilities for pVL monitoring allows the identification of treatment failure earlier, increasing the sustainability of the programme, either allowing switching to a salvage

regimen, or perhaps (in the absence of alternative treatments) by halting therapy and giving the drugs to another patient whose prognosis is better, as investigated here. The benefits of pVL testing will increase with higher levels of resistance in the population. The model does not incorporate background drug resistance levels due to uses of ART outside the modelled programme, but levels of resistance are likely to be higher in many areas due to PMTCT and sporadic drug use, and some programmes having used only double or single therapy [132, 482]. For example, in the UNAIDS/Uganda Ministry of Health DAI pilot project, only 64% of patients were ART drug naïve before enrolling in the initiative [132]. The model results suggest similar levels of benefit per person year of treatment regardless of the scale of ART provision, but in reality, scaling up programmes is likely to compromise quality, meaning higher drop-out rates, mortality and treatment failure, negating the beneficial impacts of ART and increasing the rate of drug resistance emergence.

Withdrawal of "failing treatment", where this is defined as virological or immunological failure, when the patient would still benefit from continuing ART, is unlikely to be acceptable to any ethics committee or government. However, the exploration of this has shown the benefits in terms of increasing access to (albeit less effective) treatment to more individuals, and for virological failure, slowing the emergence of drug resistance. While the net health benefits in terms of life years gained will be similar for each strategy, in a wider context, factors such as delaying orphanhood by a short time for many patients' children, or by a long time for fewer, make this comparison difficult to evaluate.

Results from this model suggest that counselling of ART patients to promote safe sexual practices is essential, and must aim to effect long-term change without behavioural disinhibition. Withdrawal of treatment at a potentially acceptable stage, that is after immunological deterioration, when ART is no longer of benefit, will not have a substantial effect on containing resistance emergence, but would slightly increase the number able to benefit from treatment. As the pace of ART rollout across southern Africa quickens, difficult decisions regarding the allocation of finite resources will have to be made. Mathematical models are increasingly being employed to determine optimal strategies for allocation of these funds [156, 204]. Analysing the implications of different treatment strategies, using data from early programmes coupled with the type of methods presented here, is needed to give programmes the best possible chance of success.

Chapter 6 Second-line therapy

Summary

In this chapter ART use is modelled more realistically than hitherto because a second-line, salvage regimen is also incorporated. A second-line regimen, designed to continue successful treatment of patients who have failed their first regimen, is a recommendation for ART roll-out in the WHO guidelines. However, ARV drugs used in these combinations tend to be more expensive than first-line regimens and there is a higher risk of treatment failure for patients who have previously failed another combination. In this chapter, the benefits of salvage regimen provision are modelled. The ART model described in Chapter 4 is modified to incorporate a second regimen and scenarios under constraints on patient numbers and drug costs are investigated. By providing a salvage regimen, patients live longer but at the cost to the programme of decreasing the number ever standing to benefit from ART. The beneficial effect of a salvage regimen is less marked when cost-related problems lead to delays in providing drugs because many patients die before they are switched to the more expensive second-line therapy. If a patient fails salvage therapy in a situation where patient management is based on clinical criteria, there is little cost-saving benefit of switching back to the cheaper first-line regimen because the patient will have progressed to AIDS and therefore be close to death at the time of the switch. If switching upon treatment failure to either first- or second-line regimens occurs earlier, facilitated by immunological or virological monitoring, there will be a shorter exposure to the reduced but continuing clinical benefits that a regimen can provide, overall reducing a patient's life expectancy (in the absence of third- or fourth-line options). The rate of treatment failure has less impact on programme costs than anticipated because patients still benefit substantially from a regimen even with viral rebound.

6.1 Background

The internationally recommended ART provision guidelines recommend two lines of treatment. Such an approach is designed to address problems related to toxicity, resistance and treatment failure. The impact of two-regimen ART provision in resource-poor settings has been modelled previously using the ASSA2000 Interventions Model, within a costing exercise, which is described in detail in Chapter 4 of Nattrass, 2004 [483]. The model assumes that the two-line triple therapy is made freely available to adults who are HIV-positive and have experienced AIDS-defining symptoms, or whose CD4 counts are below 200 cells/mm^3. The price of treatment varies depending on whether patients are on first-line or second-line treatment. The cost calculations assume that first-line treatment cost 300 South African Rand a month, and second-line treatment 450 Rand a month. These prices are in

line with the best prices available to the private sector in South Africa at the time of publication, but are substantially more than the international best-price offers available, or of WHO pre-qualified generics. Therefore, despite the costs being relevant to the situation at the time, the authors acknowledge that cheaper drug regimens than those used in the study could become available.

The ASSA (Actuarial Society of South Africa) model assumed a 20.6% chance of a patient moving to second-line treatment each year. Patients remained on the second-line regimen until they were assumed to be removed from the treatment programme. The costing model also includes a wastage factor of 5% and a 20% additional care factor, to account for patients requiring care due to serious side effects of treatment, inadequate recovery, psychological support needs and requirements for special medicines. In a similar vein to this South Africa-specific work, the mathematical model described here involves a two-line ART regimen, with patients at risk of failing both the first- and second-line drug combinations. However it is the epidemiological impact of policy rather than an analysis of cost effectiveness that is investigated here.

In the model described in this chapter, patients are assumed to fail their second regimen at a faster rate than their first because it has been demonstrated that viral suppression is often difficult to achieve in patients with extensive prior treatment, and treatment failure is more common [22, 42]. In order for the model to represent the situation in the majority of sub-Saharan Africa, limits are placed on resources. Two scenarios are envisaged: limitation by patient number, as employed by the ART model in Chapter 5, and limitation by programme cost. Limitation by patient number is a more realistic constraint in circumstances where the scarcity is human resources [434]. Limitation by cost is the alternative, and may be more applicable if ART programmes are approved which delegate drug dispensing to nurses, community workers or volunteers. This is not a costing exercise, and ignores all overheads associated with such programmes. The aim is to investigate the trade-offs associated with different strategies regarding salvage regimen provision, under the limitation of finite resources. Different approaches include the timing of switching from a failing regimen to a new one upon clinical, immunological or virological treatment failure. Upon failure of a salvage regimen, with no further treatment options, a patient may remain on the same regimen till death, be switched back to a cheaper first-line regimen, or withdrawn from treatment entirely. The implications of these various strategies are analysed in this chapter.

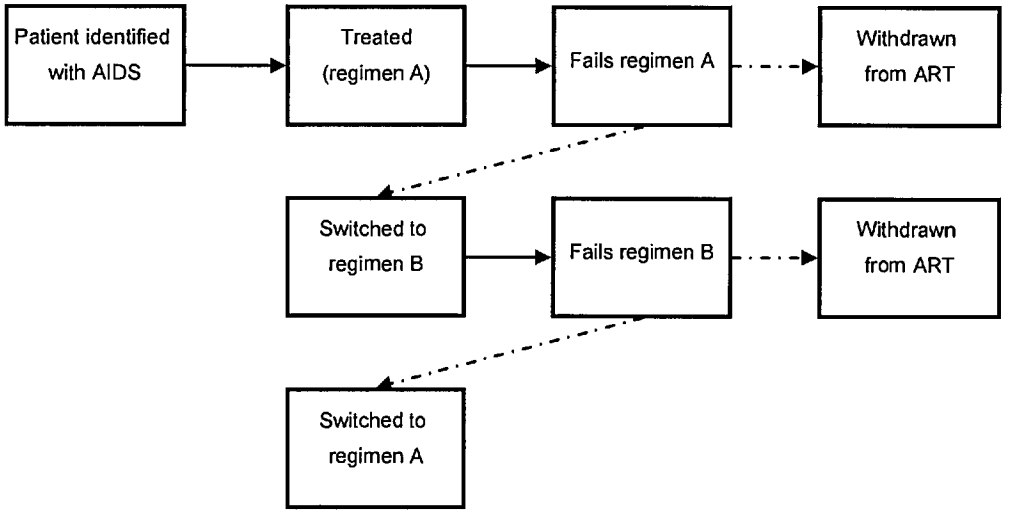
6.2 Methods

The ART model used in this chapter is based on the model described in Chapter 4, but modified in order to analyse different treatment strategies involving the provision of two ART regimens. The core structure of the initial model, incorporating heterogeneous sexual behaviour, stages of HIV infection, and treatment stages remains, but there is no explicit inclusion of drug resistance. The inclusion of a second regimen greatly increases the number of treatment compartments and the complexity of the flow diagrams for the model and therefore the inclusion of resistance including tracking resistance to separate regimens, would have led to unwieldy

calculations. The ART-resistant treatment classes from the initial model have been removed, but the model includes treatment failure, defined as viral rebound from any cause. The model assumes a permanent memory of treatment failure to a particular regimen and so can account for treatment failure due to secondary resistance, but it cannot incorporate transmitted, primary resistance. The second major modification is that, for simplicity, only individuals who have developed AIDS qualify for treatment in this model. Patients always start on regimen A, with regimen B used as second-line therapy. The flow diagram of patient management for AIDS patients in this model is shown in Figure 6.1. While the core structure of the model is the same as the model described in Chapter 4, the differences between models relate to treatment classes and can be identified by comparing Figure 6.1 with Figure 4.1. The previous model used one triple regimen only; the model in this chapter has two regimens, A and B. Upon treatment failure with either regimen, there is the possibility of withdrawal from treatment, depending on the treatment strategy. Alternatively, patients may remain on a failed regimen until death; patients failing regimen B may be transferred back onto regimen A, which is no more efficacious (because they have previously experienced treatment failure to this regimen), but it saves on costs because regimen B is more expensive than A.

Figure 6.2 is a schematic illustrating the incorporation of the flow diagram (Figure 6.1) within a simplified diagram of the model structure. For simplicity, the 'initial' period upon starting ART is not included in the diagram. Figure 6.3 is a more complex version of Figure 6.2 and illustrates the transitions between the treatment stages and eventual progression to AIDS more explicitly.

Figure 6.1 Flow diagram of patient management for an ART model incorporating second-line therapy, without drug resistance.
Dashed lines represent flow rates which may be switched on or off, depending on the treatment scenario investigated.



Values for all parameters used in the model are the same as those used in Chapter 5 and are listed in Table 4.1 of Chapter 4. The values of parameters which are not part of the ART model

used in Chapter 5 are shown in Table 6.1. The baseline assumptions regarding changes in sexual behaviour as a result of progressing to AIDS and initiating ART are assumed. As for Chapter 5, ART is initiated in 2010, with outcomes evaluated 10 years after treatment introduction.

6.2.1 State variables

For individuals in sexual activity class i, HIV infection stage j and treatment stage m relating to regimens A and B (where applicable):

S_i = susceptible individuals $\{i=1..4\}$

I_{ij}^{U} = HIV infected, untreated $\{i=1..4, j=1..11\}$

I^{Temp} = HIV infected, 'initial' phase of treatment (A)

$I_{im}^{T_A}$ = HIV infected, treated (A) $\{i=1..4, m=1..9\}$

$I_{im}^{T_A F_A}$ = HIV infected, treated (A) but treatment failure (A) $\{i=1..4, m=1..9\}$

$I_{im}^{UF_A}$ = HIV infected, treatment failure (A), withdrawn from treatment (A) $\{i=1..4, m=1..9\}$

$I_{im}^{T_B F_A}$ = HIV infected, treated (B) but previous treatment failure (A) $\{i=1..4, m=1..9\}$

$I_{im}^{T_B F_A F_B}$ = HIV infected, treated (B) but treatment failure (A and B) $\{i=1..4, m=1..9\}$

$I_{im}^{UF_A F_B}$ = HIV infected, treatment failure (A and B), withdrawn from treatment (B) $\{i=1..4, m=1..9\}$

$I_{im}^{T_A F_A F_B}$ = HIV infected, treatment failure (A and B), switched back to original regimen (A)

$\{i=1..4, m=1..9\}$

6.2.2 Other values

λ_i = force of infection

N_i = total in sexual activity group i

6.2.3 Transmission equations

The ordinary differential equations which define the model are shown below. Parameters used are as for the model described in Chapter 5, the values of which are given in Table 4.1, Chapter 4; otherwise they are detailed in Table 6.1.

(6.1) $S_i' = \theta_i \chi N_0 - S_i(\lambda_i + \mu)$ $\{i=1..4\}$

(6.2) $I_{ij}^{U\prime} = S_i\lambda_i - I_{ij}^{U}(\phi_j^{U} + \mu)$ $\{i=1..4, j=1\}$

(6.3) $I_{ij}^{U\prime} = \phi_{j-1}^{U} I_{ij-1}^{U} - I_{ij}^{U}(\phi_j^{U} + \mu)$ $\{i=1..4, j=2..10\}$

(6.4) $$I_{ij}^{U\prime} = \Theta_i + \phi_{j-1}^{U}\mathrm{H}_{ij}^{U} - I_{ij}^{U}\left(\nu+\mu+\gamma_A\right) \qquad \{i=1..4, j=11\}$$

(6.5) $$I^{Temp\prime} = \gamma_A I_{ij}^{U} - I^{Temp}\left(P+\mu\right) \qquad \{i=4, j=11\}$$

(6.6) $$I_{im}^{T_A\prime} = P\left(1-Z_P-f_P-\nu_T^P\right)\mathrm{K}_i I^{Temp} - I_{im}^{T_A}\left(\phi_m^{T_A}+\mu+\alpha_m^{T_A}+\gamma_{Bm}\right) \qquad \{i=1..4, m=1\}$$

(6.7) $$I_{im}^{T_A\prime} = \left(1-f_A-Z_A\right)\phi_{m-1}^{T_A} I_{im-1}^{T_A} - I_{im}^{T_A}\left(\phi_m^{T_A}+\mu+\alpha_m^{T_A}+\gamma_{Bm}\right) \qquad \{i=1..4, m=2..8\}$$

(6.8) $$I_{im}^{T_A\prime} = \left(1-f_A-Z_A\right)\phi_{m-1}^{T_A}\mathrm{H}_{im}^{T_A} - I_{im}^{T_A}\left(\nu+\mu+\alpha_m^{T_A}+\gamma_{Bm}+Z_A+f_A\right) \qquad \{i=1..4, m=9\}$$

(6.9) $$I_{im}^{T_AF_A\prime} = Pf_P\mathrm{K}_i I^{Temp} - I_{im}^{T_AF_A}\left(\phi_m^{TF_A}+\mu+\alpha_m^{TF_A}+\gamma_{BFm}\right) \qquad \{i=1..4, m=1\}$$

(6.10) $$I_{im}^{T_AF_A\prime} = f_A\phi_{m-1}^{T_A} I_{im-1}^{T_A} + \left(1-Z_A\right)\phi_{m-1}^{TF_A} I_{im-1}^{T_AF_A} - I_{im}^{T_AF_A}\left(\phi_m^{TF_A}+\mu+\alpha_m^{TF_A}+\gamma_{BFm}\right) \qquad \{i=1..4, m=2..8\}$$

(6.11) $$I_{im}^{T_AF_A\prime} = \left(1-Z_A\right)\phi_{m-1}^{TF_A}\mathrm{H}_{im}^{T_AF_A} + f_A\left(I_{im}^{T_A}+\phi_{m-1}^{T_A}\mathrm{H}_{im}^{T_A}\right) - I_{im}^{T_AF_A}\left(\nu+\mu+\alpha_m^{TF_A}+\gamma_{BFm}+Z_A\right) \qquad \{i=1..4, m=9\}$$

(6.12) $$I_{im}^{UF_A\prime} = \left(Z_A\phi_{m-1}^{T_A}+\alpha_{m-1}^{T_A}\right) I_{im-1}^{T_A} + \left(Z_A\phi_{m-1}^{TF_A}+\alpha_{m-1}^{TF_A}\right) I_{im-1}^{T_AF_A} + \phi_{m-1}^{UF} I_{im-1}^{UF_A} - I_{im}^{UF_A}\left(\phi_m^{UF}+\mu\right) \qquad \{i=1..4, m=1..8\}$$

(6.13) $$I_{im}^{UF_A\prime} = \left(Z_A+\alpha_m^{T_A}\right) I_{im}^{T_A} + \left(Z_A\phi_{m-1}^{T_A}+\alpha_{m-1}^{T_A}\right)\mathrm{H}_{im}^{T_A} + \left(Z_A+\alpha_m^{TF_A}\right) I_{im}^{T_AF_A} + \left(Z_A\phi_{m-1}^{TF_A}+\alpha_{m-1}^{TF_A}\right)\mathrm{H}_{im}^{T_AF_A} + \phi_{m-1}^{UF}\mathrm{H}_{im}^{UF_A} - I_{im}^{UF_A}\left(\nu+\mu\right) \qquad \{i=1..4, m=9\}$$

(6.14) $$I_{im}^{T_BF_A\prime} = \sum_{m=1}^{9}\left(\gamma_{Bm} I_{im}^{T_A} + \gamma_{BFm} I_{im}^{T_AF_A}\right) - I_{im}^{T_BF_A}\left(\phi_m^{T_B}+\mu+\alpha_m^{T_B}+\gamma_{Cm}\right) \qquad \{i=1..4, m=1\}$$

(6.15) $$I_{im}^{T_BF_A\prime} = \left(1-f_B-Z_B\right)\phi_{m-1}^{T_B} I_{im-1}^{T_BF_A} - I_{im}^{T_BF_A}\left(\phi_m^{T_B}+\mu+\alpha_m^{T_B}+\gamma_{Cm}\right) \qquad \{i=1..4, m=2..8\}$$

(6.16) $$I_{im}^{T_BF_A\prime} = \left(1-f_B-Z_B\right)\phi_{m-1}^{T_B}\mathrm{H}_{im}^{T_BF_A} - I_{im}^{T_BF_A}\left(\nu+\mu+\alpha_m^{T_B}+\gamma_{Cm}+Z_B+f_B\right) \qquad \{i=1..4, m=9\}$$

(6.17) $$I_{im}^{T_BF_AF_B\prime} = f_B\phi_{m-1}^{T_B} I_{im-1}^{T_BF_A} + \left(1-Z_B\right)\phi_{m-1}^{TF_B} I_{im-1}^{T_BF_AF_B} - I_{im}^{T_BF_AF_B}\left(\phi_m^{TF_B}+\mu+\alpha_m^{TF_B}+\gamma_{CFm}\right) \qquad \{i=1..4, m=1..8\}$$

(6.18) $$I_{im}^{T_BF_AF_B\prime} = f_B\left(I_{im}^{T_BF_A}+\phi_{m-1}^{T_B}\mathrm{H}_{im}^{T_BF_A}\right) + \left(1-Z_B\right)\phi_{m-1}^{TF_B}\mathrm{H}_{im}^{T_BF_AF_B} - I_{im}^{T_BF_AF_B}\left(\nu+\mu+\alpha_m^{TF_B}+\gamma_{CFm}+Z_B\right) \qquad \{i=1..4, m=9\}$$

(6.19) $$I_{im}^{UF_AF_B\prime} = \left(Z_B\phi_{m-1}^{T_B}+\alpha_{m-1}^{T_B}\right) I_{im-1}^{T_BF_A} + \left(Z_B\phi_{m-1}^{TF_B}+\alpha_{m-1}^{TF_B}\right) I_{im-1}^{T_BF_AF_B} + Z_A\phi_{m-1}^{TF_{AB}} I_{im-1}^{T_AF_AF_B} + \phi_{m-1}^{UF} I_{im-1}^{UF_AF_B} - I_{im}^{UF_AF_B}\left(\phi_m^{UF}+\mu\right) \qquad \{i=1..4, m=1..8\}$$

(6.20) $$I_{im}^{UF_AF_B\prime} = \left(Z_B+\alpha_m^{T_B}\right) I_{im}^{T_BF_A} + \left(Z_B\phi_{m-1}^{T_B}+\alpha_{m-1}^{T_B}\right)\mathrm{H}_{im}^{T_BF_A} + \left(Z_B+\alpha_m^{TF_B}\right) I_{im}^{T_BF_AF_B} + \left(Z_B\phi_{m-1}^{TF_B}+\alpha_{m-1}^{TF_B}\right)\mathrm{H}_{im}^{T_BF_AF_B} + Z_A\phi_{m-1}^{TF_{AB}}\mathrm{H}_{im}^{T_AF_AF_B} + Z_A I_{im}^{T_AF_AF_B} + \phi_{m-1}^{UF}\mathrm{H}_{im}^{UF_AF_B} - I_{im}^{UF_AF_B}\left(\nu+\mu\right) \qquad \{i=1..4, m=9\}$$

$$(6.21)\quad I_{im}^{T_AF_AF_B\prime} = \gamma_{Cm-1} I_{im-1}^{T_BF_A} + \gamma_{CFm-1} I_{im-1}^{T_BF_AF_B} + (1-Z_A)\phi_{m-1}^{TF_{AB}} I_{im-1}^{T_AF_AF_B} - I_{im}^{T_AF_AF_B}\left(\phi_m^{TF_{AB}} + \mu\right) \qquad \{i = 1..4, m = 1..8\}$$

$$(6.22)\quad I_{im}^{T_AF_AF_B\prime} = \gamma_{Cm} I_{im}^{T_BF_A} + \gamma_{Cm-1} \mathrm{H}_{im}^{T_BF_A} + \gamma_{CFm} I_{im}^{T_BF_AF_B} + \gamma_{CFm-1} \mathrm{H}_{im}^{T_BF_AF_B} + (1-Z_A)\phi_{m-1}^{TF_{AB}} \mathrm{H}_{im}^{T_AF_AF_B} - I_{im}^{T_AF_AF_B}\left(\nu + \mu + Z_A\right) \qquad \{i = 1..4, m = 9\}$$

where:

$$\Theta_i = 0\ \{i = 1..3\}\quad \Theta_i = PZ_P I^{Temp}\ \{i = 4\}$$

$$\mathrm{H}_{in}^{y} = 0\ \{i = 1..3\}\quad \mathrm{H}_{in}^{y} = \sum_{i=1}^{4} I_{in-1}^{y}\ \{i = 4\} \qquad \{n = 1..11\}$$

$$\mathrm{K}_i = 0\ \{i = 1..2\}\quad \mathrm{K}_i = (1-\theta_4)\ \{i = 3\}\quad \mathrm{K}_i = \theta_4\ \{i = 4\}$$

for $y = U, T, T_AF_A, T_BF_A, T_AF_AF_B, UF_AF_B, UF_A$

As for the previous model described in Chapter 5, the force of infection λ_i is determined by the infectiousness of individuals in each class (β), the rate of sexual partner change (c_i) and the proportion of the total population infected with each strain, contacts with whom are determined by the mixing matrix ρ_{ik}.

$$(6.23)\quad \lambda_i = c_i \sum_{k=1}^{4} \frac{\rho_{ik}}{N_k} \left(\sum_{j=1}^{11} \beta_j^U I_{ij}^U + \beta_9^T I^{Temp} + \sum_{m=1}^{9} \left(\beta_m^{TF}\left(I_{im}^{T_AF_A} + I_{im}^{T_BF_AF_B} + I_{im}^{T_AF_AF_B}\right) + \beta_m^U\left(I_{im}^{UF_A} + I_{im}^{UF_AF_B}\right) + \beta_m^T\left(I_{im}^{T_A} + I_{im}^{T_BF_A}\right) \right) \right)$$

where

$$(6.24)\quad N_i = S_i + I^{Temp} + \sum_{j=1}^{11} I_{ij}^U + \sum_{m=1}^{9} \left(I_{im}^{T_A} + I_{im}^{T_AF_A} + I_{im}^{UF_A} + I_{im}^{T_BF_A} + I_{im}^{T_BF_AF_B} + I_{im}^{UF_AF_B} + I_{im}^{T_AF_AF_B} \right)$$

The mixing matrix and other calculations are as for Chapter 5, section 5.2.

Figure 6.2 Salvage regimen model, stratified by stages of infection and sexual mixing, modelling treatment failure but not drug resistance.
Symbols for state variables and model parameters are denoted in the text. For simplicity, stages of infection and the 'initial' period on treatment are omitted. Treatment flows are shown in grey.

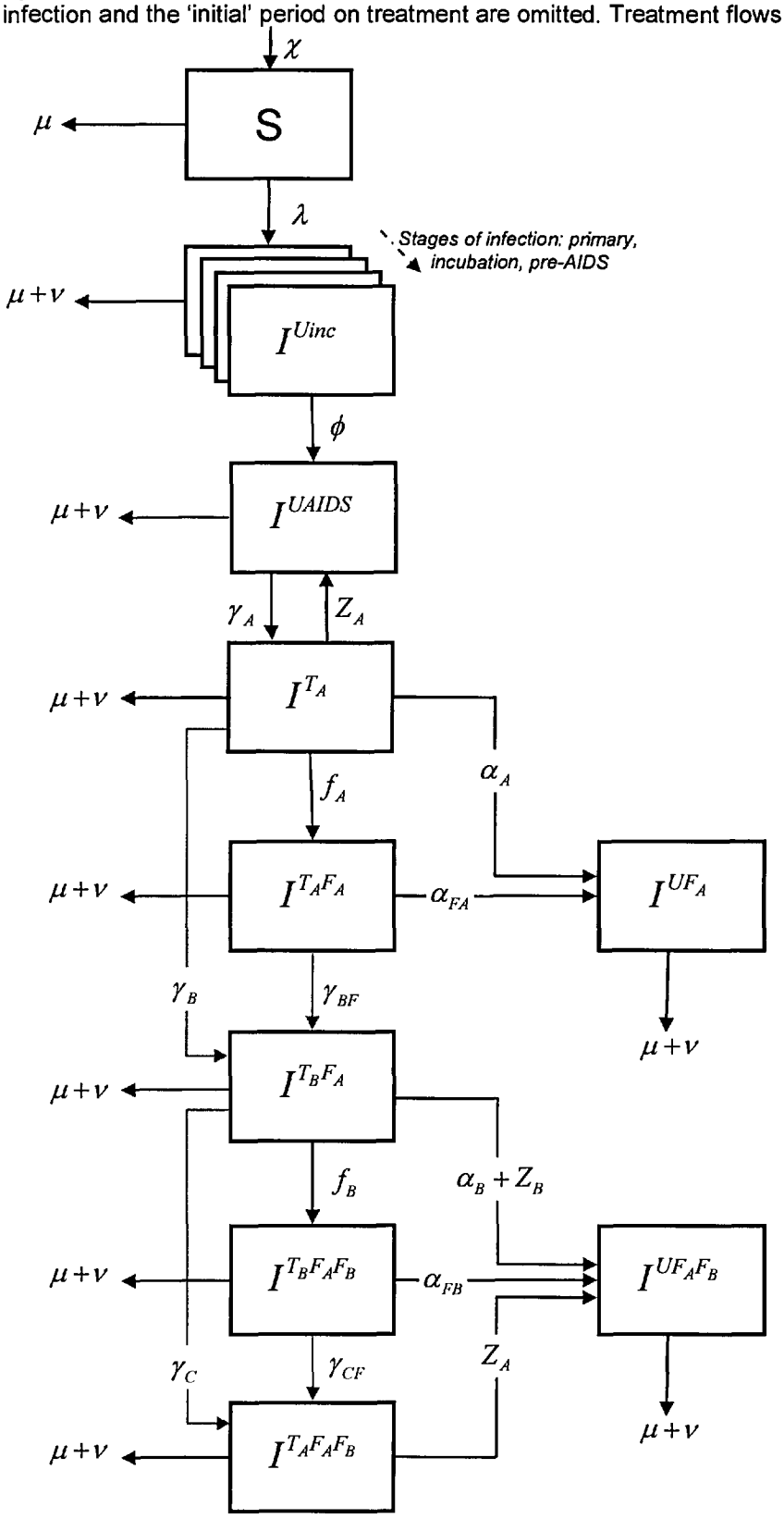


Figure 6.3 Schematic of ART model illustrating transitions between treatment compartments (stages $j=1$ to $j=9$) upon initiation of treatment.

For simplicity, the 'initial' period on treatment and withdrawal of failing treatment have not been included. Treatment flows are shown in grey.

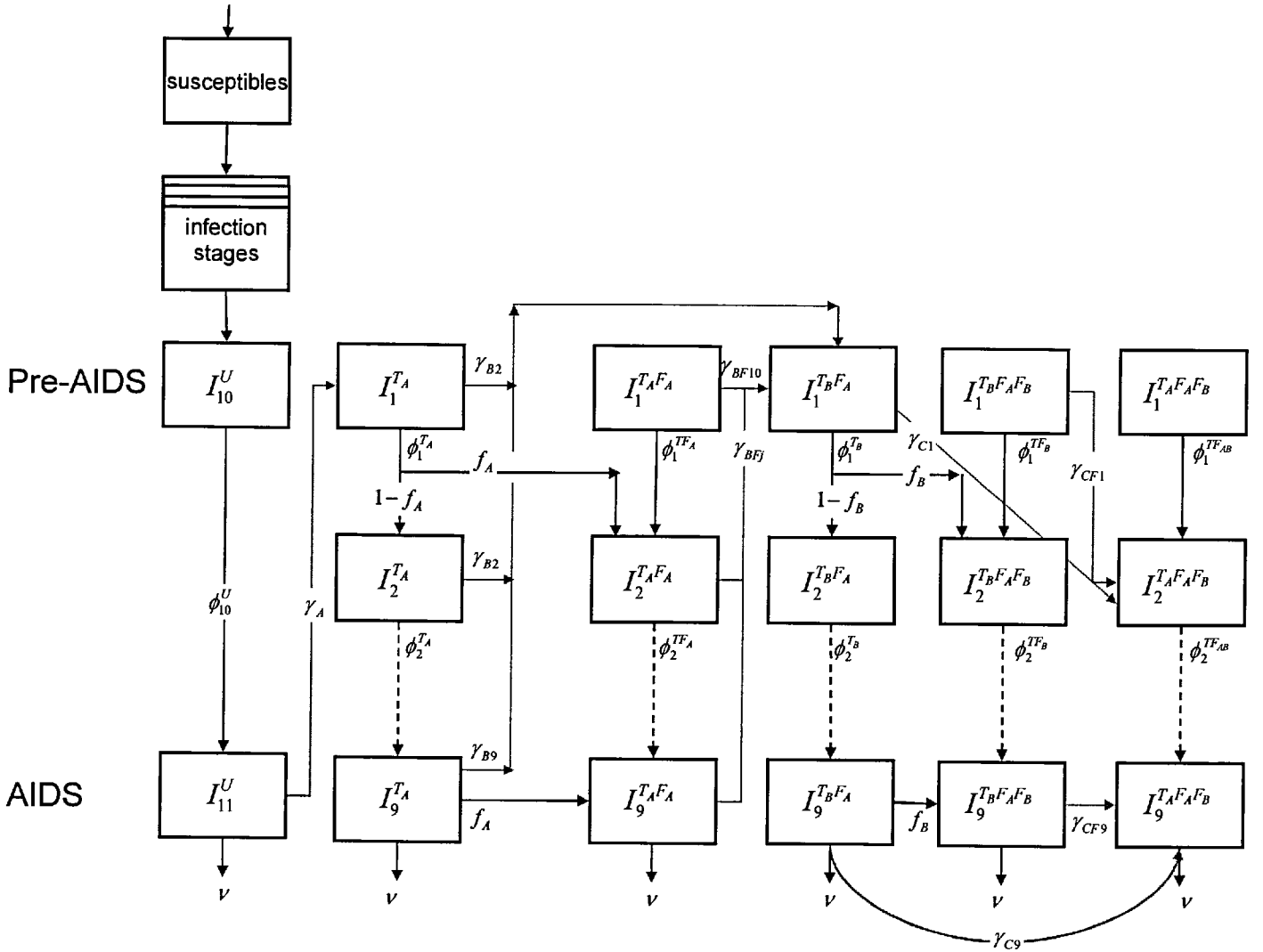


Table 6.1 Descriptions and baseline values of model parameters for the salvage regimen model, with sources.

Symbol	Parameter Description	Baseline value (range)	Source
Treatment parameters			
γ_A	Rate of treatment uptake (regimen A) for untreated AIDS patients	Varied by treatment scenario	Model assumption
$\gamma_{B1..9}$	Rate of switching to regimen B for patients on regimen A without treatment failure, treatment stages 1 to 9	Varied by treatment scenario	Model assumption
$\gamma_{BF1..9}$	Rate of switching to regimen B for patients who have failed regimen A, treatment stages 1 to 9	Varied by treatment scenario	Model assumption
$\gamma_{C1..9}$	Rate of switching back to regimen A for patients on regimen B without treatment failure, treatment stages 1 to 9	Varied by treatment scenario	Model assumption
$\gamma_{CF1..9}$	Rate of switching back to regimen A for patients who have failed both regimens, treatment stages 1 to 9	Varied by treatment scenario	Model assumption
Z_A, Z_B	Rate of withdrawal of ART due to side effects	2% LHS range: 1%-5%	Kumarasamy et al 2003 [97]
f_A	Rate of treatment failure (viral rebound), regimen A	10% – best case scenario 30% – worst case scenario	Lucas et al 2003 [41] Ledergerber et al 1999 [27]
f_B	Rate of treatment failure (viral rebound), regimen B. $f_B = qf_A$ where q = 1.5	15% – best case scenario 45% – worst case scenario	Deeks et al 1999 [42]
$\phi^U_{1..11}$	Rate of transfer to next treatment stage for untreated individuals at infection stage j, $j = 1..11$	ϕ^U_1 = 8 year^{-1} $\phi^U_{2..10}$ = 1 year^{-1} ϕ^U_{11} = 0 year^{-1}	Chapter 4
$\phi^{T_A}_{1..8}, \phi^{T_B}_{1..8}$	Rate of transfer to next treatment stage, successful viral suppression (average duration before progression to AIDS: 8 years).	1 year^{-1}	Lucas et al 2003 [41]
$\phi^{T_A}_9, \phi^{T_B}_9, \phi^{TF_A}_9, \phi^{TF_B}_9, \phi^{TF_AF_B}_9$	Rate of transfer to next treatment stage, successful viral suppression	0 year^{-1}	All patients die of AIDS at rate ν
$\phi^{TF_A}_{1..8}, \phi^{TF_B}_{1..8}, \phi^{TF_AF_B}_{1..8}$	Rate of transfer to next treatment stage, treatment failure (duration before AIDS 80% of that for successful treatment (= $x\phi^{T_A}_{Sm}$ where x =1.25).	1.25 year^{-1}	Lucas et al 2003 [41] Ledergerber et al 1999 [27]
$\beta^U_{1..11}$	Transmission probability per partnership for untreated individuals at infection stage j, $j = 1..11$	$\beta^U_1 = 54\%, \beta^U_{2..9} = 3\%$ $\beta^U_{10} = 27\%, \beta^U_{11} = 54\%$	Chapters 3 and 4
$\beta^T_{1..8}$	Transmission probability per partnership for $I^{T_A}_m, I^{T_BF_A}_m$, stages 1..8 (pre-AIDS). $\beta^T_{1..8} = w\beta^U_{10}$ where w = 2% (LHS range: 1-10%)	0.54% LHS range: 0.27-2.7%	Musicco et al 1994 [390] Perelson et al 1997 [3]
β^T_9	Transmission probability per partnership for $I^{T_A}_m, I^{T_BF_A}_m$, stage 9 (AIDS) $\beta^T_9 = w\beta^U_{11}$ where w = 2% (LHS range: 1-10%)	1.08% LHS range: 0.54-5.4%	Musicco et al 1994 [390] Perelson et al 1997 [3]

Symbol	Parameter Description	Baseline value (range)	Source
$\beta_{1..8}^{TF}$	Transmission probability per partnership for $I_m^{T_A F_A}$, $I_m^{T_B F_A F_B}$, stages 1..8 (pre-AIDS). $\beta_{1..8}^{TF} = z\beta_{10}^{U}$ where z = 75% (LHS range: 50-100%)	20.3% LHS range: 13.5-27%	Leigh Brown et al 2003 [83]
β_9^{TF}	Transmission probability per partnership for $I_m^{T_A F_A}$, $I_m^{T_B F_A F_B}$, stage 9 (AIDS) $\beta_9^{TF} = z\beta_{11}^{U}$ where z = 75% (LHS range: 50-100%)	40.5% LHS range: 27-54%	Leigh Brown et al 2003 [83]
$\alpha_{A1..9}^{T}$, $\alpha_{B1..9}^{T}$, $\alpha_{A1..9}^{TF}$, $\alpha_{B1..9}^{TF}$	Baseline rate of withdrawal of failing therapy	0 year^{-1}	Model assumption
-	Cost per year of treating one patient with regimen A	1 unit	Johnson and Dorrington 2002 [228, 483]
J	Cost per person year of treatment of regimen B relative to regimen A	1.5	Johnson and Dorrington 2002 [228, 483]
Ω	Maximum patient number for the ART programme under limited patient scenarios.	5,000 individuals	Model assumption
Φ	Maximum unit cost per year for the ART programme under limited cost scenarios.	5,000 individuals	Model assumption

The cost of the ART programme assumed here is in terms of drug purchasing only; there is no full economic costing. For simplicity, all other programme costs are excluded from this part of the budget. Treatment B costs J times as much as treatment A. From Nattrass and Dorrington's work [228, 483], J is assumed to be 1.5 in all treatment scenarios examining the trade-offs implied by providing a salvage regimen to the treated population. Scenarios involving limited patient numbers have a maximum programme capacity of 5,000 patients at one time. Scenarios involving limited drug costs have a maximum expenditure of 5,000 (arbitrary) units, where one person-year of treatment with regimen A costs one unit. Treatment B is assumed to be as effective as treatment A in terms of slowing progression to AIDS and reducing infectiousness, but once someone has failed regimen A, they are at increased risk of failing regimen B, and there is no 'initial' period.

6.2.4 Treatment scenarios

Strategies involving switching regimens and withdrawal of failing treatment are described in Table 6.2. Scenario 1 involves provision of regimen A only. Scenarios 2 to 4 additionally provide salvage regimen B, but differ with respect to management of patients who have failed both regimens and progressed to new ADCs (treatment stage $m = 9$). Patients may remain on regimen B, be transferred back to regimen A, or be removed from therapy completely. Switching regimens and ART withdrawal are assumed to occur only after development of new ADCs, that is, patient management based on clinical response. The withdrawal of ART after provision of a single regimen only is not included,

because this has been investigated previously (Chapter 5) and it is very unlikely that this would be recommended if a second-line regimen were available.

Strategies examining the timing of switching treatment are described in Table 6.3. Patients may switch regimen or be withdrawn from treatment with or without treatment failure, which is defined here as virological failure. It is assumed that even without such treatment failure, patients still eventually progress and experience new ADCs and then death, as in Chapter 5. Switching based on clinical response of patients is compared to switching based on immunological and virological responses. It is assumed that immunological decline, based on CD4 count or a proxy measure such as TLC, would not differentiate between individuals with treatment (virological) failure and those successfully treated but nonetheless experiencing declines in CD4 count before resurgence of AIDS symptoms (patients in treatment stage $m=8$, about to develop a new ADC). Under this assumption, $\gamma_{B7..8}=\gamma_{BF7..8}=1$ for switching according to CD4 count. For switching based on virological failure, detected by monitoring pVL, switching regimens occurs at an earlier stage for patients with virological failure, so that patients switch regimens at the next treatment stage after experiencing viral rebound $\gamma_{BF1..8}=1$. All patients experiencing a resurgence of symptoms and progressing back to infection stage nine switch regimen at the rapid rate of 12 year^{-1}, as used in all scenarios described in Table 6.3. Scenarios 4 to 6 use the same assumptions regarding timing of regimen switching as Scenarios 1 to 3, respectively, but additionally allow switching back to regimen A upon detection of treatment failure to regimen B to save on treatment costs.

For scenarios where regimen switching occurs before treatment stage 9 ((i.e. resurgence of AIDS), where treatment switching (γ_m) is set to one for stage m, the respective HIV progression rate for that compartment (ϕ_m) is switched to zero, so that all patients exiting that treatment compartment move to the new regimen rather than progression to the next infection stage of the old regimen. This removes the competing hazard of the two exit rates γ and ϕ, which would have accelerated progression to AIDS in the model.

Scenarios 1 to 4 were investigated using both limited cost and limited patient approaches. Scenarios A to F were investigated for limited patients only, because there are unlikely to be facilities for immunological and viral monitoring for programmes where the costs of second-line therapy are prohibitive.

Limited patient numbers: ART uptake for untreated patients developing AIDS, γ_A, is switched to zero if the total number on treatment (of both regimens), equals or exceeds the programme capacity of 5,000. As in Chapter 5,

$$T_A=\gamma_A\left(1-\left(\zeta/\Omega\right)^5\right) \quad (6.25)$$

where:
T_A is the experimental treatment uptake value used in the model

Ω is the programme capacity

ζ is the total number currently receiving ART (of either regimen), as shown in equation 6.26.

Treatment switching rates, transferring patients on regimen A to regimen B (γ_B, γ_{BF}) and back to regimen A (γ_C, γ_{CF}), when applicable, remain constant.

$$\zeta = I^{Temp} + \sum_{i=1}^{4}\sum_{m=1}^{9}\left(I_{im}^{T_A} + I_{im}^{T_A F_A} + I_{im}^{T_A F_A F_B} + I_{im}^{T_B F_A} + I_{im}^{T_B F_A F_B}\right) \quad (6.26)$$

Limited drug costs: Both treatment uptake for untreated AIDS patients and switching to treatment B are set to zero if the total drug cost equals or exceeds the drug budget of 5,000 units. The rates of switching back to regimen A (γ_C, γ_{CF}), where applicable, remain constant, because switching to the cheaper regimen A saves money.

$$T_x = \gamma_x\left(1-\left(\mathrm{M}/\Phi\right)^5\right) \quad (6.27) \quad \text{for } x = A, B, BF$$

where:
T_x is the experimental treatment uptake value used in the model
Φ is the maximum cost per year of the ART programme (arbitrary units)
M is the current total cost of the programme, as shown in equation 6.28:

$$\mathrm{M} = I^{Temp} + \sum_{i=1}^{4}\sum_{m=1}^{9}\left(I_{im}^{T_A} + I_{im}^{T_A F_A} + I_{im}^{T_A F_A F_B} + J\left(I_{im}^{T_B F_A} + I_{im}^{T_B F_A F_B}\right)\right) \quad (6.28)$$

Table 6.2 Summary of treatment scenarios 1 to 4 – switching regimens and withdrawal of failing treatment.

Scenario	Regimens available	Withdrawal of failed treatment	Treatment uptake rates (year^{-1})	Treatment withdrawal rates (year^{-1})
1	A only	**No** – kept on regimen A	$\gamma_A = 12^*$ $\gamma_{B1..9}, \gamma_{BF1..9} = 0$	$\alpha_{1..9}^{T_A}, \alpha_{1..9}^{TF_A} = 0$
2	A and B	**No** – switched to regimen B when symptoms reappear and kept on regimen B even with sequential treatment failure	$\gamma_A = 12^*$ $\gamma_{B1..8}, \gamma_{BF1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\alpha_{1..9}^{T_A}, \alpha_{1..9}^{TF_A} = 0$ $\alpha_{1..9}^{T_B}, \alpha_{1..9}^{TF_B} = 0$
3	A and B	**Yes** – switched to regimen B when symptoms reappear, then withdrawn from B with sequential treatment failure with symptoms	$\gamma_A = 12^*$ $\gamma_{B1..8}, \gamma_{BF1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\alpha_{1..9}^{T_A}, \alpha_{1..9}^{TF_A} = 0$ $\alpha_{1..8}^{T_B}, \alpha_{1..8}^{TF_B} = 0$ $\alpha_9^{T_B}, \alpha_9^{TF_B} = 12$
4	A and B	**No** – after failing both regimen A and then B, patient is switched back to regimen A	$\gamma_A = 12^*$ $\gamma_{B1..8}, \gamma_{BF1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$ $\gamma_{C1..8}, \gamma_{CF1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 12$	$\alpha_{1..9}^{T_A}, \alpha_{1..9}^{TF_A} = 0$ $\alpha_{1..9}^{T_B}, \alpha_{1..9}^{TF_B} = 0$

*For the limited cost approach, γ_A was set to 1 year^{-1} rather than 12 year^{-1} in order to favour switching of existing patients to regimen B rather than recruitment of new patients onto regimen A, because $\gamma_A, \gamma_{B1..9}$ and $\gamma_{BF1..9}$ are all dependent on the total cost of the programme not exceeding the maximum cost (equation 6.27).

Table 6.3 Summary of treatment scenarios A to F – timing of switching regimens.

Scenario	Timing of regimen switch	Switching back to regimen A	Treatment switching rates, regimen B (year^{-1})	Treatment switching rates, regimen A (year^{-1})
A	Clinical	No	$\gamma_{B1..8}, \gamma_{BF1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..8}, \gamma_{CF1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 0$
B	Immunological	No	$\gamma_{B1..6}, \gamma_{BF1..6} = 0$ $\gamma_{B7..8}, \gamma_{BF7..8} = 1$ $\phi^{T_A}_{7..8}, \phi^{TF_A}_{7..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..8}, \gamma_{CF1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 0$
C	Virological	No	$\gamma_{B1..6} = 0$, $\gamma_{B7..8} = 1$ $\gamma_{BF1..8} = 1$ $\phi^{T_A}_{7..8}, \phi^{TF_A}_{1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..8}, \gamma_{CF1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 0$
D	Clinical	Yes	$\gamma_{B1..8}, \gamma_{BF1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..8}, \gamma_{CF1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 12$
E	Immunologic	Yes	$\gamma_{B1..6}, \gamma_{BF1..6} = 0$ $\gamma_{B7..8}, \gamma_{BF7..8} = 1$ $\phi^{T_A}_{7..8}, \phi^{TF_A}_{7..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..6}, \gamma_{CF1..6} = 0$ $\gamma_{C7..8}, \gamma_{CF7..8} = 1$ $\phi^{T_B}_{7..8}, \phi^{TF_B}_{7..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 12$
F	Virological	Yes	$\gamma_{B1..6} = 0$, $\gamma_{B7..8} = 1$ $\gamma_{BF1..8} = 1$ $\phi^{T_A}_{7..8}, \phi^{TF_A}_{1..8} = 0$ $\gamma_{B9}, \gamma_{BF9} = 12$	$\gamma_{C1..6} = 0$, $\gamma_{C7..8} = 1$ $\gamma_{CF1..8} = 1$ $\phi^{T_B}_{7..8}, \phi^{TF_B}_{1..8} = 0$ $\gamma_{C9}, \gamma_{CF9} = 12$

Clinical – upon progression to stage 9 (resurgence of symptoms)
Immunological (CD4 count testing) – transfer one treatment stage before progression to AIDS (stage 9)
Virological (pVL testing) – transfer one treatment stage after treatment failure

For scenarios where ART is withdrawn as individuals exit a treatment stage preceding AIDS (stage nine), the original HIV treatment progression rates are set to zero, as stated earlier. Therefore all individuals are withdrawn from therapy before development of new ADCs.

Effect of treatment failure on programme costs: Plots illustrating the relationship between treatment failure to regimen A and programme costs use the outcome variable "duration of successful treatment with regimen A", measured in years. Treatment failure refers to viral rebound, so the duration of successful treatment is the time spent in treatment stages $I_{im}^{T_A}$ where $i=1..4$ and $m=1..8$ (neither treatment stage nine (AIDS) nor the initial period are defined as successful treatment). This outcome is plotted rather than the parameter f_A because it is a more meaningful measure which is easier to measure empirically.

The duration on successful treatment is assigned to be zero for those exiting the initial period and immediately entering the viral rebound/failure to suppress group ($I_{im}^{T_A F_A}$ where $i=1..4$ and $m=1$), as defined by the proportion f_P. Individuals exiting the initial period who don't remain on treatment (proportion $Z_P+\nu_T^P$, drop-out plus deaths) are not considered. Therefore b, the fraction spending zero time with successful viral suppression but remaining on treatment, can be defined as

$$b=\frac{f_P}{1-Z_P-f_P-\nu_T^P} \qquad (6.28)$$

For the proportion $1-b$ who maintain viral suppression on regimen A, the average duration of suppression for the proportion $f_A\phi_1^{T_A}/\left(\phi_1^{T_A}+\mu+\alpha_1^{T_A}+\gamma_{B1}\right)$ who fail after the first stage is $1/\left(\phi_1^{T_A}+\mu+\alpha_1^{T_A}+\gamma_{B1}\right)$ years, from equation (6.6) (see Figure 6.3 for a simplified illustration of the progression through treatment stages). The proportion $f_A\left(1-f_A-Z_A\right)\phi_1^{T_A}/\left(\phi_1^{T_A}+\mu+\alpha_1^{T_A}+\gamma_{B1}\right)$ which fails after the second stage has had durable suppression for $1/\left(\phi_1^{T_A}+\mu+\alpha_1^{T_A}+\gamma_{B1}\right)$ plus $1/\left(\phi_2^{T_A}+\mu+\alpha_2^{T_A}+\gamma_{B2}\right)$ years, from equations (6.6) and (6.7). For simplicity, background death rate μ is ignored and it is assumed that there is no switching to regimen B before AIDS and no treatment withdrawal for those with viral suppression. Therefore C, the average duration on successful treatment for those who ever experience viral suppression but eventually fail before progression to AIDS, is

$$C\approx\sum_{m=1}^{8}\left(f_A\left(1-f_A-Z_A\right)^{m-1}\sum_{k=1}^{m}1/\phi_k^{T_A}\right). \qquad (6.29)$$

The proportion that never experience treatment failure and stay in the viral suppression treatment stages until progression to AIDS is $\left(1-f_A-Z_A\right)^8$. These individuals have an average duration on

successful treatment of $\sum_{m=1}^{8} 1/\phi_m^{T_A}$. Therefore the average duration on successful treatment with regimen A can be expressed as:

$$D \approx (1-b)\left(C + (1-f_A - Z_A)^8 \sum_{m=1}^{8} 1/\phi_m^{T_A} \right) \qquad (6.30)$$

6.3 Results

In concordance with the results of the previous model (Chapter 5, Figure 5.5c), the number of HIV infections averted per person year of treatment compared to the no-treatment scenario is extremely small and actually negative for all scenarios (closer to zero than -0.03 infections per person year of treatment, data not shown), because it is assumed that patients only qualify for ART upon progressing to AIDS and not during pre-AIDS.

6.3.1 Switching regimen and withdrawing treatment: scenarios 1 to 4

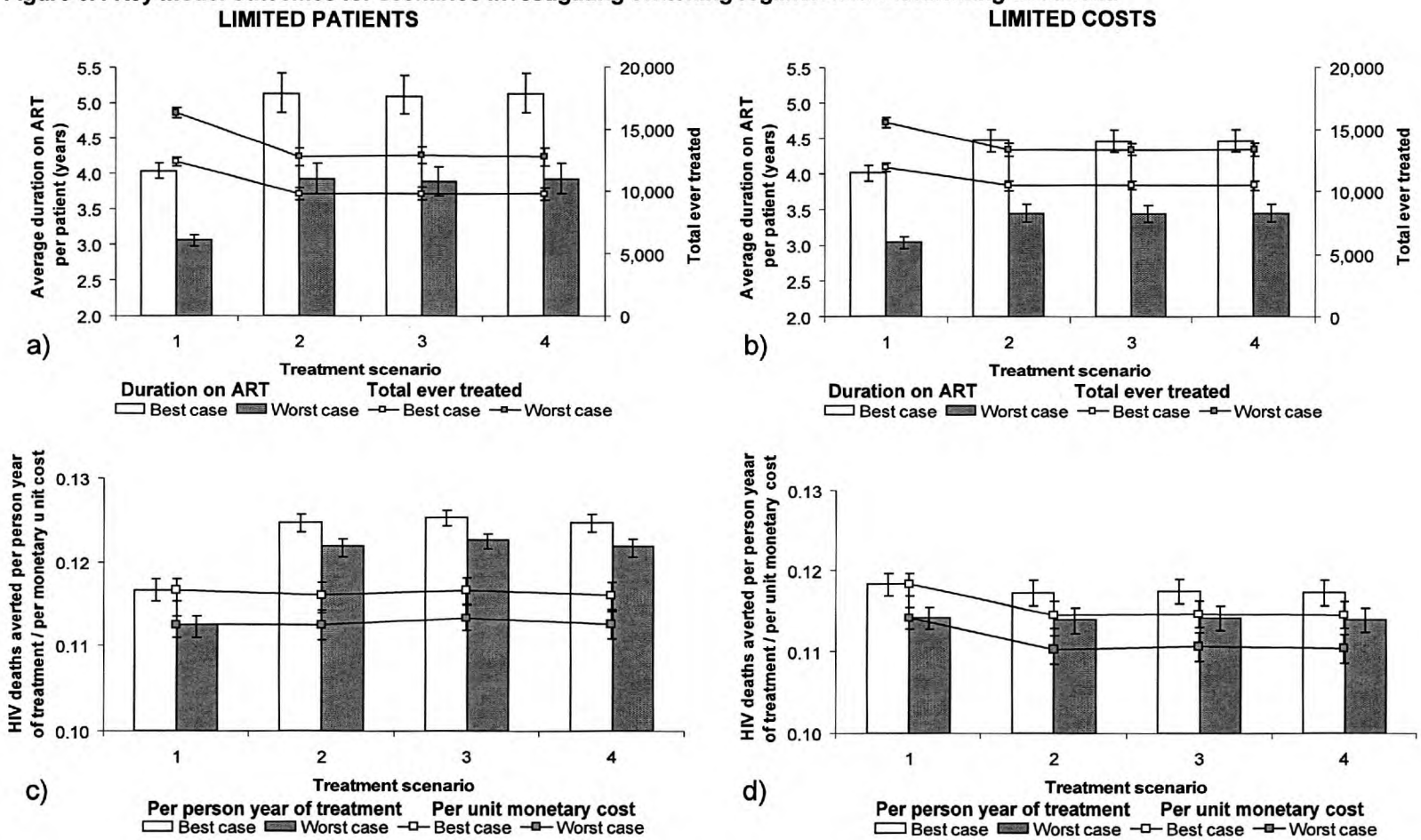
Within the model, the average duration on ART is an indicator of how long people live after commencing treatment. In scenarios where patients are withdrawn from ART, they progress to AIDS and death very rapidly in the absence of treatment. There are longer durations on ART for scenarios offering the salvage regimen (Figures 6.4a and 6.4b, Scenarios 2 to 4). By providing a salvage regimen, patients live longer, but at the cost to the programme of decreasing the number ever able to benefit from ART. The beneficial effect of a salvage regimen is less marked when cost or access to limited stocks of second-line regimens is a problem within the programme – many patients may die before money or drugs become available to transfer them to second-line therapy. For limited cost scenarios, the median duration on ART is 4.5 years for Scenarios 2 to 4, compared to a median of 5.1 years for the respective limited patient scenarios. The proportion of treated patients on regimen B is substantially less for the limited cost approach (between 18% and 23% compared to between 43% and 47% for the limited patient approach). Average duration on ART is substantially more sensitive to best and worst case scenario parameters than parameters varied by LHS, indicating the important role that ART programmes must play in limiting treatment failure and drop-out by maintaining high standards of care.

Scenarios 2 to 4 have very similar results for all epidemiological outcomes. This is because switching treatment and treatment withdrawal are assumed to occur after resurgence of symptoms and development of new ADCs (treatment stage nine), when patients have a very short life expectancy. These interventions (treatment withdrawal or switching) are not designed to extend life expectancy, but to divert resources to areas where they may be more effective. The savings made by treatment withdrawal or switching to the cheaper regimen A are for a comparatively short time, and so the benefits of doing so are minimal.

It is intuitive that more deaths are averted by providing second-line therapy when drug costs are not a limiting factor. Therefore there is an increase in deaths averted per person year of treatment, but deaths per unit cost appear relatively constant due to the resultant increase in drug costs to the programme by supplying the more expensive salvage regimen (Figure 6.4c). In contrast, for limited cost programmes, supplying a second-line regimen slightly decreases deaths averted both per person year of treatment and per unit cost (Figure 6.4d). Patients are waiting for money to be available to switch regimen, and may die of AIDS in the interim. It is decreasing the efficiency of the programme, as the small numbers who do get switched to regimen B use more resources than patients on regimen A. However, total drug costs rise considerably when there is no limit on number of patients transferring to regimen B. For the limited patient approaches, provision of salvage regimen B without treatment withdrawal or switching (Scenario 2) increases drug costs over 10 years by 7.5% (best case) or 8.3% (worst case). This is evidently very sensitive to the price of treatment with regimen B relative to regimen A, as shown by Figure 6.5a (results after 10 years of ART provision, using best case parameter values and no treatment withdrawal, Scenario 2). There is a linear increase in cost per person year of treatment with increasing cost of regimen B, but cost is not very sensitive to changes in the average duration on successful therapy (viral suppression) with regimen A. This is because the model assumes that when patients suffer viral rebound, they do not progress to AIDS at a substantially faster rate (the rate is 25% faster than for patients with viral suppression, x=1.25), which does not appear to confer much difference in the rate of transfer to regimen B. If the difference between the progression rates for viral rebound and suppression groups is more substantial (x=2), more of an impact is shown (Figure 6.5b). If progression to AIDS with viral rebound is faster in resource-poor settings due to factors such as poor nutrition and comorbidities, provision of nutritional support and access to more general healthcare and medications may be cost effective by delaying time before switching to the salvage regimen (although this does not take account of the risk of resistance emergence and spread by maintaining patients on failed regimens).

Figure 6.6 illustrates the impact of increasing cost of regimen B relative to regimen A when treatment failure rates for the two regimens are equal and relatively low $f_A = f_B$ = 0.1 year^{-1}, highlighting the effect this has on total drug costs for the programme.

Figure 6.4 Key model outcomes for scenarios investigating switching regimen and withdrawing treatment.



Figures a) and c) represent scenarios where the ART programme is limited on patient numbers; Figures b) and d) represent scenarios where it is limited on drug costs. Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range. Outcome measures are 10 years after introduction of ART compared with no treatment. Best and worst cases refer to optimistic and pessimistic parameter estimates.

Figure 6.5 Cost per person year of treatment by relative cost of the second-line regimen and average duration of viral suppression with regimen A.

The rate of progression to the next treatment stage for treatment failure to regimen A ($\phi_{1..9}^{TF_A}$) is 25% higher than that for successfully treated ($x = 1.25$ i.e. baseline) for graph a) but increased to $x = 2$ (100% higher) in graph b). Proportion failing regimen B (f_B) after each treatment stage is set at 40% rather than being related to the proportion failing regimen A (f_A). The range of duration on successful treatment is produced by varying f_A between 0.0 and 0.4. Model run with 10 years of treatment under the "limited patients" condition. All other parameters as at baseline (Table 6.1). Treatment switched to regimen B upon progressing to AIDS (clinical criteria).

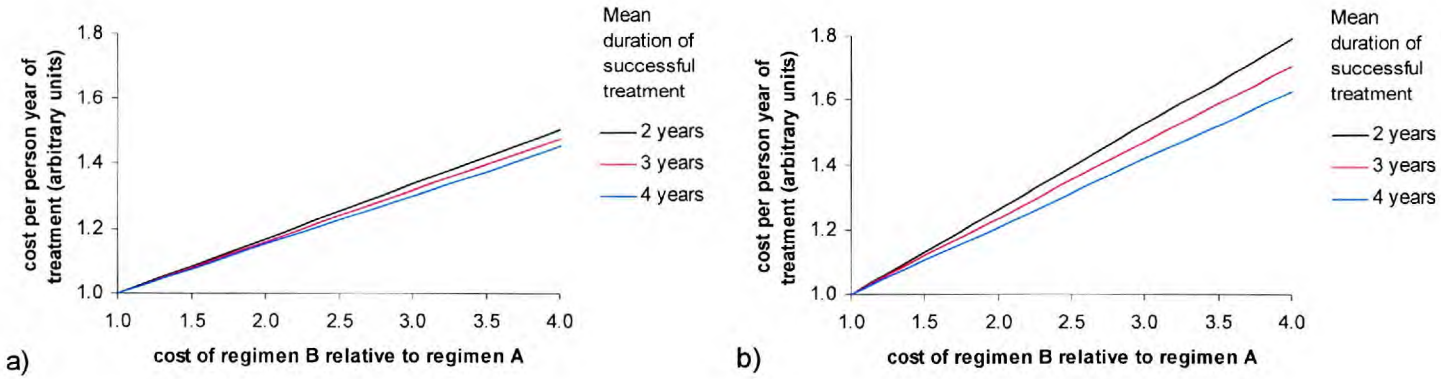
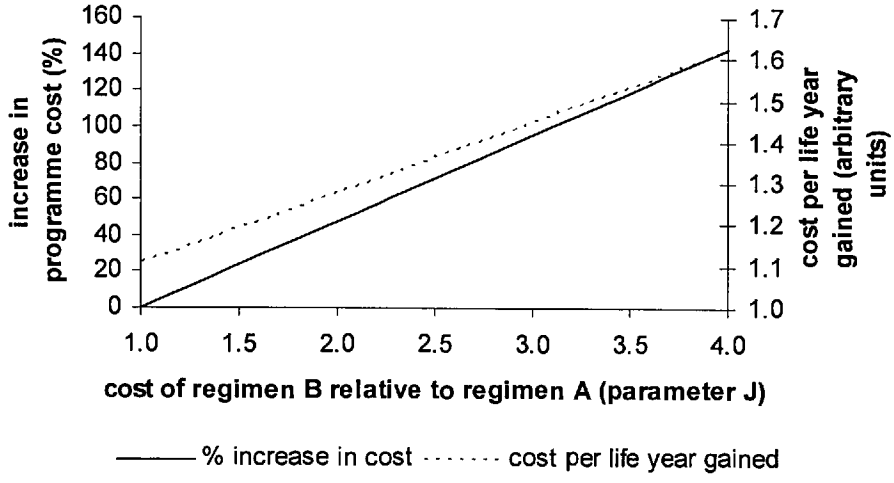


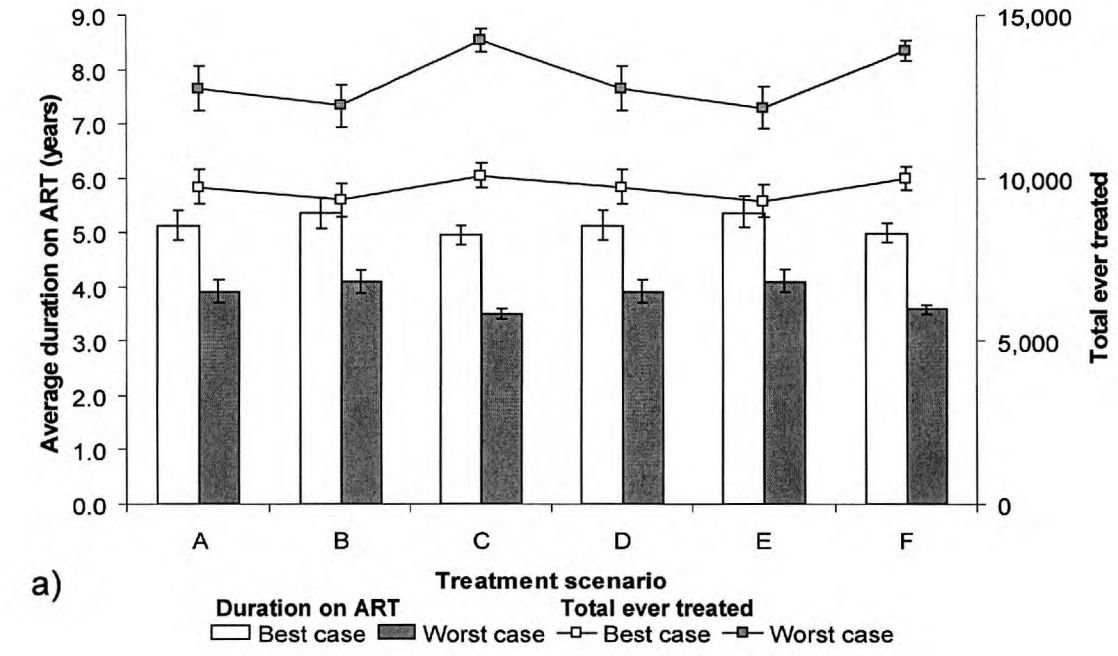
Figure 6.6 Change in programme cost and cost per life year gained with increased cost of regimen B relative to regimen A, when treatment failure rates for regimens are equal.
Graph shows increase in annual programme cost 10 years after ART introduction. Using baseline parameters for best case scenario except $f_A = f_B = 0.1$ and limited patient numbers (maximum number of patients = 5,000).

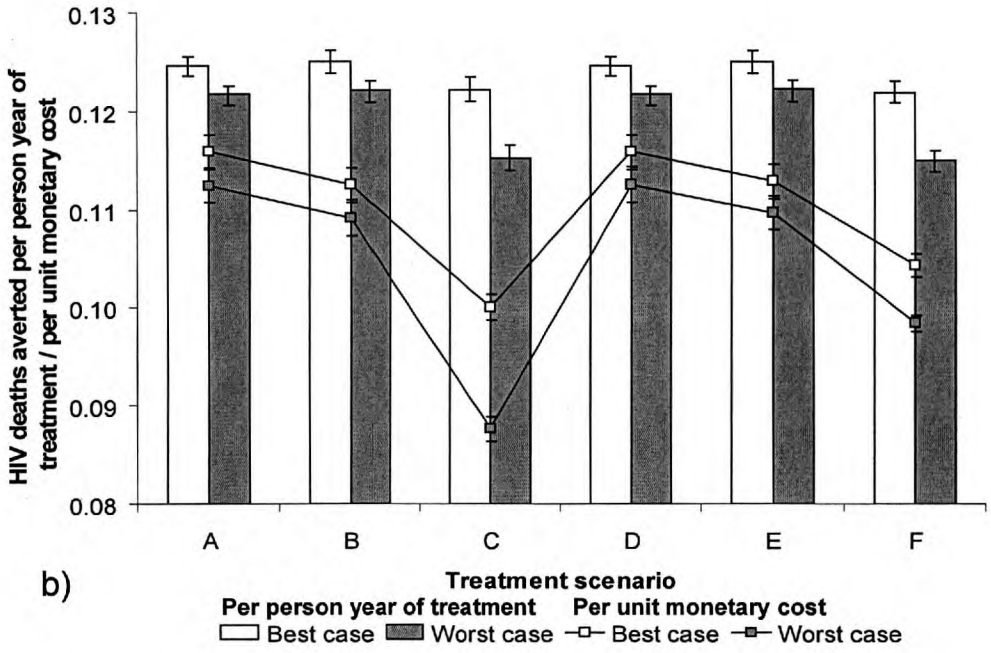


6.3.2 Timing of switching regimens: scenarios A to F

As with the previous scenarios, with limited numbers able to benefit from ART, the longer each patient benefits from treatment, the fewer patients are reached (Figures 6.7a). There is a marginal increase in average duration on ART and of deaths averted per person year of treatment when regimen switching occurs upon immunological decline but before AIDS (Scenarios B and E), because the mortality risk upon reaching AIDS which is averted by changing regimen sooner is counteracted by the absence of duration spent in the treatment compartment before AIDS. Switching therapy even earlier, upon viral rebound (Scenario C), means yet more treatment compartments are missed and not progressed through with regimen A, so the average duration on ART decreases and cost effectiveness decreases markedly because a greater proportion of patients are receiving regimen B (Figure 6.7b). Switching back to regimen A after treatment failure of regimen B compensates for this to a certain extent.

Figure 6.7 Key model outcomes for scenarios investigating the timing of switching regimens.





Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range. Outcome measures are 10 years after introduction of ART compared with no treatment. Best and worst cases refer to optimistic and pessimistic parameter estimates.

6.4 Discussion

Provision of second-line therapy increases the life expectancy of a patient on ART, but at the expense of the numbers of HIV infected individuals able to benefit. However, the precise impact will depend on the nature of rationing of resources, whether primarily it is human resources and therefore patient management which is lacking, or whether purchasing power for other commodities is limited. With decreasing drug costs (for some regimens) and increased funding, it is likely that the chronic shortage of HCWs in regions such as sub-Saharan Africa will be the most pressing restraint. An ART programme limited by cost is unlikely to be employing highly skilled healthcare personnel for dispensing drugs and frequent patient monitoring, inevitably leading to compromises on quality of care and outcomes such as adherence (and thus treatment failure), drop-out and mortality. These differences in programme performance by type of limitation have not been incorporated here.

It was found that switching regimens too early, after viral rebound, was not beneficial in terms of HIV deaths averted per unit cost or per person year of treatment. However, this does not take into account the increasing risk of resistance emergence and spread with increasing time with viral rebound under continued treatment pressure, which may show the wider community benefits of removing this treatment pressure earlier. These issues may be investigated further, but with ART scale-up, pVL monitoring has not been recommended by WHO for treatment programmes, and so treatment switching according to virological treatment failure is unlikely. Treatment switching upon immunological decline, detected by CD4 count monitoring, may be a more realistic scenario, and results in a marginal increase in the number of HIV deaths averted per person year of treatment. However, this is taking account of all HIV deaths in the modelled population – outcomes monitored by an ART programme will principally be concerned with the number of deaths of patients within the programme, not in the wider community, and fewer patients risk death if their regimen is changed before they develop new ADCs.

Figure 6.6 has shown how cost per life year gained increases with increasing expense of the salvage regimen. This illustrates that in the context of rationing and salvage regimens being more expensive than first-line therapy, maximising the number of life years gained will always be optimum if regimen B is not provided. However, the increase in life expectancy from using one regimen only may not be considered sufficiently worthwhile at the individual level, despite this strategy increasing both equity (numbers accessing treatment) and utility (life years gained). This is an important demonstration of the trade-off between individual- and community-level benefit, which has been illustrated by the results of this model.

There are two main limitations to the existing model. Firstly, for the limited cost scenario, it should be assumed that the preference would be to switch existing patients to regimen B rather than recruiting new patients to regimen A, but this could not easily be incorporated into the existing model structure. A compromise was to decrease uptake of ART for untreated individuals relative to switching of ART from regimen A to B. An individual-based model could incorporate this pattern of treatment

delivery more realistically. Secondly, the model does not incorporate the emergence of drug resistance, as employed in the ART model described in Chapter 4. This is achievable with a compartmental or population-based model, but increases the complexity and number of compartments considerably. Again, an individual-based model would provide a more systematic and coherent approach to incorporating this. The emergence, and particularly the spread, of drug resistance to first- and second-line regimens is of considerable importance, especially due to cross-resistance between regimens and the fact that prices for alternative, newer ARV drugs have not decreased substantially. If a relatively fit strain resistant to a first-line regimen emerges and was transmitted, the costs of ART treatment programmes could quickly spiral. Cross-resistance between regimens has been implicitly modelled in this chapter because patients failing regimen A are at greater risk of failing regimen B, yet transmission of resistance and scenarios where first-line regimens are rendered useless after a period of time need exploration. Therefore it is important to explore this using an individual-based model, but this compartmental, deterministic model has been a useful initial step. In fact, this analysis could have been conducted using a cohort model without simulating infection transmission (i.e. a linear model, as it is described in Chapter 2), because the effect of ART on transmission is not being investigated. However, the original transmission model described in Chapter 4 was amenable to modification to investigate this research question, despite some of its complexity being rather redundant in this case. If, however, the impact of various scenarios on transmission of drug resistance were to be investigated, a cohort model would obviously no longer be appropriate.

This chapter, together with Chapter 5, has demonstrated the trade-offs in outcomes regarding the benefits of ART. Considerations over how best to introduce ART to resource-poor settings raise many practical and ethical issues. Prioritisation of some kind must take place, and expanding access to treatment inevitably leads to compromises on standards of care. Guidance documents for distribution of ART have been produced [118], but concentrate on the process of policy making more than the ethical issues raised. The predicted impacts of different strategies from mathematical models can quantify the consequences of the choices made. For example, Wilson and Blower have examined the distribution of ART drugs following an egalitarian principle [156], attempting to minimise geographical inequalities in the chance of being enrolled into an ART programme across KwaZulu-Natal province, South Africa. Capron and Reis point out that this is only one factor to overcome in ensuring equitable distribution, and ignores two other important issues: the maximin principle and the utilitarian approach [157]. There is a need for more quantitative analysis to inform debate and aid policy makers in determining what would constitute fair distribution.

Chapter 7 Discussion

Summary

This chapter draws together the findings of the thesis. Its aim is to provide an overview of the thesis as a whole, to discuss its findings, limitations and suggest further research and future applications. Several themes have emerged from the results presented and a variety of important issues in HIV epidemiology and mathematical modelling of ART have emerged. The thesis has used mathematical models to investigate the consequences of different treatment strategies under conditions where ARV drugs are rationed and consequently important questions regarding drug distribution and prioritisation of treatment have been raised. As a result, a discussion of the ethical implications of different approaches to ART delivery when treatment must be rationed is explored. Finally, the future directions of research using mathematical models of HIV and ART are discussed.

7.1 Introduction

This thesis explores aspects of HIV ART epidemiology and control made by the predicted widespread introduction of ART in resource-poor settings. The attention of the public health community has increasingly been focussed on drug access and equity in HIV treatment [484-486], and the situation has been completely transformed over recent years. Since the "3 by 5" strategy was launched in late 2003 ART coverage in low- and middle-income countries has more than doubled, increasing from 400,000 to approximately one million people receiving treatment at the end of June 2005 [103]. Fourteen of these countries are providing ART to at least 50% of those who need it, consistent with the "3 by 5" target (estimated ART coverage for the 20 countries most in need is shown in Appendix B, Table B2). The volume of publications in this area has also markedly increased, as demonstrated by the crude analysis illustrated in Figure 7.1.

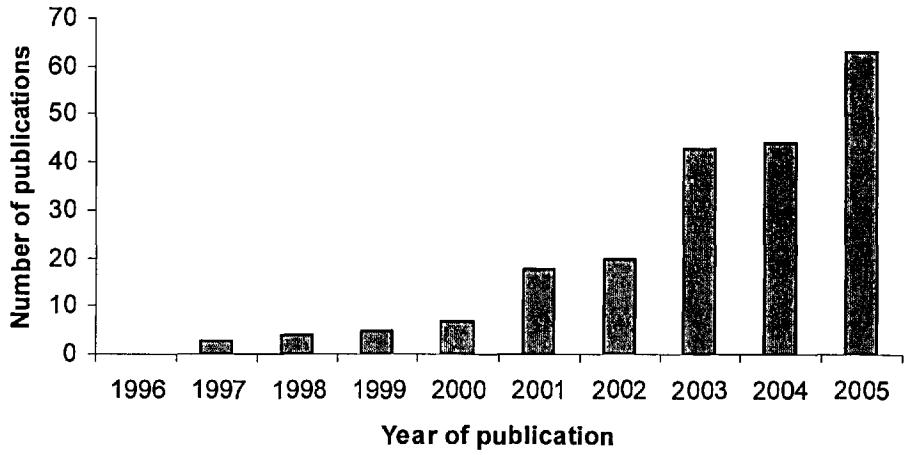


Figure 7.1 Increasing number of publications by year for antiretroviral (Title) AND Africa (Any field) in MEDLINE.
Accessed 28th January 2006.

Therefore predicting the effects of ART in resource-poor settings has never been more relevant, and there has been a recent proliferation of mathematical models examining the impact of HIV treatment in this context, as described in Chapter 2. This thesis develops a variety of models designed to further the understanding of the impact of ART in resource-poor settings. These range from simple one-stage models of HIV infection, to more realistic models which incorporate staged progression of infection with differential infectiousness and ART uptake, with heterogeneous sexual activity. A better understanding of the epidemiology of HIV and the impact of ART provision on mortality, HIV transmission, risk behaviour, drug resistance and other outcomes is necessary to allow appropriate treatment programmes to be designed and implemented.

7.2 Overview

An introduction to infectious disease modelling and a review and analysis of a range of models of ART use was undertaken and used to inform design of the mathematical models used in this thesis. Extensive review of the literature was conducted in order to parameterise the models and resulted in several changes to model structure in order to incorporate the evidence appropriately. Each chapter has included a detailed discussion of the methods and results. Mathematical models were constructed, designed to assess the impact of ART on key epidemiologic outcomes such as infections and deaths averted in the context of scale-up in resource-poor settings. The maximum impact of ART was investigated by examining the effects of unlimited treatment, but this was complemented by more realistic limited treatment scenarios, and impacts at the programme level as well as the population level were assessed.

A review was undertaken examining the work of theoretical studies attempting to assess the population impact of ART use on key outcomes such as mortality, HIV transmission and ARV drug resistance. Mathematical models examining the impact of ART broadly fall into two categories; those incorporating HIV transmission dynamics, and linear models. Linear models are generally used to inform policy makers on issues such as resource allocation, and typically only involve short-term predictions on the effect of ART. Models incorporating HIV transmission dynamics typically investigate the impact of ART over a longer time frame and are used to address more general questions surrounding ART use, such as whether the benefits of ART provision outweigh the problems and risks, and which approaches to ART provision are most effective. While linear models tend to produce quantitative results, dynamic models have tended to be used to gain more qualitative insight in this area.

An investigation of the effects of different model structures was conducted by building preliminary models using parameters arrived at after a brief review of the literature. It was concluded that HIV transmission models predicting the impact of ART use should incorporate a realistic progression through the stages of infection in order to capture the effect of the timing of treatment initiation on disease spread, because treatment is only initiated relatively late in infection. However, results from both the simplest, one-stage infection model and a model incorporating staged progression suggested that ART use would not decrease HIV prevalence in the long-term. While the use of these models in Chapter 2 has been for illustrative purposes only, it demonstrates the process of increasing model realism (and thus complexity) and comparing models, in order to identify the effects of changing model structure. However, while increased complexity can make models more realistic, it also makes them more difficult to parameterise and more difficult to analyse and interpret. For example, the complexity of the ART models described in Chapters 5 and 6 meant that information on a large number of parameters was required, leading to the extensive literature review which is presented in Chapter 4. The contrasting conclusions of some ART models from the literature demonstrates the significant effect that choice of model structure and parameter values can have on results.

Models such as those described in this thesis require estimation of a large number of parameters. Estimates of many of these values include a substantial degree of uncertainty, which can to some extent be compensated for by uncertainty or sensitivity analyses. However, such measures cannot replace evidence-based estimation of key parameters. While there may be limitations in accuracy and reliability of many data sources, all evidence can be informative in determining what range of parameter values is sensible. A review of the HIV/AIDS literature and of previous ART modelling studies provided the evidence to parameterise the models used in Chapters 5 and 6 as accurately as possible, with ranges for key parameters also used for sensitivity analyses in cases of uncertainty.

While some information has been taken from previous modelling studies, the majority of parameter values have been arrived at after review of the literature. Extremely detailed systematic reviews for each parameter were impracticable due to time constraints, but the systematic review and meta-analysis of sexual HIV transmission probabilities in Chapter 3 demonstrate the usefulness of thorough research in estimating key parameters used in HIV mathematical models. Without such reviews the choice of which studies to cite and use for parameterisation can drastically alter model output. A sensitivity analysis may be useful if it examines parameter values within the range of possibilities predicted by the data (or even beyond), but sometimes very little support for a given range is presented by authors (often because it is not possible to estimate). Unfortunately, a wide degree of uncertainty may lead to uninformative results. Because of the significant workload, the extensive review of the literature used to parameterise the ART models in this thesis, described in Chapter 4, is detailed but by no means exhaustive. Publication of reviews of this kind should be promoted by decision makers and mathematical modellers as a means of avoiding duplication of effort and some of the bias that may exist due to selection of non-representative studies for parameterisation.

Several key parameters for HIV transmission models are difficult to estimate, notably parameters relating to sexual behaviour. This problem can then confound studies providing evidence for other parameters, such as HIV transmission probabilities (as discussed in Chapter 3). Further uncertainty surrounds the potential for spread of ART-resistant viral variants. Sensitivity and uncertainty analyses are required in order to allow for this, so that model results are not interpreted with an overestimated degree of precision. However, wide ranges for multiple parameter values can lead to extreme uncertainty in model results and an exploration of the best and worst case scenarios for influential parameters, particularly relating to the quality of ART provision, can be more informative. These parameters include treatment failure, drop-out and mortality rates, as these will vary substantially with the quality of care provided, but will be correlated. Uncertainty regarding other parameters can be further explored through methods which map out results within the parameter space, for example by using LHS to efficiently provide a random coverage of parameter space, as has been done in this thesis. However, some parameters which are not known with confidence may be fixed because they are not relevant to the research question. The models used in Chapters 5 and 6 in this thesis were calibrated to HIV prevalence data from Malawi by varying sexual behaviour parameters, which are not known with a great degree of certainty, and are not of crucial importance to the research questions posed about benefits to those already infected, despite being of relevance for the continued spread of infection. A comparison of model results concerning HIV transmission using different sexual activity parameters yielded very similar results to those using the original parameter values, suggesting that the predicted effect of ART on transmission is adequately robust, although a more thorough exploration of parameter space may demonstrate this more completely.

Ongoing surveillance and behavioural surveys are required in order to parameterise and calibrate mathematical models more accurately. Such studies can highlight the need for more evidence to estimate certain parameters, and therefore suggest where additional empirical research could be undertaken. The majority of data on the long-term effects of ART have been taken from studies in industrialised studies. As the results of more ART projects in developing countries with longer durations of follow-up and with larger patient numbers are published, some of these parameters may be estimated more accurately for resource-poor settings. However, published studies often describe programmes that enjoy expert health care, frequent and sophisticated patient monitoring and availability of alternative ARVs and other medications [65], and thus will not reflect the type of programme that the WHO envisages will be typical with roll-out [29, 487].

The estimation of HIV transmission probabilities is very important epidemiologically, not only to assess the infection risk to susceptible individuals when exposed to the virus, but also to make predictions on the potential spread of HIV infection in a population, as well as to interpret current epidemiological patterns of HIV prevalence between populations and settings. As part of the literature review described in Chapter 4, investigation of evidence to parameterise HIV transmission probabilities per partnership for the models used in this thesis became a formal and extensive analysis (Chapter 3).

Despite its biological plausibility, the results of the studies included in the review and the meta-analysis cannot prove a significantly greater transmission probability for M→F transmission than for F→M transmission. However, the presence of risk factors differentially distributed between males and females may have obscured the difference in risk between the sexes. The impact of disease stage on infectiousness is also difficult to ascertain because of the lack of information provided by many studies and the scarcity of details regarding risk factors for both the HIV infected index case and the susceptible partner. For these reasons, it was not considered appropriate to provide summary estimates of HIV transmission probabilities, pooling together studies from populations with very different patterns of risk factors. The meta-analysis which was undertaken provided more qualitative insight.

Statistical analyses of per contact transmission probability have shown that assuming a constant infectiousness does not fit the data well. The relationship is confounded by differential infectiousness with stage of infection, heterogeneity in infectiousness of transmitting individuals and susceptibility of uninfected partners to infection. As with per partnership estimates, it is difficult to determine whether there is a difference in per contact transmission probability between industrialised and resource-poor settings, or between M→F and F→M transmission. Interestingly, differences in per contact transmission probability between industrialised and resource-poor settings are more marked for F→M than M→F transmission. This is most probably due to differences in risk factor distribution within the sampled population, particularly of STIs. A second meta-analysis has been undertaken by

the collaborators on this project in order to quantify per contact risk. The results include data from the higher quality sources and so are likely to provide more reliable estimates than those possible from all data sources, although all studies suffer from some of the limitations inherent in estimating infection transmission probabilities.

Uncertainty remains regarding the infectiousness of HIV by sexual contact and partnership. Whilst per partnership estimates are not uniform, it is generally thought that per partnership infectiousness is more constant than per contact infectiousness [324, 332, 361]. As a result, it is transmission probability per partnership rather than per contact that is used in the models in this thesis. The review of HIV transmission probabilities for both per partnership and per contact transmission will be an important addition to the literature, and will aid parameterisation of future HIV models in particular (and has already been used [488]).

The models in Chapters 5 and 6 incorporate differential infectiousness with stage of infection. However, there are problems with using the empirical data from the review in Chapter 3 to parameterise these models because the structure of the models means that HIV transmission is assumed to occur instantaneously upon partnership formation. The per partnership data from the review are derived from sexual partnerships that often traverse more than one stage of infection of the index case. It is therefore difficult to incorporate an average transmission probability per partnership across all stages of HIV infection that also takes account of the expected variation in infectiousness by each stage. A compromise was reached, ensuring sufficiently different transmission probabilities between the incubation stage and the symptomatic pre-AIDS and AIDS stages, yet a reasonable average transmission probability. The parameters used were in agreement with data for symptomatic infection, but are likely to underestimate infectiousness for asymptomatic infection. This is because the duration of primary infection is so short. Since sexual partner change rates were not known with certainty and values were determined by fitting the model to prevalence data from Malawi, the poor fit for asymptomatic infectiousness becomes less important. Furthermore, no scenarios in Chapters 5 and 6 involved initiation of ART during asymptomatic infection. An alternative solution would be to remove the primary infection stage from the model structure completely, and raise the transmission probability for the single, asymptomatic stage. The eight stages of incubation may be regarded as unnecessary, considering that the models only consider the impact of ART when intiaited at pre-AIDS and AIDS stages, yet their inclusion does not considerably increase the complexity in terms of programming or notation, as one differential equation is simply replaced with eight virtually identical equations. A pair formation or individual based model could account for transitions between stages with their respective infectivities in a more realistic way. This exercise has highlighted that care must be taken in how empirical data are used to inform mathematical models.

The results presented in Chapter 5 suggest that unlimited ART provision initiated at late stage infection (AIDS) increases HIV prevalence. The effect of additionally treating pre-AIDS patients depends on the behaviour change of treated patients, but at best is not likely to reduce HIV

prevalence, and using more pessimistic assumptions, is likely to substantially increase prevalence. Different levels of coverage of ART for those in need do not affect benefits such as life years gained per person year of treatment and have minimal effect on infections averted when treating AIDS patients only. Scaling up treatment of pre-AIDS patients results in more infections being averted per person year of treatment, but the absolute number remains small. As coverage increases, the emergence and risk of spread of drug resistance increases, probably to a greater degree than shown by model predictions, due to potentially deteriorating standards of care as scale increases.

CD4 count testing allows the identification of pre-AIDS patients. Additionally, the implementation of laboratory facilities for pVL monitoring allows the identification of treatment failure earlier, increasing the sustainability of the programme, either allowing switching to a salvage regimen, or perhaps (in the absence of alternative treatments) by halting therapy and giving the drugs to another patient whose prognosis is better, as investigated in Chapter 5. The benefits of pVL testing will increase with higher levels of resistance in the population. An important assumption in the modelling presented is that whenever laboratory tests are included they are adequately performed in a timely fashion. This of course depends upon appropriate facilities and processes, which if not in place will undermine the benefits of additional tests.

The withdrawal of failing treatment (associated with clinical, immunological or virological failure) increases the numbers who can benefit from ART, but effectiveness per person is compromised. Only withdrawal upon virological failure would have a substantial impact on drug resistance emergence, but is not currently recommended because patients are still benefiting from ART clinically. Withdrawal of treatment at a potentially acceptable stage, that is after immunological deterioration, when ART is no longer of benefit, will not have a substantial effect on containing resistance emergence, but would increase the number able to benefit from treatment. As the pace of ART rollout across southern Africa quickens, difficult decisions regarding the allocation of finite resources will have to be made. HIV epidemics in sub-Saharan Africa are not amenable to direct control through treatment, regardless of the extent of ART roll-out, if therapy is initiated at an appropriate stage of infection, at pre-AIDS or AIDS. Therefore treatment must be integrated with prevention methods. Counselling of patients to promote safe sexual practices is essential, and must aim to effect long-term change, further reducing risk behaviours as well as stopping behavioural disinhibition. In the absence of substantial behaviour change of treated patients, prevalence is likely to increase. Of course, if there was population-level behavioural disinhibition and a general increase in risk behaviour, it is highly likely that prevalence would increase even further, despite this effect not having been investigated in the models described here. The chief aims of an ART programme, such as maximising the total number ever treated or effectiveness of treatment per patient, will determine which treatment strategy is most effective in terms of prolonging the life of those infected, but much more is required to shift the pattern of spread of infection.

Chapter 6 presents an ART model that incorporates a second-line, salvage regimen. A second-line regimen, designed to continue successful treatment of patients who have failed their first regimen, is a fundamental recommendation for ART roll-out in WHO guidelines. Unfortunately, ARV drugs used in these combinations tend to be more expensive than first-line regimens, and there is a higher risk of treatment failure for patients who have previously failed another combination.

Provision of second-line therapy increases ART patients' life expectancy on treatment but, with a constrained programme, at the expense of the numbers of HIV infected individuals able to benefit. With decreasing drug costs (for some regimens) and increased funding, it is likely that the chronic shortage of HCWs in regions such as sub-Saharan Africa will be a more pressing constraint than ARV drug costs. Currently the restrictions on which drugs (branded or generic) can be purchased through different sources of funding can create a situation where both first- and second-line drugs need to be purchased to facilitate spending. Whilst such a situation may be politically expedient it is less rational in an economic framework where resources should be used efficiently. Where an ART programme is limited by cost, or where staff recruitment and retention is constrained by the need to maintain a sustainable and integrated health system, the programme is unlikely to employ highly skilled healthcare personnel for dispensing drugs and frequent patient monitoring, inevitably leading to compromises on quality of care and outcomes such as adherence (and thus treatment failure), drop-out and mortality, and also limiting what is feasible for monitoring and treatment.

The results of the model incorporating second-line regimens are limited because they do not include the evolution of drug resistance. Resistance as a cause of treatment failure is a reason to switch regimen to prevent the continued selective pressure of drugs, increasing the fitness of resistant types. Thus switching can be part of a strategy, which is not considered here, to suppress the evolution of resistance. However, this would require regular pVL testing which is beyond the current capacity of most health care in resource-poor settings. Treatment switching upon immunological decline, detected by CD4 count monitoring, is a more realistic scenario, and results in a marginal decrease in the number of HIV deaths averted per monetary unit. However, this is taking account of all HIV deaths in the modelled population – outcomes monitored by an ART programme will principally be concerned with the number of deaths of patients within the programme, not in the wider community, and fewer patients risk death if their regimen is changed before they develop new ADCs.

Chapters 5 and 6 demonstrate the trade-offs in outcomes generated by ART. Considerations over how best to introduce ART to resource-poor settings raise many practical and ethical issues. Prioritisation of some kind must take place, and expanding access to treatment inevitably leads to compromises on standards of care. Guidance documents for distribution of ART have been produced [118], but concentrate on the process of policy making more than the ethical issues raised. The predicted impacts of different strategies from mathematical models can quantify the consequences of

the choices made. There is a need for more quantitative analysis to inform debate and aid policy makers in determining what would constitute fair distribution.

7.3 The ethics of distribution of ART in resource-poor settings

Where resources are insufficient to treat all those in need, prioritisation of some kind must take place. Wilson and Blower have examined the distribution of ART drugs following an egalitarian principle, attempting to minimise inequalities in the chance of being enrolled into an ART programme across KwaZulu-Natal province, South Africa [156]. However, Capron & Reis point out that this is only one issue to consider in ensuring fair distribution and ignores two other important factors: the maximin principle and the utilitarian approach, which are introduced below [157].

Wilson and Blower investigated distribution from an egalitarian perspective, but examined equity in terms of access to ARV drugs rather than in terms of health outcomes, which should be the ultimate goal of such an approach. The maximin principle aims to maximise the wellbeing of the worst off and is therefore more likely to address inequalities in health status, but this principle is not necessarily egalitarian: a policy which maximises the increase in health outcomes for the worst-off group may coincidentally increase disparity by also improving other groups' outcomes even further. Equity in allocation of resources would be fair if everyone had equal need, as long as equal need were defined as equal capacity to benefit as well as equal proximity to death. However, if for example the HIV epidemic hit the urban centres first and then spread to the surrounding rural areas later, a greater proportion of infected people would be at an advanced stage of disease in cities, and therefore in more urgent need of treatment. Therefore care must be taken in deciding what the ultimate aim of a resource allocation strategy really is and how that goal is most likely to be achieved.

The utilitarian principle aims to maximise overall benefits to the population, with equity only a secondary concern. This highlights the "fair chances versus best outcome" problem: to what extent should producing the best outcome be favoured over giving every patient an opportunity to compete for limited resources? [113, 489].

ART is not like medical interventions such as organ transplants or oral rehydration therapy, where one or a small number of treatments produces the desired health outcome; it must be taken continuously for continuous benefit. Therefore classical arguments for best prognosis from an intervention (should the six year old girl or the forty year old father of two receive the life-saving organ transplant?) are not as relevant. In the context of rationing, the choice between whether the child or the adult with dependants receives the life-saving place on the treatment programme remains, but prioritising patients with a better prognosis (the utilitarian argument) is less relevant. A patient at a more advanced stage of disease may benefit for less time due to higher risk of IRIS and treatment failure, but if the patient leaves the programme, their place can be reallocated. The only "waste" would be from ineffective treatment, which may be higher for a programme preferentially treating those at the most advanced stage, where a significant proportion of patients will die or drop-out during

the first six months of treatment, arguably before the patient and their dependants have been able to enjoy any real benefit from therapy.

The more that treatment effectiveness is compromised by a programme, perhaps by preferentially treating those at a more advanced stage of infection, or simply due to relatively poor standards of care, the quicker the turnaround in the programme and the more people stand to benefit, thus improving equity but at the expense of effectiveness per patient. A programme reporting success because it has reached many people may have provided compromised standards of care and therefore may be overseeing high mortality rates, whereas an initiative reporting successful outcomes in terms of progress of patients and low mortality rates may have reached fewer people, reducing equity, and concomitantly allowing higher mortality rates in the surrounding population outside of the intervention. As more ART programmes become established in Africa, their evaluation may be misleading if only certain outcomes are monitored and reported. For example, a programme with higher death and treatment failure rates than other ART initiatives may be reflecting an unofficial or unreported policy of prioritising patients with more advanced disease. More ominously, programmes may select patients with the best prognosis if there is pressure from donors or governments to report favourable outcomes such as low mortality rates.

The treatment scenarios A to G described in Chapter 5, which investigate different strategies regarding timing of treatment uptake and withdrawal, may be interpreted as adopting different ethical stances. Scenario A, the "clinical management" or "most in need" approach, which enables treatment of AIDS patients only, adopts the maximin principle, which in this case is also egalitarian because the health status of untreated HIV infected individuals in the population is not improved by this strategy, so it is reducing disparities in health status. However, using another interpretation, it is not an egalitarian approach, because there is not equal access to healthcare, but HIV may be unique in that virtually all patients will eventually progress to AIDS and become eligible for ART, and so all infected individuals will have such a chance at some point in the future. In an even wider context, provision of ARV drugs rather than cheaper medication for other diseases prevalent in the population could be regarded as inequitable, but much funding for ART programmes has been earmarked for HIV/AIDS initiatives alone.

Scenario B adopts a "first come first served" approach and treats people at pre-AIDS and AIDS. This is also an egalitarian approach, but purely in terms of improving equity in access (or chance of access) to healthcare at one point in time, and not in equalising health outcomes. It does not follow the maximin principle. Scenario C prioritises patients with pre-AIDS, which involves a more utilitarian perspective, as less of the potential benefit of ART is "wasted" by individuals at more chance of suffering IRIS, treatment failure and other complications.

The generally accepted opinion within the medical community is that treatment should be prioritised to the worst off and therefore closest to death: "in [MSF's] experiences, putting those with greatest risk of death first is most in keeping with the notion of fairness held by people living with

HIV/AIDS," [70]. This adoption of the maximin principle is also egalitarian, since it aims to equalise health status rather than merely access to healthcare. In healthcare provision more generally, such a strategy could divert resources to interventions that produce very small benefits for people who require enormous resources to obtain any benefit at all. This is not the case with ART; patients with late-stage disease can respond well to therapy, albeit with more complications which may add to the cost. Where treatment is unsuccessful, the ART course of drugs is not permanently spent, as would be a heart of liver transplant. Rather, the now empty space in the programme can be filled by another patient.

The utilitarian approach would be to start ART at pre-AIDS (although treating the greatest number could also be viewed as the main outcome, and therefore as a utilitarian rather than egalitarian principle [113]). ART programmes cannot decrease HIV incidence in a mature HIV epidemic unless accompanied by prevention initiatives, as has been shown in Chapter 5, and so the difference in terms of life years saved per person year of treatment is minimal. Instead, a utilitarian approach may argue that, say, six years' extension of life for one pre-AIDS patient is worth more than three years' extension each for two AIDS patients, once the quality of these years is taken into account (with periods spent recovering from ADCs and/or IRIS). Alternatively, delaying the orphanhood of two sets of families by three years may be more valuable in terms of nutrition, educational attainment and psychosocial wellbeing for the children than a six year delay for one family. However, such comparisons are difficult to quantify.

In scenarios A to C there is no withdrawal of failing treatment and therefore these represent beneficence approaches – the commitment of the treatment programme is to the current patient only, and to maximise their welfare. Scenarios E to G involve withdrawal of ART at the clinical, immunological and virological stages, respectively. Withdrawal of failing treatment allows ART to be redistributed more efficiently, increasing both equity (the numbers ever able to benefit from treatment) and utility, especially if the risk of emergence and spread of ARV resistance is also taken into account. Scenario E assumes withdrawal only upon progression to AIDS, at which point ART is of little further benefit to that patient. Scenarios F and G offer a vastly different ethical position to Scenario E because they involve withdrawal of treatment that is still providing significant clinical benefit to the patient.

The ethical problem with withdrawing therapy brings into consideration the "weak maximising principle" discussed by Jonathan Glover [490]: "it is right to save the larger number of stranded people or to be guided by numbers of lives expected to be saved when originally allocating scarce medical resources. But it is not right to throw out someone already in a lifeboat to make room for someone with a better chance of survival, nor is it right to remove someone with poor prospects from intensive care in order to treat someone with better prospects, even if such acts would result in more lives saved." The alternative strong maximising policy allows positive interventions of the kind the weak policy rules out in order to enhance utility. Therefore, according to the weak maximising policy,

we cannot withdraw failing treatment, whereas with the strong maximising policy we can. However, withdrawal of ART is not denying the patient a chance of recovery; it is hastening death rather than determining it, and so the situations are not truly analogous.

Withdrawal of failing treatment upon progression to AIDS in order to transfer ART benefits to others (Scenario E) has little impact in terms of improving equity, as shown in Figure 5.5 of Chapter 5, and would probably jeopardise the acceptability of programmes to patients, as it may be interpreted as abandonment of care and counter, at least in appearances, to the beneficence principle. While timing of regimen change following treatment failure and the implications of continued treatment pressure with viral rebound are discussed in WHO guidelines [29], there is no discussion of withdrawal of ART except to say that, "individuals who cannot tolerate or fail the first and second line regimens would be referred for individualised care by specialist physicians," which is unlikely to be practicable due to the scarcity of such expertise, but it is far easier to state ideal circumstances in policy documents than to discuss less palatable but perhaps more realistic options. Maintaining patients on ART and therefore under treatment pressure with viral rebound may lead to sequential mutations increasing the fitness of resistant strains, which could jeopardise the future use of the most tolerable and cheap treatment regimens.

The question of utility becomes more relevant when evaluating the impact of provision of salvage therapy, which is often more expensive than first-line regimens. Chapter 6 has illustrated how cost-effectiveness (in terms of cost per life year gained) decreases with increasing expense of the salvage regimen. This situation reflects the trade-off between individual- and community-level benefit that ART strategies face.

The danger of the emergence of drug resistance raises another ethical dilemma – do we treat patients to the best of our ability now, but jeopardise the future performance of the programme? Do future, unidentified lives have, in some way, less value? And can or should we hope that technology will continue to expand the regimen options available? Tony Hope discusses the difference in emotive response between an identified person and a 'statistical' person, using the example of equal resources being used for one organ transplant to a known patient or to provision of cholesterol-lowering statin drugs for many, of whom a few, unknown individuals will avoid fatal heart attacks [491]. Glover states that we "find it much harder to envisage the reaction of the families as yet unknown to us when the 'statistical' lives are lost".

Prioritisation based on medical criteria, as investigated in this thesis, may be a starting point from which to explore the impacts of other policies for ART distribution, based on other factors such as psychosocial (including ability to adhere, the prediction of which is highly controversial), contribution to society (HCWs, teachers, professionals), marginalised groups (women, CSWs, MSM, IDUs), reciprocity (participants in HIV-related research), compensatory justice (infections from unsterile injections, transfusions, rape) and social utility (pregnant women), as discussed by Macklin [113]. Such interventionist strategies are fraught with controversy because they can imply that some

people's lives are more worth saving than others, with more tension between equity and utility. This could influence the social climate including the disenfranchising of whole sections of society, which could have a knock-on effect on prevention efforts. Despite the drawbacks, treating different people will have different impacts, especially when taking dependents into consideration. Large scale ART programmes in sub-Saharan Africa will not have the luxury of committees deliberating on a case by case basis. More rigorous analyses of the impact of various prioritisation strategies can inform policy makers and help stimulate debate surrounding the ethics of various strategies, and the weighting that different ethical principles should be given. There is a need for more quantitative analysis to inform debate and aid policy makers in determining what would be acceptable as fair distribution.

7.4 Future directions

As mentioned earlier, the situation regarding ART use in resource-poor settings has been completely transformed over a short period. Evidence from pilot projects in various developing countries is beginning to be reported. There must be a continuous process of evaluating these programmes and using the evidence to adjust model parameters. However, results have tended to be generated with short-term follow-up from well-equipped projects that cannot be characteristic of the large-scale programmes envisaged by WHO [29]. It is crucial that active surveillance of scaled-up programmes continues. Initiatives such as global resistance surveillance will be key to alerting policy makers as to the impact of ART and allowing mathematical modellers to inform their work. Models can also be used to guide future data collection and highlight areas where knowledge is currently lacking, as well as help to design future studies. Data from programmes which are representative of the standards achieved by large-scale ART roll-out would refine the parameterisation of ART models, providing more reliable information on rates of clinical treatment failure and mortality on ART. The use of sexual behaviour surveys could assess the effect of ART, and the effect of the counselling which should accompany the use of ART, on individual's risk behaviour. Information to inform other model parameters will be harder to produce. For example, while data on rates of virological and immunological treatment failure with ART and survival rates with such treatment failure for patients maintaining the same regimen could be produced, ethics committees may deem that researchers have a moral duty to transfer patients to a salvage regimen as soon as treatment failure is detected.

The dynamic models constructed for this thesis could be adapted to address different research questions, especially the investigation of resistance spread, which could be examined in more detail. However, the complexity of these models means that further modification would make them unwieldy. Throughout this thesis, deterministic, population-based transmission models have been used to investigate the epidemiology of HIV and the impact of ART. Further investigation is likely to benefit from the construction of individual-based models, to complement this work and to add more realistic dimensions. Individual based models offer an attractive alternative and offer solutions to

some of the limitations encountered with the existing models. These include the difficulty in parameterising HIV transmission probabilities as a result of the systematic review in Chapter 3 because deterministic models assume instantaneous HIV transmission upon partnership formation, and the complexity of modelling treatment failure and resistance evolution to first- and second-line ART regimens, as discussed in Chapter 6. Both types of modelling approach have their advantages. Deterministic models are, by definition, well defined and for a given set of parameters produce identical outputs. Individual based network models tend to be stochastic, giving a range of outputs for any given set of input parameters and therefore requiring more analysis to interpret.

In the context of further work concerning ARV drug resistance, the impact of ART for children and PMTCT must be assessed. The interim report on the progress of the "3 by 5" initiative highlighted the urgency of scaling up access to HIV care and ART for HIV-infected children, half of whom will die before their second birthday in the absence of treatment [103]. An estimated 660,000 children, mainly in sub-Saharan Africa, are currently in need of ART, and an estimated 4 million in need of cotrimoxazole prophylaxis. There is some concern regarding the effects of ARV monotherapy for PMTCT on subsequent pregnancies. The threat of drug resistance is of relevance for PMTCT, and potentially for treatment of ARV-resistant strains transmitted perinatally to children from PMTCT-experienced mothers. Models explicitly incorporating diagnosis are also required, as demand for VCT services is likely to increase if scale-up is achieved.

7.5 Conclusions

Epidemiology and mathematical modelling are tools that together can help in gaining a better understanding of the impact of ART in resource-poor settings, which is essential in evaluating the impact of widespread scale-up and the need for active surveillance. Although more work is clearly needed to advance our understanding of the implications of ART in such settings, this thesis has furthered the understanding of the potential impact that ART may have at the programme and population level, and provides a basis from which further work can advance. A better understanding of the impact of introduction of ART in resource-poor settings is required in order to inform policy makers on appropriate treatment strategies, surveillance mechanisms and other data collection exercises with which to assess the performance of treatment programmes. Mathematical models were developed to further the understanding of the epidemiology of HIV and ART use, and particularly the effectiveness of a range of alternative treatment strategies and policy options, in the context of resource-poor settings. The work presented in this thesis demonstrates how a variety of models have been used to explain existing, and predict future, patterns of HIV transmission and other epidemiological outcomes. The results show that ART cannot be used as a prevention tool, regardless of the scale of roll-out. The consequences of scale-up will depend on the degree of behaviour change of the treated and the general population, the quality of ART programmes and the

frequency of emergence and relative fitness of ART-resistant HIV strains. As more information is fed back from existing ART initiatives, these models could be adapted to form more reliable predictions regarding the impact of ART.

Mathematical models are increasingly being employed to determine optimal strategies for allocation of these funds [156, 204]. Analysing the implications of different treatment strategies, using data from early programmes coupled with the type of methods presented here, is needed to give programmes the best possible chance of success.

GLOSSARY

Acquired Immunodeficiency Syndrome (AIDS): The late stage of the illness triggered by infection with the human immunodeficiency virus (HIV). According to the official definition published by the CDC, a person is diagnosed with AIDS when he or she is HIV-positive and has a **CD4 count** of less than 200 cells/mm^3 and/or certain OIs or malignancies common with advanced immune deficiency.

AIDS-defining condition or illness (ADC): The terminology given to a list of diseases, the presence of which confirms that a patient has developed **AIDS**. There are several definitions including the CDC classification system (more relevant to industrialised countries [492]) and the revised WHO clinical staging system (more relevant to resource-poor settings [143]).

Antiretroviral therapy (ART): Any drug, agent or therapy used against HIV or other **retroviruses**. An ARV drug is any compound that stops or suppresses the reproduction or activity of HIV (or another **retrovirus**) in a patient's bloodstream. In this thesis, ART refers to triple therapy with at least two **drug classes**, formerly known as "HAART".

Assortative sexual mixing: The extent to which people with similar numbers of sexual partners pair with each other.

Baseline measurement: An initial measurement (such as **CD4 count** or **pVL**) made before starting therapy.

Basic reproductive number R_0: The average number of secondary infections produced by an infected person over his or her lifetime in a totally susceptible population.

Behavioural disinhibition: A potential increase in risk behaviours upon introduction of **ART**, perhaps engendered by a sense of security, or because HIV-infected individuals become more sexually active as their health improves.

Beneficence principle: More generally, beneficence refers to doing good, but in a medical context it refers to the ethical principle that requires healthcare providers, other things being equal, to do what will favour the patient's best interest.

CD4: A protein structure on the surface of a human T-lymphocyte cell to which HIV attaches, allowing entry and infection of a cell. Normally, CD4 ("cluster of differentiation antigen 4") acts as an accessory

molecule important in immune regulation, forming part of larger structures (such as the T-cell receptor) through which T-cells and other cells signal each other.

CD4 (T4) or CD4+ cells: Cells expressing the **CD4** protein structure on their surface. These cells normally orchestrate the immune response, signalling other cells in the immune system to perform their special functions. Also known as **T** helper cells.

CD4 count: The most commonly used surrogate marker for assessing the state of the immune system. This measurement quantifies the number of T-lymphocytes carrying the **CD4** molecules on their cell surface. The normal range for CD4 counts is 800 to 1500 cells/mm^3 of blood. As the CD4 count declines, the risk of developing **OIs** increases.

Cipla: Indian drug company supplying and manufacturing generic pharmaceuticals including ARV drugs to southern Africa.

Clade: See **HIV clade**.

Clinical treatment failure: Defined as an HIV-related infection or a decline in physical health despite at least three months of ART [22], or the occurrence or recurrence of HIV-related events (after at least three months on an ARV regimen), excluding **immune reconstitution syndromes** [493].

Concurrency /concurrent partnership: Partnerships that overlap in time.

Cotrimoxazole: A bactericidal drug combination consisting of trimethoprim and sulfamethoxazole that is used to prevent and treat infections in patients with HIV/**AIDS**.

Disassortative sexual mixing: The extent to which people with many sexual partners pair with people with few partners.

Discordant couple: A pair of (usually long-term) sexual partners, in which one is infected with an STI and the other is not.

Disinhibition: See **behavioural disinhibition**.

Drug class: ARV drugs are classified by their various modes of action. The three main categories are **NRTIs**, **NNRTIs** and **PIs**. The newest ARV drug class is entry/**fusion inhibitors**.

Drug resistance: Reduction in the sensitivity of a pathogen to the effects of a particular drug; alternatively, an increase in the ability of a pathogen to resist the action of a drug. Resistance is thought to result mainly from genetic mutation. In HIV, mutations can change the structure of viral enzymes and proteins so that an ARV agent can no longer interact with the protein to block viral replication.

Drug sensitivity: The extent to which an organism is inhibited by a drug. Drug sensitivity testing determines the concentration of drug required to produce a specific amount of growth inhibition in culture.

Egalitarian principle: The moral doctrine that equality ought to prevail throughout society, and that differences in social status, wealth and other features such as health and/or healthcare should be recognised and eliminated.

Exponential growth rate r: The rate at which an infectious disease epidemic increases.

Force of infection λ: The rate at which susceptible individuals become infected by an infectious disease.

Fusion inhibitor: The most recently introduced class of ARV drugs. Fusion inhibitors, such as enfuvirtide (T-20), inhibit the binding of HIV virions to host cell receptors.

Generation time T_g: The interval between the infection of a primary case and the average time of infection of their contacts.

Genotypic resistance assay: HIV gene sequencing to detect **drug resistance mutations** that are present in the relevant viral genes (i.e. **reverse transcriptase** (RT) and **protease**) that confer HIV **drug resistance**.

Global Fund: The Global Fund to Fight **AIDS**, Tuberculosis and Malaria.

Highly active antiretroviral therapy (HAART): See **ART**.

Hepatotoxicity: Toxic to the liver.

HIV clade: A subtype of HIV made up of a group of related HIV isolates classified according to their degree of genetic similarity (such as the percentage of identity within their envelope genes). There

are currently 3 groups of HIV-1 isolates M, N, and O. Isolate M (major strains) consists of at least 10 clades, A through J. Group O (outer strains) may consist of a similar number of clades.

Immune restoration/reconstitution: The regeneration of memory and naïve T-cells in response to specific antigens.

Immune restoration/reconstitution inflammation syndrome (IRIS): Consists of a variety of conditions that take place when patients, usually those with profoundly low **CD4 counts**, initiate **ART**. The syndrome leads to the development or recrudescence of infections that were already present in the host and are now exacerbated by the restoration of the immune system.

Immunological treatment failure: Failure to increase 25-50 cells/mm^3 above **baseline CD4 count** over the first year of **ART** or experiencing a decrease to below the **baseline CD4 count** on therapy [22].

Index case: The initial patient in the population sample of an epidemiological investigation. In the context of this thesis, it refers to the (first) infected partner in a **discordant couple**.

Infectiousness: See **transmission probability**.

***Mycobacterium avium* and *Mycobacterium intercellulare* complex (MAC):** A group of bacteria responsible for pulmonary and non-pulmonary infections, particularly in the immuno-compromised such as AIDS patients (usually with a **CD4 count** below 95 cells/mm^3).

Médecins Sans Frontières (MSF): An international humanitarian aid organisation providing emergency medical aid in more than 80 countries, including some pilot **ART** programmes.

Mutagenesis: The production of **mutations**.

Maximin principle: The maximin principle or the maximin criterion states that the aim of policy makers should be to maximise the wellbeing of the worst off; that is, maximise the minimum.

Mutation: An alteration in the genetic code of an organism. For example, an exchange of a single base in deoxyribonucleic acid (DNA) for a different one may result in a change in amino acid in a specific protein (see also **primary mutation** and **secondary mutation**).

Non-nucleoside analogue reverse transcriptase inhibitor (NNRTI): A class of ARV drugs that bear little resemblance to DNA components, but inhibit **reverse transcriptase** function by binding close to the active site of the enzyme and preventing it functioning properly.

Nucleoside analogue reverse transcriptase inhibitor (NRTI): The first class of ARV drugs introduced which resemble the building blocks of DNA, but are chemically modified to inhibit replication of the HIV gene by **reverse transcriptase**. These interact at the active site of the enzyme and when incorporated into the growing DNA, cause chain termination.

Opportunistic infection (OI): An illness caused by an organism that usually does not cause disease in a person with a normal immune system. People with advanced HIV infection suffer OIs of the lungs, brain, eyes and other organs.

***Pneumocystis jiroveci* pneumonia (PCP):** A form of pneumonia which is caused by a microorganism called *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). It is a life-threatening OI which remains a leading cause of death in people with AIDS in industrialised countries, but is less common in other settings such as sub-Saharan Africa.

Polymerase Chain Reaction (PCR): A sensitive technology that can be used to quantify an amount of DNA in a sample. It can detect quantities of HIV RNA by converting the viral RNA to DNA.

PEPFAR: A US-based five year US$15 billion global initiative to combat the HIV/**AIDS** epidemic.

Pharmacokinetics: The process of absorption, distribution, metabolism, and excretion of a drug or vaccine.

Phenotypic resistance assay: Measures the drug susceptibility of a virus by determining the concentration of drug that inhibits viral replication in tissue culture. Results are usually expressed as the fold-change in susceptibility of the test sample compared with a laboratory control isolate.

Public Health Laboratory Service UK (PHLS): Now part of the Health Protection Agency of the UK, which is an independent body designed to protect the health and well-being of the population (http://www.hpa.org.uk/).

Plasma viral load (pVL): The number of viral particles (for example, HIV) in a sample of blood plasma, as determined by assessing the number of HIV RNA copies. pVL is an indicator of viral

replication occurring in a patient. It is increasingly employed as a surrogate marker for disease progression and to monitor the effectiveness of **ART**.

Primary mutation: A **mutation** that may change the conformation (shape) of viral protein, resulting in the decreased ability of a drug to inhibit the function of that protein, making the virus resistant, to some degree, to the effects of the drug. The most common mechanism is that the conformational change causes a decrease in a drug's ability to interact with the active site of the specific targeted viral protein. Such **mutations** may also decrease the fitness of the virus, causing it to replicate less efficiently.

Primary (transmitted) resistance: Patients acquiring drug-**resistant** infection through HIV transmission.

Prophylaxis: Treatment to prevent the onset of a particular disease (primary prophylaxis), or the recurrence of symptoms in an existing infection that has been brought under control (secondary prophylaxis, maintenance therapy).

Protease: An enzyme produced by HIV that cuts long viral proteins produced during replication into smaller-sized proteins that are functional and necessary for viral maturation.

Protease inhibitor (PI): The third class of ARV drugs, introduced in 1995. PIs bind to and block the HIV **protease** enzyme from working, thereby preventing the production of new infectious viral particles.

Quasispecies: Refers to the "swarm" of closely related virus species present in any single given patient. These minor genetic differences between individual viruses in a patient are due to the natural level of **mutation** that is seen every time each virus replicates.

Replication capacity: The ability of an organism (e.g. a virus) to replicate in a given environment.

Reproductive number: The average number of secondary infections produced by an infected person over his or her lifetime (see also **basic reproductive number**).

Resistance: The ability of a virus to multiply in the presence of elevated concentrations of a drug. Partial resistance usually refers to the incomplete escape from drug pressure.

Retrovirus: A type of virus that stores its genetic information as single-stranded RNA. After a retrovirus penetrates a cell, it creates a DNA version of its genes using a special enzyme, reverse transcriptase. This DNA then becomes part of the cell's genetic material, which also comprises DNA.

Reverse transcriptase (RT): An enzyme essential for the replication of HIV. This enzyme is unique to HIV-like viruses and converts the viral RNA into DNA, so that the HIV genome can be inserted into the cell's DNA.

Ribonucleic acid (RNA): A family of single-stranded molecules structurally similar to DNA, composed of similar bases of nucleic acids (but using Uracil instead of Thymine), and differing in the sugar (ribose) used to form the backbone of the molecule. In cells, messenger RNA transmits the code that instructs the cell's chemical machinery to produce structural proteins and enzymes. In HIV, RNA is the molecule that carries the genetic information in the virus. In the process of infection, the HIV genome must be converted to DNA to successfully infect a cell.

Secondary mutation: This may be the attempt of a virus to overcome the decreased ability to replicate caused by the conformational (shape) change imparted by a **primary mutation**. Secondary mutations result in another conformational change to a viral protein and may not cause drug **resistance** by themselves, but may cause increased **resistance** in the presence of **primary mutations** or other secondary mutations. Spontaneous secondary mutations can occur without a **primary mutation** present.

Secondary resistance: Patients acquiring drug-resistant infection as a result of ARV treatment failure

Serial interval: See **generation time**.

Total lymphocyte count (TLC): Surrogate marker for assessing the state of the immune system, counting all lymphocytes. Alternative to **CD4 count** in resource-poor settings because it is less complex, not requiring flow cytometry to measure lymphocyte subsets. However, it is less specific.

Transmission probability: The proportion of exposures that results in transmission of infection. The definition of "exposure" depends on the mode of transmission. For HIV, examples of types of infectiousness include per sexual contact, per sexual partnership, per injection, per blood transfusion, and per live birth.

Transmission interval: See **generation time**.

Treatment regimen failure: A broad term that incorporates all possible reasons for failure (e.g. adherence, toxicity, pharmacokinetics, suboptimal virological potency, resistance etc). Treatment regimen failure is often associated with **virological**, **immunological** and/**or clinical treatment failure** [22].

Undetectable virus: The threshold at which measurements of **pVL** are not detectable depends on the assay used. Common thresholds are <400 copies/ml or <50 copies/ml.

UNAIDS Drug Access Initiative (DAI): An initiative launched by UNAIDS in 1997 in order to develop innovative, effective models to improve access to drugs to treat HIV and **OIs**. The DAI works with the Ministries of Health in participating countries. In the initial phase, participating countries were Côte d'Ivoire, Chile, Uganda and Vietnam.

Utilitarian principle: The ethical theory proposed by Jeremy Bentham and James Mill that all action should be directed toward achieving the greatest happiness, or the greatest welfare, for the greatest number of people. The morally right action is the action which promotes or tends to promote the best overall consequences.

Viral fitness: The ability of any HIV-1 variant to replicate in a given environment (e.g. in vitro cell cultures in the presence or absence of drug).

Viral load: See **plasma viral load (pVL)**.

Virological treatment failure: Defined as virus still being detectable 48 weeks after initiating **ART**, or if it is detected again after treatment has previously lowered pVL to undetectable levels [22], or a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a confirmed HIV RNA level >400 copies/mL after suppression of viraemia [22].

Voluntary counselling and testing (VCT): The process by which an individual undergoes confidential counselling to enable them to make an informed choice about learning their HIV status and to take appropriate action.

Wild-type virus: An HIV virus with no drug **resistance mutations** (virus resistant to ARV drugs contains **mutations**.)

Zidovudine: An ARV drug of the class **NRTI**. Also known as lamivudine, 3TC and azidothymidine (AZT).

Appendix A

Publications arising from this thesis or from work related to this thesis:

Chapter 2

Baggaley RF, Ferguson NM and Garnett GP (2005) The epidemiological impact of antiretroviral use predicted by mathematical models: a review. Emerging Themes in Epidemiology 2005, 2:9.

Chapter 3

Baggaley RF, Boily MC, White RG and Alary M (2006) Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. AIDS 2006, in press.

Chapters 4 and 5

Baggaley RF, Garnett GP and Ferguson NM (2006) Modelling the impact of antiretroviral use in resource-poor settings. PLoS Med 3(4):e124, in press.

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The epidemiological impact of antiretroviral use predicted by mathematical models: a review

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Abstract

This review summarises theoretical studies attempting to assess the population impact of antiretroviral therapy (ART) use on mortality and HIV incidence. We describe the key parameters that determine the impact of therapy, and argue that mathematical models of disease transmission are the natural framework within which to explore the interaction between antiviral use and the dynamics of an HIV epidemic. Our review focuses on the potential effects of ART in resource-poor settings. We discuss choice of model type and structure, the potential for risk behaviour change following widespread introduction of ART, the importance of the stage of HIV infection at which treatment is initiated, and the potential for spread of drug resistance. These issues are illustrated with results from models of HIV transmission. We demonstrate that HIV transmission models predicting the impact of ART use should incorporate a realistic progression through stages of HIV infection in order to capture the effect of the timing of treatment initiation on disease spread. The realism of existing models falls short of properly reproducing patterns of diagnosis timing, incorporating heterogeneity in sexual behaviour, and describing the evolution and transmission of drug resistance. The uncertainty surrounding certain effects of ART, such as changes in sexual behaviour and transmission of ART-resistant HIV strains, demands exploration of best and worst case scenarios in modelling, but this must be complemented by surveillance and behavioural surveys to quantify such effects in settings where ART is implemented.

Introduction

The epidemiological impact of widescale use of (highly active) antiretroviral therapy (HAART, or ART) among HIV patients in industrialised countries has been explored by a number of mathematical modelling studies [1-5]. The consequences of ART use are far from intuitive. Successful ART decreases plasma [6] and seminal viral load [7,8] and so is thought to reduce HIV infectiousness. However, its main function is to increase the life expectancy of infected individuals [9,10], and over time this causes the pool of potential transmitters of infection to grow. These two factors - decreased infectivity but increased duration of infectiousness - have opposing effects on transmission. In addition, increases in risk behaviour could result from increased optimism about HIV prognosis due to the availability of ART. This is an area of uncertainty, with contradictory evidence [11-15].

Mathematical models can be used to address questions regarding the potential impact and effectiveness of various strategies. In terms of ART use, they can be used to investigate:

1) optimising the efficient use of ART;

2) the epidemiological consequences of ART and interaction with behavioural changes/interventions;

3) the likely course of drug resistance evolution

a. Within the individual;

b. Between individuals;

4) achievable levels of coverage and effectiveness;

5) the effective and efficient use of second line treatments; and

6) demographic/health care impact.

This review will briefly describe a range of models investigating the impact of ART use in various settings and evaluate the utility of these dynamic models.

The range of ART models

Mathematical models examining the epidemiological impact of ART broadly fall into two categories; those incorporating HIV transmission dynamics, where incidence of new infections is dependent on HIV prevalence [1,2,4,5], and simpler linear models [16-18]. A summary of ART models is provided in Table 1. Aalen et al [17] constructed a model describing men who have sex with men (MSM) in England and Wales and the use of ART. This Markov multi-stage model represented stages of HIV infection based on CD4 count. The authors considered a variety of treatment scenarios, and incorporated asymptomatic and symptomatic individuals and the concept of eligibility for treatment, making the simulation of treatment uptake and its impact more realistic than previous work. Wood et al [16] constructed a health economic model to predict the future impact of low-level ART use in South Africa from 2000 to 2005. The authors modelled total drug cost, cost per life year gained and the proportion of per person healthcare expenditure required to finance ART in each scenario. The study involved a cost effectiveness analysis comparing the epidemiological impact of ART with other interventions such as prevention of mother-to-child transmission (PMTCT). Freedberg et al [18] also used stages of disease determined by CD4 count and predicted the incremental cost per quality-adjusted year of life gained by ART in the US. Wilson and Blower [19] used a spatial mathematical model to explore ART allocation strategies among health care facilities in the province of KwaZulu-Natal, South Africa, with an emphasis on maximising equity in access to treatment.

In an investigation into the impact of an expanded response (incorporating prevention interventions and care and support activities) on the HIV/AIDS pandemic, Stover et al 2002 did not include the effect of ART because, "there is little empirical data available on the magnitude of the preventive effect of treatment (reduced viral load and hence infectiousness) and care" [20]. However in a later publication, the authors investigated the effects of combining treatment with effective prevention efforts, using the same model (the Goals model [21]), calibrated to sub-Saharan Africa [22]. The Goals model is a Microsoft Excel™ spreadsheet model using linear equations, designed to improve resource allocation for national HIV/AIDS programmes. It feeds into the dynamic epidemic projection package (EPP) and Spectrum, used by the UNAIDS/WHO to produce national HIV/AIDS estimates [23,24], to predict the impact of an intervention. The authors concluded that a prevention-centred strategy provides greater reductions in incidence, but more modest mortality benefits, than treatment-centred scenarios. A combined approach would yield further benefits, but focusing on treatment at the expense of prevention could diminish this effect.

Auvert et al 2004 used a linear model to estimate the proportion of the South African population requiring ART under the then current WHO guidelines (treating all individuals with a CD4 cell count less than 200 cells/mm^3 [25]) and to predict the impact of ART on the short term spread of HIV in this setting [26].

Such linear models have generally been used to inform policy makers on issues such as resource allocation, and typically involve only short-term predictions of the effect of ART for health care providers, as estimated by cost-effectiveness analysis [16,18]. The models are relatively straightforward in that they look at the health states of individuals, associated treatments and events that individuals experience, but fail to take account of the non-linear feedback process underlying infectious disease epidemics. Linear models are limited by the accuracy of estimates of HIV incidence used to parameterise the models, which is all the more important because their predictions and conclusions are usually more quantitative in nature than those provided by dynamic models, which have tended to be used to give more qualitative insight. Models incorporating HIV transmission dynamics typically investigate the impact of ART over a longer time frame and are used to address more general questions surrounding ART use, such as whether the benefits of ART provision outweigh the problems and risks, and which approaches to ART provision are most effective. Both types of model are required, to inform policy makers in resource-poor settings about the costs of ART provision in the short term

Table 1: Summary of existing ART models, by date of publication.

Study	Model structure	Setting	Assumptions	Key outcomes (pertaining to ART) and comments
Zaric et al 1998 [74]	Dynamic, difference equations	MSM and IDU, US cities/ regions	Infection stratified into HIV and AIDS stages. Allows acquired and transmitted drug resistance. Rate of resistance evolution: 95% per year for non-adherents, 5% per year for adherents. Increased life expectancy due to ART: 1.5-fold for adherents, 1.2-fold for non-adherents, 1.2-fold for adherents infected with drug resistant HIV.	The most important factor affecting emergence of drug resistance is adherence to ART.
Aalen et al 1999 [17]	Linear	MSM, England and Wales, 1990s	Markov multi stage model (stage based on CD4 count). Explicit diagnosis and treatment. Estimated HIV incidence in the MSM population, which was fixed at 1200 cases/year for all but one scenario, where incidence was halved from 1995 onwards.	Decrease in AIDS incidence due to ART. Number receiving treatment will increase 50–100% by 2001 compared to pre-1996.
Wood et al 2000 [75]	Linear model	IDU, Vancouver, Canada 1999–2006	Treatment uptake: 80% (scenario 1), 20% (scenario 2). Median increase in life expectancy due to ART: 7 years. No drug resistance or stratification by infection stage or sexual activity class. Prevalence estimates used in DemProj, part of the Spectrum suite of models (information at http://www.futuresgroup.com/software/Goals/goals.pdf) (3 scenarios: prevalence reduced from 7% in 1999 to 5% in 2006, prevalence remains at 7%, prevalence increases to 9% in 2006.	Calculated life expectancy and AIDS deaths 1999–2006 for each scenario. Concluded that low level ART use is not sufficient to increase life expectancy in this population and called for expansion in ART coverage.
Wood et al 2000 [16]	Linear health economic model (based on previous model [75])	South Africa 2000–2005	Median increase in life expectancy due to ART: 6 years (range: 5–7). Treatment uptake: 25% of infected adults. Spectrum AIDS Impact model was used to adjust the population projections for current and projected HIV-associated mortality.	Providing ART for 25% of the infected population could prevent a 3.1 year decline in life expectancy and more than 430,000 incident cases, but with disproportionate expenditure ($19 billion at 2000 prices) compared to preventing mother-to-child transmission.
Blower et al 2000 [5]	Dynamic, deterministic	MSM, San Francisco, US, up to 2010	Changes in sexual behaviour: no change to doubling of risk. Treatment coverage rates: 50–90% uptake per year. ART reduces infectivity 2- to 100-fold. Acquired drug resistance: 10–60% per year (infections can revert back to ART-sensitive). Resistance is transmitted, but is less fit than wild type. No stratification by stage of infection or sexual activity class. Increased life expectancy due to ART: 1.5- to 3.0-fold.	Increasing ART usage would decrease the death rate and substantially reduce HIV incidence (wide range of results due to uncertainty in parameter estimations).
Blower et al 2001 [63]	Dynamic, deterministic (used previous model [5])	MSM, San Francisco, US, 1996–2005	Treatment uptake and drug resistance evolution rates as for [5]. No change in risk behaviour. Assumed no resistant strains could arise that were as transmissible as wild type. Transmissibility range: 1–90% as fit as wild type. Implicitly allows superinfection with wild type virus of subjects with primary resistance.	Prevalence of ART resistance is already high in San Francisco and will continue to increase substantially through 2005. Transmitted drug resistance will remain low, only increasing gradually, with a doubling time of around 4 years and a predicted median 15.6% (range 0.05–73.21%) new infections resistant to ARVs by 2005.
Freedberg et al 2001 [18]	Linear health economic model	US	Monte Carlo simulation of a hypothetical cohort of infected patients. Disease progression predicted by CD4 count (6 categories) and viral load (5 categories). Detailed description and associated costs of HIV-related morbidity, opportunistic infections and death. Virologic failure represented as 0.5 log increase in viral load for 2 consecutive months. Increased life expectancy due to ART: 2 years.	The cost-effectiveness ratio for ART was $13,000–$23,000 per quality-adjusted life year gained. Initial CD4 count and drug costs were the most important determinants of costs, clinical benefits, and cost effectiveness.

Table 1: Summary of existing ART models, by date of publication. *(Continued)*

Tchetgen et al 2001 [76]	Dynamic, deterministic	MSM (assumes same population as Blower et al [5])	No stratification by sexual activity or stage of infection (model is for all stages except AIDS; progression to AIDS exits an individual from the model population). Models diagnosis separately from treatment initiation. No sexual behaviour change due to ART. Drug resistance emerges at 1.2–13.5% per year for adherent patients and 67.3–85.9% per year for non-adherent patients. Resistant strains are half as transmissible as wild type. Untreated resistant infections may revert to wild type infections (10% per year). 60% of treated patients adhere. Increased life expectancy due to ART: approximately 3-fold. ART reduces infectivity by 74%. Withdrawal rates also vary by adherence.	Although screening for adherence is likely to reduce levels of drug resistance compared to treating all patients, HIV and AIDS incidence rates are likely to increase unless screening accuracy is extremely high.
Dangerfield et al 2001 [77]	Dynamic, deterministic	MSM, UK 1981–1998	Five stages of infection with varying infectivity broadly corresponding to primary infection, incubation, pre-AIDS and early and late AIDS. Three levels of sexual activity with proportionate mixing. No drug resistance. Proportion initiating ART at each stage (models 1,2 and 3 respectively): incubation = 0%, 0%, 60%; preAIDS = 0%, 10%, 25%; early stage AIDS = 0%, 10%, 35%. No uptake for late stage AIDS, which is defined as the final few months of care – authors assume patients only reach this stage as a result of treatment failure. Infectivity decreases to a constant level for all those treated, which is 35–40-fold less than for pre-AIDS.	Three models were designed, differing by prognosis of patients experiencing treatment failure for models 1 and 2. Model 3 stratifies life expectancy on ART by stage of infection at which treatment is initiated.
Law et al 2001 [4]	Dynamic, deterministic	MSM, Australia 1996	Population-level changes in sexual behaviour: no change to doubling of risk. Decrease in infectivity due to ART: 10-fold (range: 100-fold to none). Proportion of individuals diagnosed and treated increases with progression of disease, as determined by CD4 count. HIV diagnosis modelled separately to ART initiation, median 2-fold decrease in risk behaviour upon diagnosis (range: 25–75% reduction). No stratification by sexual activity group. No incorporation of drug resistance. Stratified by stage of infection in terms of CD4 count (>500 cells/ml, 200–500, <200, AIDS). Proportion treated by disease stage: >500 = 35%, 200–500 = 52%, <200 = 72%, AIDS = 90%.	Changes in risk behaviour were linearly associated with increases in incidence, while decreases in infectivity were non-linearly associated with decreases in incidence. Decreases in infectivity of 2-, 5- and 10-fold would be counterbalanced (in terms of incidence) by increases in risk behaviour of 40, 60 and 70%, respectively.
Velasco-Hernandez et al 2002 [1]	Dynamic, deterministic (used previous model [5])	MSM, San Francisco, US.	Previous model [5] is used to derive an analytical expression for R_0. Used assumptions as for the previous model. Changes in risk behaviour: 50% reduction to 100% increase (whole population). Relative fitness of resistant strains: 1% to "approximately as transmissible".	Median R_0 = 0.90 if risky sex decreased, 1.0 if risky sex remained stable, and 1.16 if risky sex increased. R_0 decreased as ART coverage increased. The probability of epidemic eradication is high (p = 0.85) if risky sex decreases (median 25% reduction), moderate (p = 0.5) if it remains stable, and low (p = 0.13) if it increases (median 50% increase). Concluded that ART can function as an effective HIV prevention tool, even with high levels of drug resistance and risky sex, and could eradicate a high prevalence (30%) HIV epidemic.
Law et al 2002 [78]	Dynamic, deterministic (extension of previous model [4])	MSM, Australia 1996	Incorporation of other sexually transmitted infections (STI), but not dynamically-assumed 100% increase in prevalence of STI among all MSM regardless of HIV status, due to increased risk behaviour as a result of ART interaction. STI infection increased HIV infectivity 3.5-fold (range: 2–5-fold).	Decreases in infectivity of 2-, 5- and 10-fold would be counterbalanced (in terms of incidence) by increases in risk behaviour of 30, 50 and 65%, respectively i.e. even more modest increases than in previous publication [4]. Even small increases in STI as a result of increased risk behaviour could have an important multiplicative effect increasing HIV incidence.

Table 1: Summary of existing ART models, by date of publication. *(Continued)*

Johnson & Dorrington 2002 [79]	ASSA2000 Interventions Model (dynamic deterministic spreadsheet model)	South Africa	Stages of infection: stages I to IV of the WHO clinical staging system, with decline in sexual activity at advanced stages. Includes voluntary counselling and testing (VCT) with a corresponding (though transient) decrease in risk behaviour for both infected and uninfected individuals. Reduction in viral load due to ART: 1.76 log_{10}. Reduction in infectivity: 67% per log reduction in viral load. 4 sexual activity classes. Only AIDS patients qualify for treatment. Model assumes a phased roll-out achieving 90% coverage by 2006. First 6 months of ART: death rate = 8.2%, discontinuation rate = 9.1%. Thereafter: death rate = 5.8%/year, discontinuation rate = 5.8%. Resistance not explicitly modelled.	ART provision is highly effective at preventing new infections, through reduced infectivity and assumed impact of VCT, and the high coverage level. ART plus VCT reduces incidence of AIDS, but because of increasing numbers starting treatment, the overall number of AIDS cases increases to a peak in 2015. Approximately one million deaths would be averted between 2001 and 2015 if ART is added to a set of AIDS prevention initiatives.
Nagelkerke et al 2002 [80]	Dynamic, deterministic	Botswana and India	Stratified by gender and 2 sexual activity groups (higher group represents CSWs and their clients). No changes in sexual behaviour due to ART, but "effective counselling" of those on ART could decrease infectivity of those developing drug resistance by 50%. ART reduces infectivity to zero. Rate of acquired resistance: 25% per year (range: 5–25%). Transmitted resistance possible (resistant strains appear to be as transmissible as wild type). Rate of treatment uptake: all those infected are recruited at rate 50% per year. No stratification by stage of infection.	Compared impacts of an ART programmes to other HIV interventions. Concluded that after transient success, ART would be ineffective within 30 years due to widespread drug resistance. Assumes high treatment uptake rates and pessimistic assumptions regarding transmission of drug resistant strains.
Gray et al 2003 [2]	Dynamic, stochastic	Rakai, Uganda, 2000–2020	Assumes ART reduces HIV log viral load by 27.0–42.5%, representing decreases in log viral load from 5.32 to 3.06 log_{10} copies/ml [49], and 5.23 to 3.82 log_{10} copies/ml [48]. These generate an average decrease in infectivity of 95.7% (0.0023 to 0.0001 per coital act) and 43.5% (0.0023 to 0.0013) respectively. Sexual activity decreases with increasing viral load. Behavioural disinhibition: increased risk by 50–100% (among those on ART only). Treatment uptake: scenario 1: all with viral load >55,000 copies/ml; scenario 2: all subjects, irrespective of viral load (20% of infected persons in Rakai had viral loads >55,000 copies/ml [81]). Range of treatment coverage: 0–100%.	Concluded that ART alone cannot control mature HIV epidemics such as that in Rakai. Behavioural disinhibition would counter decreases in HIV infectivity due to ART.
Xiridou et al 2003 [82]	Dynamic, deterministic	Young MSM, Amsterdam, The Netherlands	Steady and casual partnerships. Stages of infection: primary, incubation, AIDS. Sexual activity assumed to cease after development of AIDS. 42% subjects in incubation stage are diagnosed. Diagnosis during incubation results in a 25% (0–50%) reduction in risky behaviour. ART reduces infectivity by 74.5%. Increased life expectancy (before development of AIDS) due to ART: 9.5 years.	A 75–99% reduction in infectivity due to ART will be counterbalanced by increases of 50% (range: 30–80%) in risky behaviour with steady partners, but not by increases of up to 100% with casual partners. Increasing HIV testing from 42% to 80% and ART coverage from 70% to 85%, would mean even a 100% increase in risk taking with steady partners would not outweigh the effect of ART on HIV incidence.
Xiridou et al 2004 [3]	Dynamic, deterministic (extension of previous model [82])	Young MSM, Amsterdam, The Netherlands	Extension of original model [3] to allow for initiation of ART during primary infection. Proportion of men diagnosed during incubation and successfully treated: 60–80%. Proportion initiating ART during primary infection: 1–10%. ART reduces infectivity during incubation by 50–99%. Population-level increase in risk behaviour for both steady and casual partnerships: 0–100%. Mean incubation time to AIDS for initiating ART during incubation: 15–30 years. Decreases in infectivity and increases in life expectancy for those initiating ART during primary infection were forced to be larger than for those initiating ART during incubation.	Investigates the role of primary infection in HIV transmission. Estimates that among all new infections only 11% occur during primary infection. The effect of ART during primary infection on transmission is therefore limited. However, in a community with higher risk behaviour among casual partnerships, the fraction of transmission attributed to primary infection increases to 25%.

Table 1: Summary of existing ART models, by date of publication. *(Continued)*

Clements et al 2004 [38]	Dynamic, deterministic (based on previous models [4, 78])	MSM, Australia 1995–2006	Assumed a 10% annual increase in population-level risk behaviour from 1996. A stable proportion receive ART from 1998, which then declines from 70% in 2001 to a median of 50% of diagnosed on ART by 2006.	HIV incidence was predicted to have declined during 1996–1998 due to ART, with a slow increase 1998–2001 due to increased risk behaviour while ART usage remained fairly stable. From 2001, a continued increase in risk behaviour coupled with a moderate decline in ART use would lead to a 50% increase in incidence by 2006.
Auvert et al 2004 [26]	Linear	Township near Johannesburg South Africa, 2002	Used results from cross-sectional study. Under WHO guidelines, all with CD4 counts <200 initiated treatment. Under USDHHS guidelines, all with CD4 counts <350 or viral load >55,000 copies/mL initiated treatment. Reduction in infectivity due to ART calculated using infectivity estimates by viral load category used by Gray et al [2] and comparing change in distribution of viral load in the community with and without ART.	Investigated short term impact of ART on incidence. The proportion of infected subjects eligible for ART was 9.5% (95% CI 6.1–14.9%) under WHO guidelines and 56.3% (95% CI 49.1–63.2%) under USDHHS guidelines. The population impact of ART on HIV transmission is small (reduction in annual risk of transmission 11.9% (95% CI 7.1–17.0%)) under WHO guidelines, but higher under USDHHS guidelines (71.8% (95% CI 64.5–77.5%))
Boily et al 2004 [30]	Dynamic, deterministic	MSM population	STI (gonorrhoea) increasing HIV infectiousness is modelled dynamically. Stratified into 6 sexual activity groups with proportionate mixing. Two stages of HIV infection: incubation and AIDS. AIDS patients treated with ART resume the sexual activity of asymptomatic individuals within their activity class. ART reduces infectivity by 25% (pessimistic), 50–90% (moderate), 99% (optimistic). Treatment uptake rates: 10–90% per year, for AIDS patients only, or for all infected subjects. Withdrawal rate (due to treatment failure, resistance and toxicity): 0–50% per year	Zero to 55% new bacterial STI could be attributed to widescale ART use, due to more modest increases in risky behaviour (0–25%) at the population level. These increases have a negative impact on HIV if coverage is too low. Increasing ART coverage helps to prevent more HIV infections despite larger increases in risk behaviour and STI that is predicted to ensue. No individual-level increase in risk behaviour; population-level increases in risk behaviour over time are due to ART slowing the depletion of high-risk infected individuals, so these populations are replenished.
Salomon et al 2005 [22]	The Goals model (linear spreadsheet model) (based on previous models [20, 21])	Sub-Saharan Africa, calibrated to 3 regions: East, West/Central and Southern, up to 2020.	Goals model adjusts UNAIDS/WHO EPP (epidemic projection package) and Spectrum model incidence and prevalence estimates. 5 different risk groups (single and married men and women, and CSWs). Median increase in life expectancy due to ART: 3 years. No drug resistance. Includes STI transmission. 3 stages of infection: primary, incubation and symptomatic. ART reduces infectivity by 99% (optimistic) or 66% (pessimistic). Number of partners reduced by 50% plus 2 times higher condom use (optimistic) or no change (pessimistic) for those treated. Risk behaviour of the general population does not change (optimistic), or condom use declines by 10% (pessimistic). Treatment uptake: 50% ART coverage (of those in need) by 2005, increasing to and remaining at 80% from 2010–2020. This "treatment-centred" response, where little prevention activity occurs, was compared to a "prevention-centred" response where no ART scale-up occurred, and a "combined response", with optimistic and pessimistic assumptions of the effect of ART on prevention efforts being investigated	Explored the potential impact of ART in the context of a broader strategy for HIV/AIDS control, comparing deaths and new infections averted to baseline projections without interventions. A prevention-centred strategy provides greater reductions in incidence and mortality reductions similar to those of treatment-centred strategies by 2020, but more modest mortality benefits over the next 5–10 years. If treatment scale-up leads to reduced effectiveness of prevention efforts, benefits (in terms of infections and HIV/AIDS deaths averted) are considerably smaller than for initiatives which complement each other. The number receiving ART in 2020 ranges from 9.2 million in a pessimistic treatment-only scenario, to 4.2 million in a combined response scenario with positive treatment-prevention synergies.
Wilson & Blower 2005 [19]	Spatial model	KwaZulu-Natal, South Africa	Incorporates heterogeneity in treatment accessibility with distance to health care facilities, and heterogeneous distribution of people infected with HIV.	Determining the optimal ART allocation strategy among health care facilities, aiming to maximise equity. Authors' strategy gave more equal access to ART than allocating therapy to the state capital only, or equal allocation to all health care facilities.

(Wood et al [16], for example), as well as to predict the likely impact of scaling up ART use.

To date, policies designed to ameliorate the HIV/AIDS epidemic in Africa have been heavily based on policies from industrialised countries [27]. However, the epidemiological and economic contexts are so different that there is an urgent requirement to assess whether existing policy options and targets are optimal for resource-poor settings.

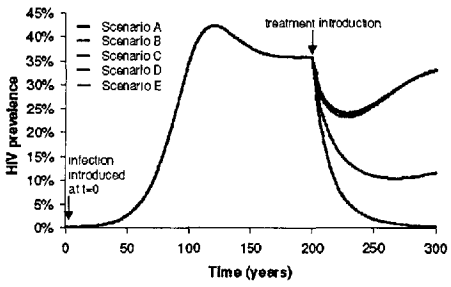


Figure 1

Model predictions of the effect of ART on a mature epidemic, under various assumptions. Model simulations of the potential impact of ART on a mature epidemic, varied by treatment uptake rate, reduction in infectivity due to treatment and impact on risk behaviour at the population level (see Endnote for model description). The model used only incorporates one stage of HIV infection and so individuals initiate treatment at an earlier stage of infection than is realistic, and there is homogeneous sexual mixing. Scenario A – ART uptake = 50% per year, sexual activity post ART = unchanged (2.5 partners per year), reduction in infectivity due to ART = 50-fold. Scenario B – ART uptake = 50% per year, sexual activity post ART halves (1.25 partners per year), reduction in infectivity due to ART = 50-fold. Scenario C – ART uptake = 50% per year, sexual activity post ART = unchanged (2.5 partners per year), reduction in infectivity due to ART = 1000-fold. Scenario D – ART uptake = 90% per year, sexual activity post ART = unchanged (2.5 partners per year), reduction in infectivity due to ART = 1000-fold. Scenario E – ART uptake = 90% per year, sexual activity post ART = reduced by 20% (2 partners per year), reduction in infectivity due to ART = 1000-fold.

Dynamic model structures

Most dynamic models of HIV transmission investigating the impact of ART are deterministic, with a frequency-dependent (density-independent) transmission term. This means that the rate of (sexual) contact between one individual and others within a population does not depend on the density of the population, as it would, for example, in the case of contacts for air-borne infection transmission. HIV transmission models often incorporate relatively complex patterns of sexual behaviour, with model populations stratified into sexual activity groups by rate of partner change, and assuming different degrees of mixing between groups. However, to date most models specifically designed to examine ART impact have assumed homogeneous risk behaviour (although some of these models have investigated changes in risk behaviour of the general population as a result of ART introduction and/or a change upon diagnosis of HIV [4,5]). More realistic incorporation of sexual behaviour is likely to improve the ability of models to capture the observed timescale of African HIV epidemics, namely steady state being reached over decades rather than centuries. Figure 1 shows projections from a homogeneous sexual activity model, illustrating how, with a homogeneous population, realistic prevalence levels (representing epidemics in sub-Saharan Africa) can only be reached over unrealistic timescales (a full description of the model is provided in the Endnote). However, such homogeneous models can simulate HIV epidemics over realistic timescales if they are assumed to represent the 'at-risk proportion' of the total population only. This means that the population is crudely divided into two groups; one group practices no risky behaviour at all, whereas the other has a relatively high rate of (unprotected) sexual partner change. This structure produces an epidemic curve over a realistic timeframe (decades rather than centuries), without producing unreasonably high prevalence levels for the entire population (at-risk and not at-risk).

More sophisticated models incorporating sexual behaviour include partner models [28,29] and network models [30,31]. Gray et al [2] use a stochastic simulation incorporating individuals and their contacts, although some assumptions are not clear in the available publication. The need for complexity will depend on the nature of the research question [32]. For example, where changes in sexual behaviour as a result of ART are to be investigated, a more sophisticated description of sexual behaviour is required [30]. Where the effect of ART on transmission is to be investigated, a more realistic pattern of infectivity is required [2,4]. However, while increased complexity can make models more realistic, it also makes them more difficult to parameterise and it more difficult to analyse and interpret model output.

Behaviour change

The possibility of widescale use of ART leading to changes in patterns of risk behaviour, particularly a disinhibition effect, has been of considerable concern. There are competing possible effects; at the individual level, treated patients may increase the frequency of sexual activity due to the severity of their symptoms decreasing, but may receive effective prevention counselling upon treatment initiation, which would decrease the frequency of risky activities. At the population level, in areas with substantial treatment coverage and successful treatment outcomes, there may be an increase in complacency among the general population regarding an HIV diagnosis, leading to increases in risk behaviour. Despite considerable debate [11-15], this relationship has not been convincingly demonstrated in industrialised countries where ART is readily

available. A recent paper suggests that recent increases in risk-taking behaviour among MSM may be the result of non-volitional changes at the individual level over time [33]. The depletion of the pool of high-risk individuals in the pre-ART era made it more difficult for the remaining high risk-taking individuals to find partners to engage in risky sex with, but ART has facilitated the differential replenishment of this group. Therefore individuals who previously had to reduce their levels of risky sex could resume their initial high-risk behaviours.

The threat of behavioural disinhibition it is unlikely to be an immediate concern as ART is rolled out in high prevalence, resource-poor settings, where initial coverage is likely to be low and the effectiveness of ART programmes remains to be seen. Furthermore, the behavioural effects resulting from ART use in resource-poor settings are unlikely to follow patterns of industrialised countries. A person's decision to have sex, protected or unprotected, is influenced by a different set of considerations in resource-poor settings than those common in industrialised countries. Key is an individual's ability to negotiate her or his own sexual activity – as defined by fear of stigma, financial need, or the status of women within society. An individual is also less likely to be aware of his or her serostatus, due to lack of testing facilities and/or fears regarding a positive result. The provision of treatment may increase interest in voluntary counselling and testing (VCT) services, which may in turn lead to a decrease in frequency of risk behaviour by those infected. In Cote d'Ivoire for example, individuals reported low sexual activity following an HIV diagnosis, and this was not increased by the offer of ART [34]. Despite the inaccuracies of sexual behaviour data, these results are encouraging.

Given that it is difficult to predict how individuals might change their sexual behaviour as a result of ART introduction in different regions, models are faced with either estimating behavioural parameters from epidemiological data, or exploring pessimistic and optimistic scenarios using parameter values assumed to be at the ends of the spectrum of possible outcomes. Law et al 2001 modelled the effect of ART on the HIV epidemic in Australia in 1996 among the homosexual population [4] and predicted the outcome of the competing effects of increased life expectancy, decreased infectiousness and increases in unsafe sex of uninfected MSM on HIV incidence. Their assumption of a range of no change to a doubling of risky sex was essentially arbitrary, but demonstrated that increases in sexual behaviour (and life expectancy) could negate the beneficial impact of decreased infectiousness on incidence. Blower et al 2000 produced similar results for the homosexual population in San Francisco [5], again using the range of no change to a doubling in sexual risk-taking. Velasco-Hernandez et al have investigated the conditions under which ART in HIV infected individuals may drive an epidemic to extinction [1]. As can be shown by the model output in Figure 1, for ART to eliminate HIV, an extensive reduction in risk activity at the population level, accompanying ART use (such as a 50% reduction in the partner acquisition rate) is required, together with high levels of treatment uptake and large decreases in infectiousness induced by ART. As behaviour change is notoriously difficult to generate and initial coverage rates for ART in resource-poor settings are likely to be low, this optimistic scenario is highly unlikely.

The early impact of widescale ART use in resource-poor settings where HIV prevalence is currently high will probably not involve substantial population-level increases in risky behaviour. The effectiveness of local ART programmes will likely have to be demonstrated across a broad swath of the population before the perceived threat of AIDS as a disease declines. In lower prevalence regions where high coverage rates are feasible, such changes may occur. Careful monitoring of potential changes in risk behaviour would be very useful, if feasible. Any model designed to explore the impact of sexual behaviour change in resource-poor settings, be it an increase or a decrease, should explicitly model HIV diagnosis separately from treatment initiation, as shown by Law et al [4], because 1) it is knowledge of HIV status and the associated counselling that may change behaviour, 2) the advent of therapy in the sick may change their desire and/or ability for sexual functioning and 3) the attitude of those who know they are infected with HIV may change between not being treated, where they perceive a risk of transmitting to partners, to being treated, where the magnitude of risk may be perceived as smaller. This is one area where the introduction of ART could be used for prevention as well as treatment, through facilitating VCT.

Stage of HIV Infection

Some researchers believe that ART could be used as a direct prevention tool due to its effect on viral load leading to a decrease in infectivity and therefore incidence [26,35,36]. However, the competing effects of increasing prevalence due to the effect of ART on life expectancy and potential behavioural disinhibition would make this a risky strategy. Furthermore, models that predict dramatic reductions in incidence due to ART have used unrealistic treatment uptake rates. As described, some have argued that even high prevalence (30%) epidemics can be driven to extinction by ART, when assuming a treatment coverage rate of 50% to 90% [1,5]. The 50% level was estimated from data collected in a telephone sample interview of 462 MSM from four US cities conducted between November 1996 and February 1998 [37]. This was when HAART was in its infancy and treatment was initiated in a large

proportion of HIV positive individuals, regardless of infection stage or CD4 count, because a "hit hard, hit early" consensus existed for patient management. Furthermore, the study only included self-identified, HIV-positive MSM, and so individuals unaware of or reluctant to admit their serostatus would have been missed. It is now more common to initiate treatment at a later stage of infection, due to side-effects and the risk of evolution of drug resistance. The proportion of HIV-infected people currently being treated, even in industrialised countries, is likely to be substantially below that required for any prospect of disease elimination.

More realistic patterns of ART use are incorporated in the models of Law et al [4,38] and Gray et al [2], where the proportion of individuals treated increases with severity of HIV disease as determined by CD4 count [4] or plasma viral load [2]. By explicitly modelling changes in infectiousness and sexual activity over time, it has been shown that ART alone cannot be relied upon as a sole prevention tool.

Gray et al [2] and Nagelkerke et al [39] explicitly modelled the impact of ART in resource-poor settings (Uganda, and Botswana and India, respectively). Nagelkerke et al 2002 assumed that those receiving ART and infected with drug-sensitive virus had zero infectivity, which does not reflect the true situation, despite viral load being substantially reduced [39]. Assumed rates of resistance evolution seem optimistically low for ART use in resource-poor settings, only being varied between 5% and 25% of those on ART failing treatment per year, whereas rates as high as 60% have been predicted by others [40-42]. Despite this the model predicted that after transient success, ART would be rendered ineffective within 30 years due to wide-scale emergence of drug resistance, based on resistant virus being as transmissible as sensitive virus.

Gray et al's conclusions were relatively pessimistic [2], contrasting with Blower et al [5]. Gray et al concluded that ART alone cannot control mature HIV epidemics such as that in Rakai, Uganda. This conclusion concurs with Garnett et al 2002 [43], who believe that ART cannot make an impact on a mature epidemic unless treatment is initiated with high coverage and earlier in infection (i.e. with higher CD4 cell counts) than is currently recommended in treatment guidelines. Such early treatment is unfeasible financially and unwarranted clinically, since it would lead to earlier evolution of resistance and treatment failure, leaving individuals running out of treatment options, perhaps even before the onset of AIDS.

The dependence of the epidemiological impact of ART use on the timing of treatment initiation is worth considering in more detail. The progress of HIV infection to AIDS can broadly be divided into four stages: primary infection, incubation, the period preceding AIDS ("pre-AIDS") and AIDS. While there is much between- and within-patient variation, on average, infectiousness is highest during primary infection, pre-AIDS and AIDS. Some experts believe that primary infection carries the highest risk of transmission, because it is associated with high plasma HIV RNA levels and continued sexual activity [44]. However, while some studies are aiming to evaluate the effect of treating individuals in primary infection [3], the vast majority of HIV infections are not diagnosed until well into the incubation period. If primary infection is defined as the period before detectable antibodies against the virus emerge, then testing can only identify those who have completed the primary stage. However, if primary infection is used to describe the high initial viraemia then infection could be diagnosed before this has ended. Treatment could not start earlier than the incubation stage which follows primary infection except in rare circumstances where exposure is known to have occurred. In resource-poor settings, diagnosis is frequently at a very late stage of infection [45,46], partly because of the non-specific nature of symptoms and the difficulty in accessing healthcare. Therefore, initiating treatment at diagnosis or when CD4 counts descend to a certain benchmark, such as 350 or 200 cells/mm^3 (as recommended by current guidelines [25,47]), will mean that the highly infectious period of primary infection and the long period of incubation escape the controlling effects of treatment.

In models examining the impact of ART on HIV incidence, inclusion of the variation in infectiousness as a function of infection stage is crucial for producing realistic predictions. As ART can only be initiated upon HIV diagnosis, it will have no effect on transmission from most individuals undergoing primary infection, when risk of transmission is high. By the time an individual has developed AIDS, their sexual activity will have decreased, and so this group of infected individuals will not contribute as much to HIV transmission as the duration of this phase would suggest. Figure 2 shows runs from a four-stage HIV infection model, with various treatment coverage scenarios, determined by stage of infection. Treatment is introduced into a population with a mature HIV epidemic and a high basic reproductive number for the at-risk fraction of the population (R_0~5), so it is not surprising that even aggressive implementation of ART to individuals, regardless of stage of infection, cannot lead to elimination. Figure 2 illustrates that ART under more realistic assumptions regarding treatment delivery, in terms of treatment initiation, will have far less impact on incidence. In this model, there is a single treatment regimen and high, but plausible, rates of drug resistance evolution (30% per year), meaning that the effects on transmission are short-lived, coinciding with the effectiveness of the regimen. This

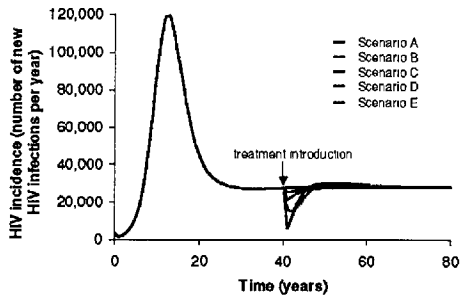


Figure 2
Predictions of the impact of ART by stage of infection at which treatment is initiated. Predictions of the impact of the introduction of ART in terms of HIV incidence, by stage of infection at which treatment is initiated (for a brief description of the four stage infection model used, see Endnote). Scenario A – No treatment. Scenario B – ART uptake: AIDS patients only (after a mean of 1 month). Scenario C – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months). Scenario D – ART uptake: AIDS patients (after mean 1 month) and pre-AIDS (after mean 6 months) and incubation stage (after mean 4 years). Scenario E – ART uptake: all four stages, after mean 1 month.

illustrates the urgent need for cheap and reliable second-line treatment options to be available for ART roll-out.

Despite our view that Blower et al are over-optimistic [5], Gray et al's assumptions of the effects of ART may similarly be over-pessimistic [2]. The authors assume that ART leads to an average proportional reduction in HIV log viral load of between 26.8% and 43.6%, based on data from the Women's Interagency HIV Study (WIHS) [48] and the John Hopkins Clinic [49] respectively. However, other studies distinguish between patients who respond to a regimen (who typically experience reduction in viral load to undetectable levels (<50 copies/ml)), those who do not respond and those who subsequently experience treatment failure (viral rebound). With these distinctions, an individual responding successfully to ART will have a far greater reduction in viral load than Gray et al assume. Furthermore, the proportion reduction was the value recorded one month and three months after treatment initiation for the WIHS and John Hopkins Clinic patients, respectively. It can take much longer than this for complete reduction of viral load, often to undetectable limits [50] (models generally do not explicitly account for a delay between treatment initiation and effect, but it can be assumed that this is implicitly accounted for in the treatment uptake rate). Gray et al also included the possibility of behavioural disinhibition; the average number of partners for those on treatment was increased by 50% or 100%. Again, the values appear pessimistic and were essentially chosen arbitrarily, probably in order to complement other models [4,5].

Emergence of ART drug resistance

Many models of ART have concentrated on predicting the emergence and spread of ART drug resistance, which has been of concern [51-54]. Once again it is very difficult to make such predictions, as the spread of drug-resistant virus is highly dependent on the replicative fitness of the resistant strains that evolve and their ability to superinfect individuals infected with wild-type strains (i.e. to co-infect someone already infected with wild-type virus, and successfully replicate). Superinfection is perhaps only likely in the successfully treated individual, where suppression of viral load allows the target cell population to recover, hence increasing the chance of successful replication and establishment of a new strain. In the untreated individual, it is unlikely that low frequency resistant virus, typically less fecund than wild type in this environment, would be able to compete against the established viral population sufficiently successfully to allow long-term persistence of the invading strain.

In a context where ART use is common in core groups, the possibility of superinfection of those on ART means that the likely maximum rate of spread of resistance epidemics may be similar to the speed of the initial HIV epidemic. HIV co-infection with different wild-type viruses [55,56], and by wild-type strains re-infecting patients harbouring drug-resistant viruses after a short period of treatment interruption [57,58], have both been documented. Chakraborty et al postulate that it is possible for patients infected with wild type HIV-1 isolates and under successful ART to become exposed to drug-resistant strains that would have significant selective advantage, leading them to outcompete the original wild-type strain and instigate treatment failure [59]. They concede that the probability of an individual undergoing successful treatment of a wild-type strain being exposed to a drug-resistant strain is low, but the large-scale roll-out of ART in high prevalence, resource-poor settings may increase this probability substantially.

The rate at which drug resistance evolves within the individual is likely to become higher in resource-poor settings than industrialised countries; even though there are reports of patient adherence being no lower than in the West [60], potential interruptions in supply due to transport problems and a lack of sophisticated laboratory monitoring systems will limit the success of any ART

regimen. However, even with high levels of drug resistance evolving within the individual ("secondary resistance"), transmission of such strains ("primary resistance"), while increasing in many industrialised settings [54,61], is reported to be substantially less frequent than for wild-type HIV [61,62], because there is usually a fitness cost for mutations. Mathematical models may have the ability to predict best- and worst-case scenarios for resistance spread [39,63], but it must be conceded that the degree to which drug resistance and risky behaviour increase as ART use rolls out in Africa and other resource-poor areas cannot yet be quantified.

Blower et al 2001 predicted that acquired resistance will continue to rise, but transmitted resistance is likely to increase only gradually, with a doubling time of around four years and a predicted median of 15.6% of new HIV infections likely to be resistant to antiretroviral drugs by 2005 [63]. This conclusion was due to an assumption that of all possible ART-resistant HIV strains that could possibly evolve, none could be as transmissible as wild-type. The study also assumed that individuals infected with ART-sensitive virus undergoing treatment cannot be co-infected or superinfected by an ART-resistant strain.

Despite the conclusion that transmitted ART resistance will stabilise at low levels, the predicted range around the 15.6% value is very wide (0.05% to 73.21%) [63]. The authors argue that the higher values in the range generated from their sensitivity analysis have a very low probability. However, the choice of parameter distributions in the Monte Carlo sampling of parameter space undertaken in their study was arbitrary (in the sense of not being motivated by prior data) and entirely determines the probability of pessimistic scenarios.

The authors themselves acknowledge that they are "predicting the unpredictable" [63], but argue that their theoretical predictions [5] are in close agreement with empirical data [64]. Both display an increase in primary resistance between 1997 and 2001, but this is a short time period and the increase may reflect the expansion in use of ART over this time. Furthermore, the uncertainty interval around predictions made by the authors is large enough for a wide range of empirical data to fit the model. Blower et al acknowledge that transmission of ART resistance may vary widely by location and that frequent comparison to empirical data is necessary. However, Blower et al in 2005 recommend that large-scale surveillance for detecting transmitted resistance in Africa will be unnecessary for the next decade because transmitted drug resistance will not reach more than 5% during that time [65]. This is due to the assumption that ART use will remain at low levels, although the authors suggest that in urban locations rates of treatment may be higher. They recommend close monitoring of treated patients, but in areas where resources are constrained, this is unlikely to be practicable (WHO guidelines do not consider resistance testing, or even viral load testing, to be a priority in these regions [25,66]). We would argue that surveillance of the prevalence of drug resistance among patients is required in all locations where ART is used, and that the predictive utility of models with high degrees of uncertainty in their input parameters, and hence also their results, is limited.

In this context, it should be noted that increases in levels of acquired resistance are not inevitable – in Switzerland, where more than 80% of prescribed ART is dispensed by one of the highly experienced Swiss HIV Cohort centres, prevalence of drug-resistant HIV in newly infected individuals has been decreasing since 1996 [67]. However, we would argue that such an effect is less likely in resource-poor settings with restricted access to high-quality care and laboratory facilities and potential problems of drug sharing, black market resale of drugs and inappropriate prescribing of mono and dual therapy outside of official ART programmes [53]. The differences between ART programmes in industrialised and developing countries will be so marked that predicting programme impact and patterns of drug resistance from those in former setting is not necessarily informative.

If one relaxes the assumption that no resistant strain can exceed the transmission fitness of wild-type even in the presence of ART use, even greater variation in predicted levels of transmitted drug resistance after 10 years of ART provision is possible (Figure 3). The scenarios illustrated assume a conservative rate of 10% per year for the evolution of resistance in the treated patient and do not allow for the possible enhancement of that rate in individuals suffering viral rebound (an increase in viral load following a previous decrease due to ART) without initial resistance, but who are then maintained on the same regimen (due to a lack of virological testing). Nevertheless, the results show that if a relatively fit variant emerged, the effectiveness of current ART regimens could be compromised after a very short period. There appears to be little change in model results when superinfection alone is allowed to occur, but when heterogeneous sexual activity is incorporated, resistance transmission is predicted to emerge more rapidly. This is due to superinfection allowing resistance to be transmitted through core groups receiving ART.

These results do not suggest a *likelihood* of drug resistance transmission but merely demonstrate the potential effects of various scenarios. It is more for biological studies (in particular resistance testing) and within-host models of HIV infection to examine the possibility that such strains could emerge [68-70]. Even in instances where laboratory

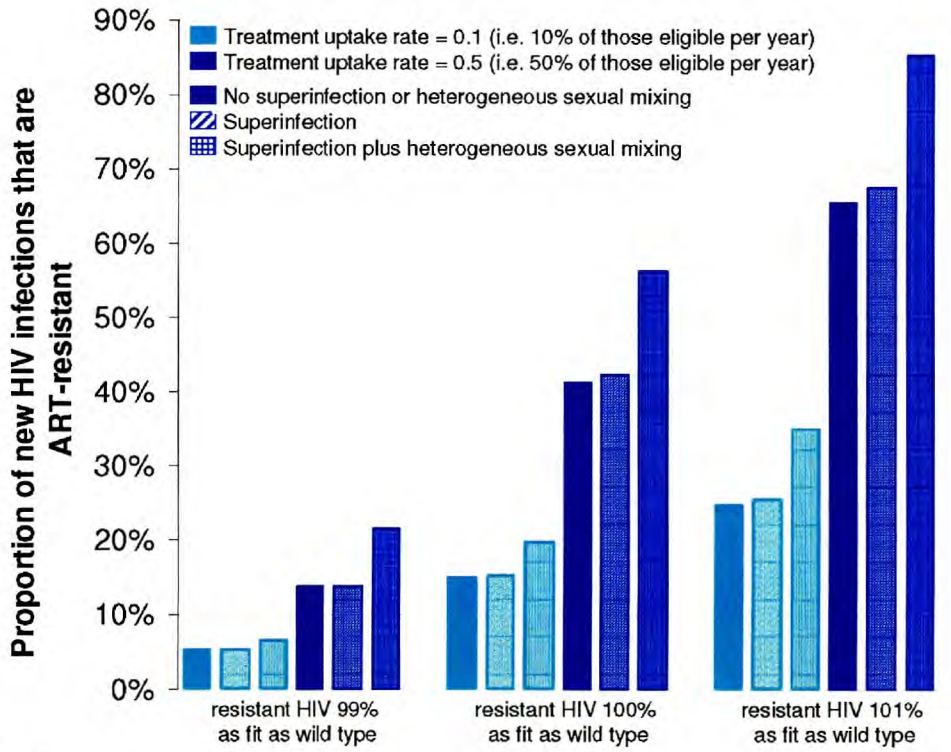


Figure 3

Model predictions of transmission of ART drug resistance by relative fitness of strains. Predictions of the spread of transmitted (primary) ART resistance under various scenarios, using a simplified ART model (see Endnote). Model output is 10 years after ART introduction. ART is introduced once the epidemic has reached equilibrium. Superinfection refers to the infection with ART-resistant HIV of individuals previously infected with ART-sensitive HIV and successfully undergoing treatment. These are the only individuals without viral outgrowth, and thus will have a pool of target cells rendering them susceptible to infection. Evolution of drug resistance within an individual is at a rate of 10% per year.

tests reveal infections with virus deemed "resistant" to more than one drug class (either phenotypically or genotypically), these infections often still respond to treatment. A multidrug-resistant HIV strain would require a large number of compensatory mutations to be of a comparable fitness to wild type strains. However, ongoing treatment pressure in the presence of viral rebound could lead to sequential mutations increasing the fitness of a resistant strain; therefore, there is an argument for close monitoring of patients and implementation of drug resistance surveillance systems as ART is rolled out in resource-poor settings.

Parameterisation

To aid the design of successful ART programmes in resource-poor settings, more information on the impact of ART provision is crucial – data on morbidity and mortality, tolerability, treatment failure and the possible emergence of drug resistant strains are very important. This information also increases the reliability of model

predictions by providing more accurate ranges of parameter estimates. Population-level monitoring for changes in risk behaviour and patterns of ARV drug resistance are also required. Information on the performance of ART programmes in these settings is starting to be generated. Pilot programmes such as the Médecins Sans Frontières (MSF) initiatives (established in seven low- and middle-income countries: Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand and Guatemala) are starting to report back preliminary findings. The six-month outcomes from the MSF projects were positive [71]: the probability of survival at six months was estimated as 89.5% (95% CI 86.8–92.1), with high patient attendance and adherence rates comparable to those in industrialised countries. However, pilot programmes may not be representative of future large-scale ART roll-out, where health-care infrastructure and expertise are likely to be poorer. Other programmes, such as those of the Drug Access Initiative (DAI), formed in 1998 by UNAIDS in collaboration with the Ministries of Health of Chile, Côte d'Ivoire, Uganda and Vietnam, have been running for longer. Reports from the first two years of the initiatives in Côte d'Ivoire have been positive [72], with immunologic and virologic outcomes similar to those reported from industrialised countries. The only resource-poor country to implement ART provision on a large scale is Brazil, which has made ART available free of charge to all eligible patients since 1996, and has produced positive outcomes [73]. The experience of Brazil can give information on the impact of long-term, large-scale ART provision, but is a very different setting to sub-Saharan Africa. As with data from industrialised countries, care must be taken in interpreting and assessing the applicability of results. Modelling provides the tools to predict the consequences of possible activity; by constraining ourselves to examining only those scenarios that are supported by current, gathered data, we can be ignoring other, distinct possibilities, such as the case in which an ART-resistant strain as fit as wild-type could evolve.

Conclusion

We have argued that HIV transmission models predicting the impact of ART use should incorporate a realistic progression through stages of HIV infection in order to realistically capture the timing of treatment initiation. Further elaboration of models is required (depending on the research question being posed), in areas such as time of diagnosis, sexual behaviour and assumptions regarding drug resistance evolution and transmission. All modelling studies are eventually dependent on the availability of setting-specific surveillance and behavioural data, and collection of such data is important for all regions where large scale ART use is introduced.

More investigation is required in order to determine the effect of introducing ART on a substantial scale in resource-poor settings with different stages and magnitudes of HIV epidemic. Models addressing questions of ART implementation in such settings, utilising data from fledgling ART projects where possible, will be of great use in designing cost effective programmes.

List of abbreviations

AIDS Acquired Immunodeficiency Syndrome

ART Antiretroviral therapy

HAART Highly Active Antiretroviral Therapy

HIV Human Immunodeficiency Virus

MSM Men who have Sex with Men

PMTCT Prevention of Mother to Child Transmission

VCT Voluntary Counselling and Testing

Endnote

Model assuming one stage of HIV infection

The model assuming one-stage of HIV infection, used to produce Figure 1, is illustrated in Figure 4, with state variables, parameter symbols and model equations given below. Superinfection with an ART-resistant strain is possible for individuals undergoing successful treatment only (I_S^T, S = ART-sensitive, T = treated), as these are the only individuals without viral outgrowth, and thus will have a pool of target cells rendering them susceptible to infection. Treatment failure can occur with (κ) or without (f) the evolution of drug resistance. Individuals who have developed treatment failure not accompanied by resistance (I_S^{TF}, F = treatment failure) are at increased risk of developing drug resistance (κ_F) because of viral replication in the presence of continued drug pressure. Figure 3 uses a version of this one-stage model, modified to incorporate heterogeneous sexual mixing, with four different sexual activity groups.

The advantage of one-stage models of infection is that they are relatively simple and analytically tractable; that is, the relationship between each parameter and the outcome of the models, for example in terms of R_0[1], can be exactly specified without recourse to simulation and sensitivity analysis. However, while a model should not incorporate complexity for its own sake, stages of HIV infection play a crucial role in the impact of ART, because treatment is only initiated at late stages of infection, and infectivity and sexual activity vary with the course of infection. Similarly, incorporating heterogeneous sexual activity within a model is more important for some research questions than for others. If we want to investigate the potential impact of a transmissible ARV-resistant HIV

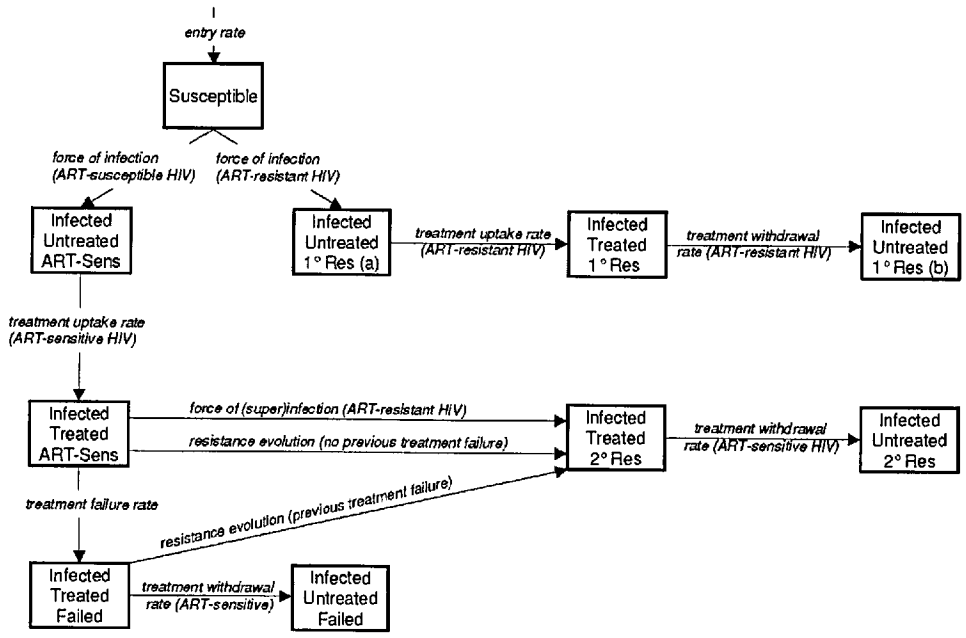


Figure 4
Model of HIV transmission and treatment, with one stage of infection only. Schematic illustration of the structure of the one stage HIV transmission model. 1° Res designates those with primary (transmitted) resistance, while 2° Res designates those with secondary (acquired) resistance. ART-Sens denotes people infected with ART-sensitive virus. For clarity, death rates are not shown.

strain through a population, its spread would appear very different in a model of homogeneous sexual activity, compared to one with heterogeneity and various assumptions regarding mixing between activity classes, where infection would travel through core groups first before spreading into the general population.

State Variables

S = susceptible individuals

I_S^U = ART-sensitive HIV infected individuals, untreated

I_S^T = ART-sensitive HIV infected individuals, treated

I_S^{TF} = ART-sensitive HIV infected individuals, treated but viral rebound

I_S^{UT} = ART-sensitive HIV infected individuals, suffered viral rebound, withdrawn from treatment

I_{R2}^T = ART-resistant HIV infected individuals, treated

I_{R2}^U = ART-resistant HIV infected individuals, untreated

I_{R1a}^U = ART-resistant HIV infected individuals (transmitted resistance), untreated

I_{R1}^T = ART-resistant HIV infected individuals (transmitted resistance), treated

I_{R1b}^U = ART-resistant HIV infected individuals (transmitted resistance), withdrawn from treatment

λ_S = force of infection for ART-sensitive virus phenotype

λ_R = force of infection for ART-resistant virus phenotype (and force of (super)infection for ART-resistant virus phenotype, infecting an HIV wild type infected individual under treatment pressure)

Parameters

For individuals of infection status I_i^j:

i refers to viral phenotype (S (ART-sensitive) or R (ART-resistant));

j refers to treatment status (U (untreated) or T (treated)).

σN_0 entry into model population (rate of recruitment into sexually active class). N_0 is the size of the population at time $t = 0$.

μ death rate due to causes other than HIV infection

ν_i^j excess death rate due to HIV infection for an infected individual in class I_i^j

γ_S treatment uptake rate for individuals infected with ART-sensitive HIV

γ_R treatment uptake rate for individuals infected with ART-resistant HIV

f rate of treatment failure (viral rebound) without ART resistance evolution

κ rate of resistance evolution without previous viral rebound

κ_F rate of resistance evolution with previous viral rebound

α_S rate of treatment withdrawal for individuals initially infected with ART-sensitive HIV

α_R rate of treatment withdrawal for individuals initially infected with ART-resistant HIV

β_i^j HIV transmission probability per partnership for an infected individual in class I_i^j

c Number of sexual partnerships per year

ω_1^U Probability of I_{R1}^U transmitting ART-resistant HIV

ω_1^T Probability of I_{R1}^T transmitting ART-resistant HIV

ω_2^U Probability of I_{R2}^U transmitting ART-resistant HIV

ω_2^T Probability of I_{R2}^T transmitting ART-resistant HIV

ι Factor reduction in transmissibility for an infected individual in class I_S^{TF}

Transmission equations

$$\frac{dS}{dt} = \sigma N_0 - S(\lambda_S + \lambda_R + \mu)$$

$$\frac{dI_S^U}{dt} = S\lambda_S - I_S^U(\mu + \nu_S^U + \gamma_S)$$

$$\frac{dI_S^T}{dt} = \gamma_S I_S^U - I_S^T\left(\mu + \nu_S^T + f + \kappa + \lambda_R\right)$$

$$\frac{dI_S^{TF}}{dt} = fI_S^T - I_S^{TF}\left(\mu + \nu_S^U + \alpha_S + \kappa_F\right)$$

$$\frac{dI_S^{UF}}{dt} = \alpha_S I_S^{TF} - I_S^{UF}\left(\mu + \nu_S^U\right)$$

$$\frac{dI_{R2}^T}{dt} = I_S^T(\kappa + \lambda_R) + \kappa_F I_S^{TF} - I_{R2}^T\left(\mu + \nu_R^T + \alpha_S\right)$$

$$\frac{dI_{R2}^U}{dt} = \alpha_S I_{R2}^T - I_{R2}^U\left(\mu + \nu_R^U\right)$$

$$\frac{dI_{R1}^{Ua}}{dt} = \lambda_R S - I_{R1}^{Ua}\left(\mu + \nu_R^U + \gamma_R\right)$$

$$\frac{dI_{R1}^T}{dt} = \gamma_R I_{R1}^T - I_{R1}^T\left(\mu + \nu_R^T + \alpha_R\right)$$

$$\frac{dI_{R1}^{Ub}}{dt} = \alpha_R I_{R1}^T - I_{R1}^{Ub}\left(\mu + \nu_R^U\right)$$

$$N = S + I_S^U + I_S^T + I_S^{TF} + I_S^{UF} + I_{R2}^T + I_{R2}^U + I_{R1}^{Ua} + I_{R1}^T + I_{R1}^{Ub}$$

The forces of infection for ART-sensitive (λ_S) and ART-resistant (λ_R) HIV are given below. They are determined by the infectiousness of individuals in each class (β) and the probability that ART-resistant rather than ART-sensitive virus is transmitted in the case of mixed infections (ω).

$$\lambda_S = \frac{c}{N}\left(\begin{array}{l}\beta_S^U\left(I_S^U + I_S^{UF} + \iota I_S^{TF}\right) + \beta_S^T I_S^T + \beta_P^T\left(\left(1-\omega_2^T\right)I_{R2}^T + \left(1-\omega_1^U\right)I_{R1}^T\right) \\ +\beta_R^U\left(\left(1-\omega_2^U\right)I_{R2}^U + \left(1-\omega_1^U\right)\left(I_{R1}^{Ua} + I_{R1}^{Ub}\right)\right)\end{array}\right)$$

$$\lambda_R = \frac{c}{N}\left(\beta_R^T\left(\omega_2^T I_{R2}^T + \omega_1^T I_{R1}^T\right) + \beta_R^U\left(\omega_2^U I_{R2}^U + \omega_1^U\left(I_{R1}^{Ua} + I_{R1}^{Ub}\right)\right)\right)$$

Model assuming four stages of HIV infection

The model used to produce Figure 2 is essentially the same as for the one stage infection model, but with infection divided into four stages (primary infection, incubation, pre-AIDS and AIDS) as shown in Figure 5. The forces of infection are determined by the infectiousness of individuals in each class, the probability that ART-resistant rather than ART-sensitive virus is transmitted in the

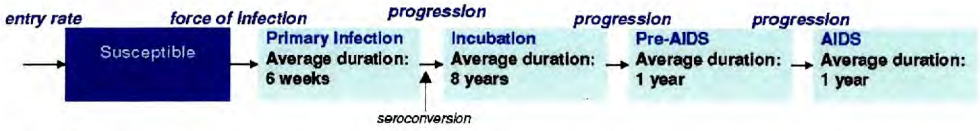


Figure 5
Model of HIV transmission and treatment, with four stages of infection. Schematic illustration of the structure of the stages of HIV infection for the four stage model. Individuals progress from one stage to the next exponentially, with an average duration in each stage as shown in the figure. Individuals have no HIV-related mortality during primary infection or incubation, a very slightly elevated baseline death rate during pre-AIDS and an average one year life expectancy once AIDS has developed.

case of mixed infections and the rates of sexual partner change, which decrease as individuals reach the final stage (AIDS). The rest of the model structure is as for the one-stage model. Full details of this model, equations and parameter estimates are not shown here but are available on request.

Competing interests

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Authors' contributions

RB drafted the manuscript and constructed the mathematical models. All authors reviewed articles and read and approved the final manuscript.

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Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis

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Background: The role of iatrogenic transmission within the HIV/AIDS pandemic remains contentious. Estimates of the risk of HIV transmission from injections and blood transfusions are required to inform appropriate prevention policy.

Objectives: Systematic review and meta-analysis of the literature on HIV-1 infectivity for parenteral transmission and blood transfusion.

Review methods: All identified studies with relevant transmission probability estimates up to May 2005 were included.

Statistical methods: When appropriate, summary estimates for accidental percutaneous and blood product exposures were derived.

Results: Infectivity estimates following a needlestick exposure ranged from 0.00 to 2.38% [weighted mean, 0.23%; 95% confidence interval (CI), 0.00–0.46%; $n = 21$]. Three estimates of infectivity per intravenous drug injection ranged from 0.63 to 2.4% (median, 0.8%); a summary estimate could not be calculated. The quality of the only estimate of infectivity per contaminated medical injection (1.9–6.9%) was assessed. Instead we propose a range of 0.24–0.65%. Infectivity estimates for confirmed contaminated blood transfusions range from 88.3 to 100.0% (weighted mean, 92.5%; 95% CI, 89.0–96.1%; $n = 6$).

Conclusions: Infectivity estimates for infected blood transfusions are larger than for other modes of HIV transmission. Few studies on transmission risk per contaminated injection were found. However, transmission risk per needlestick injury, where needles are more likely to be rinsed or disinfected between recipients (especially for medical injections), may be representative of non-intravenous medical injections and lower than the risk from intravenous injections, which are likely to be deeper and to involve more fluids. Further work is needed to better estimate transmission probability related to contaminated injections and its likely contribution to overall HIV transmission.

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Introduction

There has been considerable debate concerning the relative contribution of different modes of transmission to the HIV-1 epidemic in Africa [1–6]. The main mode of transmission, especially in resource-poor settings, is considered to be unprotected heterosexual sex. However, one group of researchers believe that the role of iatrogenic transmission, particularly unsafe medical injections, has been vastly underestimated [1,7]. Accurate estimates of transmission probabilities for contaminated injections are currently lacking, but are needed to assess the risk of infection through this route, and its contribution to the HIV/AIDS pandemic, within resource-poor settings in particular [8,9]. More data are available for single, accidental percutaneous injuries with needles or other sharp objects contaminated with infectious material from HIV patients, usually among health care workers and laboratory workers. This information can help in estimating the risk per contaminated medical injection. A limited number of studies have estimated the risk of HIV transmission per injection drug user (IDU) injection; this information can also help estimate the risk from medical injections, as well as the risk from IDU. The other main iatrogenic risk is unsafe blood transfusions. Therefore in this paper we present the results of a systematic review and meta-analysis on HIV-1 infectivity per single exposure for parenteral modes of transmission (per contaminated medical injection, IDU injection and accidental percutaneous exposure) and blood product transfusion. The results can be used to assess the relative contributions of these modes of transmission.

Methods

The systematic review was undertaken according to the QUORUM checklist [10], revised for review of non-randomized control trial studies.

Searching

For parenteral modes of transmission, a search was performed using the criteria for publication titles to contain: HIV AND (infectivity OR infectiousness OR transmission OR probability) AND (parenteral OR occupational OR percutaneous OR needle OR drug use OR intravenous OR health care). Databases used were PubMed MEDLINE at PubMed (National Library of Medicine (NLM) http://www.ncbi.nlm.nih.gov/entrez/query.fcgi), EMBASE (http://gateway.ovid.com/athens) and Science Direct www.sciencedirect.com. Parenteral exposure is defined as subcutaneous, intramuscular or intravenous contact with blood or other body fluid of an HIV-1 infected individual, but not mucocutaneous contact. Percutaneous injuries involving splashes of infected fluid onto open wounds were excluded. For blood transmission, the parenterally-related terms were exchanged for: iatrogenic OR blood OR transfusion OR haemophilia OR hemophilia.

Titles (and abstracts, where available) were scanned for relevance, identifying papers requiring further consideration. Bibliographies of all relevant articles were checked for additional relevant publications. There was no restriction by study design or language of publication.

Selection

Exclusion criteria were all abstracts-only pre-1995, and infectivity estimates based on sample sizes of less than 10. Where the most recent report of a prospective study was an abstract, further study information was also taken from the most recent preceding publication, with both abstract and publication cited in the tables. A report by the Public Health Laboratory Service [11,12] was useful to decipher truly independent results and to obtain details on studies for which primary sources were unavailable.

Quantitative data synthesis

To improve comparability of studies, all confidence intervals were recalculated using the Wilson 'score' method without continuity correction [13] as recommended by Newcombe [14], (except for Hudgens *et al.* [15,16]). Forest plots were constructed using MS Excel (Microsoft Corp., Redmond, Washington, US).

Meta-analysis

For accidental percutaneous and blood product exposures, summary estimates and associated 95% confidence interval (95% CI; based on a fixed effects model) are presented on the forest plots. Two different weighting schemes [sample size (sz) or precision (p)] were derived for comparison. Summary estimates used sample sizes for weights (referred to as pooled estimates, p_{sz}) or used the inverse variance method [17] with the precision, defined by the wider bound of the asymmetric Wilson 'score' confidence interval [upper bound for needlestick (Si^{UB}) and lower bound for blood (Si^{LB}) exposure], divided by z, used for weights rather than the standard error. This is because needlestick transmission risk is small and blood transmission risk is large, so many studies with 0% (100%) seroconversion for needlestick (blood transfusion) exposure give a standard error of zero and infinite weights.

$$S_i^{UB} = \frac{2n_i\theta_i + z^2 + z\sqrt{z^2 + 4n_i\theta_i(1-\theta_i)}}{2(n_i + z^2)} - \theta_i \quad (1)$$

for needlestick transmission, and

$$S_i^{LB} = \theta_i \frac{2n_i\theta_i + z^2 - z\sqrt{z^2 + 4n_i\theta_i(1-\theta_i)}}{2(n_i + z^2)} \quad (2)$$

for blood transmission; where n_i is the sample size for study i, and $z = 1.96$ denotes the standard normal deviate associated with a two-tailed probability $\alpha = 5\%$.

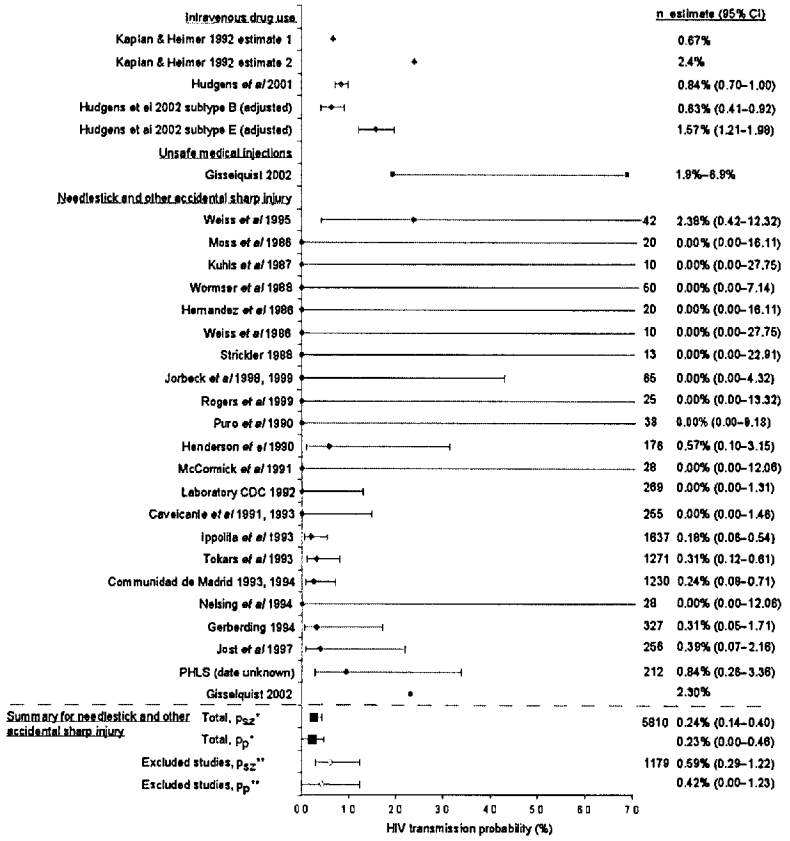


Fig. 1. Summary of studies estimating transmission probability for parenteral exposure to HIV. Bars represent 95% confidence intervals (CI) except for Gisselquist [19], which is a range. p_{sz}: estimate weighted by sample size; p_p: estimate weighted by precision (adapted inverse variance method) – see details in method. *For needlestick and other accidental sharp injury only, without excluded studies and Gisselquist 2002 estimate [19] (no sample size available). **All excluded studies except for superseded publications and those without sample sizes.

We tested heterogeneity between studies using the heterogeneity statistic [17].

Results

Summary of the search

Sixty estimates for parenteral (medical, IDU and accidental injections) and 14 for blood product exposure were found. After evaluation, 30 articles were included for parenteral exposure [15,16,18–45], providing 26 estimates, and 10 articles were included for blood product exposure [46–55], providing 11 estimates. The 30 included studies providing estimates of parenteral transmission consisted of three papers describing IDU risk [15,16,18], 26 papers providing 21 estimates for accidental percutaneous injury [20–45] (where five publications were accompanied by a more recent abstract from which the estimate was taken [27,28,34,35,

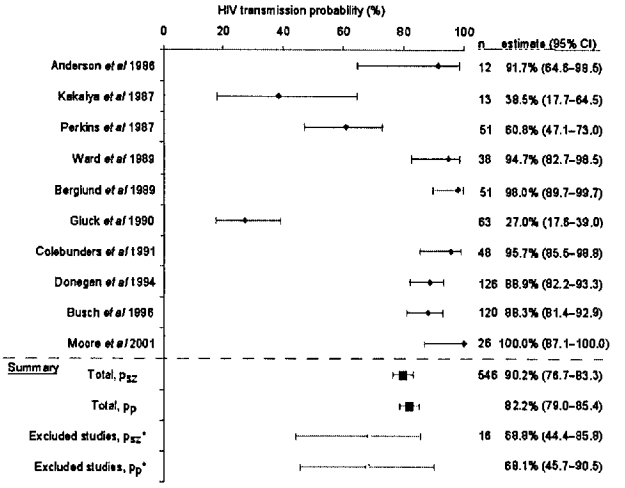


Fig. 2. Summary of studies estimating transmission probability per contaminated blood product transfusion. Bars represent 95% confidence intervals (CI). p_{sz}: estimate weighted by sample size; p_p: estimate weighted by precision (adapted inverse variance method) – see details in method. *All excluded studies except for superseded publications and those without sufficient data.

37–41,56]), and one reporting both percutaneous injury and contaminated injection risks [19]. The 11 estimates for blood product exposure included two from Ward *et al.* [49], but only the estimate in which blood products were proved to be contaminated was included in summary estimates. Forest plots of infectivity estimates are presented in Figs 1 and 2. Summaries of the characteristics of included and excluded studies are available on request.

Parenteral exposure

Nineteen of the 25 estimates were derived from prospective studies (one for IDU and 18 for needlestick injury), in which study participants were typically followed up for about 9 to 12 months following one contact/exposure for needlestick or many injection events for IDUs. Studies tended to be prospective in that health care workers or laboratory workers were encouraged to report exposures, after which they were followed up, rather than enrolment in a study before exposure. Two studies of needlestick transmission were retrospective with health care workers sometimes reporting more than one contact/exposure [20,21], one was of unspecified design [44], while Gisselquist [19] used data from a case–control study [57] to derive an estimate. The remaining two estimates, one for IDU [18] and one for contaminated injections [19], were also indirectly derived from mathematical models (one for each type of exposure).

Injection drug users

Infectivity estimates for IDU ranged from 0.63% [16] to 2.4% [18] (median = 0.8%) [15,16,18] (Fig. 1). Kaplan and Heimer favoured their lower estimate of 0.67% per exposure [18], and Hudgens *et al.* [15] concluded that their 0.84% estimate was consistent with this. Given the heterogeneity of estimates between studies and subtypes, it was inappropriate to combine results.

Contaminated injections

The only study available evaluated the estimated infectivity per contaminated injection as 1.9–6.9%, a very wide range, based on data of limited quality from nosocomial outbreaks in Russia, Romania and Libya [19] and on a large number of assumptions.

Accidental percutaneous injury

Infectivity estimates for accidental percutaneous injury are more reliable than those for IDU and contaminated injections, primarily because the number of exposures is usually one per person, and the infection status of the index case can be determined relatively easily. In the few instances where an individual experienced more than one exposure, these were counted as separate events in our analysis. All studies calculated transmission probabilities as the proportion of exposure events resulting in transmission, except for Gisselquist [19], who calculated the HIV transmission probability for deep injuries only, to be used as an approximation for contaminated medical

Table 1. Summary transmission probabilities for contaminated accidental needlestick or sharp injuries and blood product transfusion, under various inclusion criteria and for pooled data and weighted average methods.

	p_{sz}* (95% CI)		p_p** (95% CI)	
Needlestick and other sharps injury				
Included studies (Table 1) [20–45]	0.24%	(14/5810; 0.14–0.40)	0.23%	(0.00–0.46)
Excluded studies[a] [69–78]	0.59%	(7/1179; 0.29–1.22)	0.42%	(0.00–1.23)
Studies explicitly stating no other risk factors present [20,21,25,31,34–37,43,79,80]	0.22%	(4/1833; 0.08–0.56)	0.13%	(0.00–0.54)
AIDS patients only[b] [20,22,29,34,35,38]	0.41%	(5/1231; 0.17–0.95)	0.37%	(0.00–1.00)
All symptomatic patients (AIDS and ARC)[c] [20–23,29,34,35,38,42,45]	0.40%	(7/1745; 0.19–0.83)	0.35%	(0.00–0.86)
Blood product transfusion				
Included studies [46–55]	80.2%	(438/546; 76.7–83.3)	82.2%	(79.0–85.4)
Excluded studies [81–83]	68.8%	(11/16; 44.4–85.8)	68.1%	(45.7–90.5)
Included studies, donations proved to be contaminated[d] [49,50,52–55]	91.9%	(374/407; 88.8–94.2)	92.5%	(89.0–96.1)

ARC, AIDS-related complex; CI, confidence interval; *p_{sz}: estimate weighted by sample size; **p_p: estimate weighted by precision (adapted inverse variance method) – see details in method.

[a]Does not include reports of prospective studies superseded by a more recent publication.

[b]Estimate includes Tokars *et al.* [38], which did not control for zidovudine post-exposure prophylaxis. Excluding this study gave a pooled estimate of 0.30% (1/332; 95% CI, 0.05–1.69) and a weighted average of 0.05% (95% CI, 0.00–1.51).

[c]Estimate includes Tokars *et al.* [38], which did not control for zidovudine post-exposure prophylaxis, and Nelsing *et al.* [42], in which a 'large majority' were AIDS patients. Excluding these studies gave a pooled estimate of 0.49% (3/614; 95% CI, 0.17–1.43) and a weighted average of 0.28% (95% CI, 0.00–1.50).

[d]Donors proven to have been infected with HIV at the time of donation, or donation tested and shown to be contaminated.

injections. The author makes a large number of assumptions, and deep injuries may involve transfer of more infective fluid than contaminated injections. As no confidence intervals were provided or could be derived, this estimate was excluded from summary estimates.

Infectivity estimates for needlestick exposure from all 22 studies ranged from 0.00% [21–30,32–35,42] to 2.38% [20] ($p_p = 0.23\%$; 95% CI = 0.00–0.46%; $p_{sz} = 0.24\%$; 95% CI = 0.14–0.40%). Transmission of HIV via this route is uncommon and therefore the majority of studies produced estimates of 0.00% ([21–30,32–35,42], $n = 13$); the average sample size for these studies was 67 injuries, compared with 644 injuries for studies providing non-zero estimates. When including studies reporting at least one transmission event only and excluding Gisselquist [19], estimates ranged from 0.18% [36,37] to 2.38% [20] ($p_p = 0.25\%$; 95% CI = 0.01–0.49%). Estimates of included studies with p_p and p_{sz} gave similar results, but we prefer to report p_p which produced wider confidence intervals (Table 1). There was no evidence of heterogeneity between studies (df = 20; $P = 1$).

Analysis of subsets of studies is shown in Table 1. The estimate based on studies with no other reported risk factors for HIV transmission ($p_p = 0.13\%$; 95% CI = 0.00–0.54%) was not significantly different from the overall estimate ($p_p = 0.23\%$). The infectivity of symptomatic patients (AIDS or AIDS plus AIDS-related complex patients) approximately doubles (p_{sz}) or triples (p_p) the risk. However, results should be interpreted with caution because of the small sample sizes.

Blood product transfusion

Infectivity estimates for transmission per transfusion with infected blood products are presented in Fig. 2. Eight of the 10 estimates are based on retrospective and two on longitudinal studies following transfusion with infected blood products [52,55]. Infectivity estimates ranged from 27.0 to 100.0%, with summary estimates of $p_p = 82.2\%$ (95% CI = 79.0–85.4%) and $p_{sz} = 80.2\%$ (95% CI = 76.7–83.3%). However, the 10 studies displayed considerable heterogeneity ($Q = 198.36$; χ_9^2: $P < 0.0001$). The six studies which could confirm that donations were contaminated [49,50,52–55] were more homogeneous ($Q = 5.99$; χ_6^2: $P = 0.42431$) and produced higher infectivity estimates (range, 88.3–100.0%; $p_p = 92.5\%$; 95% CI = 89.0–96.1%).

Discussion

Transmission probabilities are difficult to measure for most modes of transmission, partly because of difficulty in confirming the infected source, and also because they depend on other risk factors, such as HIV viral load [58] and exposure to antiretroviral therapy [59]. The lack of data for both IDU and contaminated medical injection exposure means that transmission probabilities can only be indirectly derived from studies on HIV transmission per accidental percutaneous injury. The risk of infection from percutaneous accidents depends on factors that influence exposure to a greater volume of blood (e.g. visible blood on the device, procedures involving needle placement directly into a vein or artery, etc), viral load (e.g. clinical status of the source patient, post-exposure prophylaxis), which affect the 'effective' viral dose received [57,60]. The type of injection equipment affects infectivity because syringes with detachable needles retain – and probably transfer – substantially more blood than integral cannula syringes with a permanently

attached needle [61–63]. Laboratory studies have suggested that a greater volume of blood is transferred by deeper injuries and by hollow-bore needles (especially those with larger gauges) [64].

The reliability of data from studies estimating infectivity per single contaminated medical injection or IDU injection is affected by more factors than studies on accidental percutaneous exposure. The estimates produced by Kaplan and Heimer [18] and Hudgens *et al.* [15,16] are compatible with each other and are based on good quality data, considering the difficulty in obtaining information in this area, with thorough analyses. Since HIV-1 subtype E is predominantly contained in Southeast Asia and is potentially more infectious than other types, the adjusted estimate for subtype B, 0.63% (95% CI, 0.41–0.92%) is used as the average risk per IDU injection, which is in close accord with Kaplan and Heimer's estimate of 0.67%. Gisselquist's estimate of transmission risk per contaminated injection [19] is not comparible with these estimates and the methodology has been criticized [65]. The risk from contaminated injections is likely to be less than for IDU because IDU injections are intravenous, whereas medical injections in sub-Saharan Africa are usually intramuscular, blood contamination of needles after use for intramuscular injection is infrequent [65], and washing of needles substantially reduces risk [66].

While deliberate injections may involve more transfer of fluid from the device than for accidental punctures, the fluid may contain less infectious material because health care workers will often have cleaned needles between patients. The combined result of these competing effects is unknown and subjective. The true infecivity of contaminated injections is unlikely to be less risky than accidental injuries or to be more risky than for IDU injections. To reflect this uncertainty we propose a transmission probability estimate for contaminated injections ranging between our estimates for these modes: 0.24–0.65%, with a point estimate being the midpoint of 0.45% risk per exposure. Unlike sexual transmission probabilities, these estimates are unlikely to vary substantially by geographical location. Recent estimates of per contact HIV infectivity for sexual transmission in Africa are comparable to this [67,68]. The frequency of sexual exposure is far higher than the frequency of unsafe injections, and so heterosexual sex is the main mode of transmission, with unsafe injections playing a minor role.

Infectivity estimates for infected blood transfusions are much higher than for other modes of HIV-1 transmission due to the far larger viral dose per exposure than for other routes. Relatively few studies aiming to quantify the infectivity of HIV-1 via blood transfusion were found, perhaps because it was clear from the start that this risk was likely to be extremely high, and because this source of infection was identified and eliminated fairly early in the epidemic, at least in industrialised countries. However, the frequency of unsafe blood transfusions compared to sexual contacts is extremely small.

Conclusion

Infectivity estimates per IDU injection range from 0.63% [16] to 2.4% [18], median = 0.8%. The only estimate for medical injections was 1.9–6.9% [19]. The estimate per accidental percutaneous injury is $p_p = 0.23\%$ (95% CI = 0.00–0.46%). We propose a transmission probability estimate per contaminated injection of 0.45% (range, 0.24–0.65%). The transmission probability per contaminated blood product exposure is $p_p = 92.5\%$ (95% CI 89.0–96.1%). In view of this and the frequency of unsafe injections and blood transfusion compared to unprotected sexual contacts, the role of iatrogenic transmission in resource-poor settings has not been underestimated.

It is important to provide reliable estimates of transmission probabilities for iatrogenic modes of transmission, in order to predict their relative impact on the HIV/AIDS pandemic. Our estimates are based on the most comprehensive review of the literature and best studies, and will be critical when assessing the contribution of these routes of infection to HIV incidence and designing appropriate prevention strategies.

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Modelling the Impact of Antiretroviral Use in Resource-Poor Settings

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Abbreviations: ADC, AIDS-defining condition; ART, antiretroviral therapy; LHS, Latin hypercube sampling

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ABSTRACT

Background

The anticipated scale-up of antiretroviral therapy (ART) in high-prevalence, resource-constrained settings requires operational research to guide policy on the design of treatment programmes. Mathematical models can explore the potential impacts of various treatment strategies, including timing of treatment initiation and provision of laboratory monitoring facilities, to complement evidence from pilot programmes.

Methods and Findings

A deterministic model of HIV transmission incorporating ART and stratifying infection progression into stages was constructed. The impact of ART was evaluated for various scenarios and treatment strategies, with different levels of coverage, patient eligibility, and other parameter values. These strategies included the provision of laboratory facilities that perform CD4 counts and viral load testing, and the timing of the stage of infection at which treatment is initiated. In our analysis, unlimited ART provision initiated at late-stage infection (AIDS) increased prevalence of HIV infection. The effect of additionally treating pre-AIDS patients depended on the behaviour change of treated patients. Different coverage levels for ART do not affect benefits such as life-years gained per person-year of treatment and have minimal effect on infections averted when treating AIDS patients only. Scaling up treatment of pre-AIDS patients resulted in more infections being averted per person-year of treatment, but the absolute number of infections averted remained small. As coverage increased in the models, the emergence and risk of spread of drug resistance increased. Withdrawal of failing treatment (clinical resurgence of symptoms), immunologic (CD4 count decline), or virologic failure (viral rebound) increased the number of infected individuals who could benefit from ART, but effectiveness per person is compromised. Only withdrawal at a very early stage of treatment failure, soon after viral rebound, would have a substantial impact on emergence of drug resistance.

Conclusions

Our analysis found that ART cannot be seen as a direct transmission prevention measure, regardless of the degree of coverage. Counselling of patients to promote safe sexual practices is essential and must aim to effect long-term change. The chief aims of an ART programme, such as maximised number of patients treated or optimised treatment per patient, will determine which treatment strategy is most effective.

Introduction

Antiretroviral therapy (ART) has greatly reduced HIV/AIDS-related mortality and morbidity in industrialised countries [1]. Because it reduces a patient's viral load, it is also believed to reduce infectiousness [2], and so has been suggested as a prevention tool in its own right, as well as a treatment [3]. As prevention efforts in resource-poor settings have not always met with success, especially in high-prevalence areas of Africa [4,5], this could be an important additional goal of the accelerated roll-out of ART across the continent. In order to maximise the benefit of ART to patients and their communities, its impact on HIV epidemics should be evaluated, and different approaches to ART delivery should be investigated.

The effect that ART will have on transmission will rely not only on its effect on life expectancy, infectiousness, and treatment failure rates, but also on the stage of infection at which treatment is initiated, levels of coverage (which rely on the availability of resources and identification of patients qualifying for ART), and the scale and stage of HIV epidemic that the community is experiencing.

Previous mathematical models have predicted that ART will have a striking effect on transmission when coverage is high. Models based on the HIV epidemic among men who have sex with men in San Francisco [6] and Australia [7] have produced optimistic outcomes, provided that risk-taking behaviour (e.g., sexual partner change rate) does not increase substantially. However, it is unlikely that treatment of patients in resource-poor settings will be at an early stage of infection (i.e., before CD4 cell counts reach 200 cells/ml or less); many are diagnosed only when their CD4 counts have reached less than 50 cells/ml [8,9]. Models need to explore more realistic patterns of ART use in such settings, incorporating the problems of late presentation of HIV infection, rationing of finite resources, limited health care facilities, and inadequate nutrition.

Among the issues that need addressing are inclusion and exclusion criteria for ART programmes, which may involve tuberculosis status (and with that perhaps a proven record of good adherence from a Directly Observed Therapy Short-Course, or DOTS, programme) and infection stage. ART may be targeted at patients with AIDS most in need and closest to death, or it may also be used for those with "pre-AIDS" (defined as the disease state at which the virus escapes immune system control, and CD4 counts decline, but no AIDS-defining conditions [ADCs] appear). Patients treated at the pre-AIDS stage are likely to have a better prognosis than those treated after they have developed full AIDS, because of preserved immune function, and they are likely to avoid the complications associated with immune reconstitution syndrome [10]. Given that data are limited on effectiveness of ART programmes in resource-poor settings, further investigation of possible optimal approaches—to include cost-effectiveness analyses—would be valuable before programme roll-out [11].

Mukherjee et al. [12] believe that the implementation of ART cannot wait until sufficient infrastructure is in place, and they discuss the problem of limited laboratory infrastructure, suggesting that a stepwise progression as more resources become available would be appropriate. They recommend initially implementing an ART programme based on clinical management (or at most total lymphocyte count), with sequential addition of CD4 count testing, viral load testing, and resistance testing. Our analysis investigated the effect of sequential adoption of these laboratory facilities on key outcome measures. The adoption of CD4 count testing allows for the identification of infected individuals who present without an ADC, but are still at a relatively late stage of infection, with a CD4 count in decline (pre-AIDS patients). The adoption of viral load testing can assist with the identification of such individuals, but additionally can identify treatment failure with viral rebound, which can precede by a substantial period a further decline in CD4 count or a reappearance of opportunistic infections [13–15]. However, where funds for HIV/AIDS diagnosis and treatment are limited, the expense of such facilities restricts the number of patients being treated. Furthermore, these facilities allow the identification of individuals who are more likely (pre-AIDS patients) and less likely (those failing therapy) to benefit from ART, leading to difficult ethical considerations concerning prioritisation.

In the current study, we explore many of these issues by predicting and comparing through modelling the epidemiological impacts of alternative strategies, and in the process provide a clear illustration of the trade-offs involved.

Methods

Model and Assumptions

A compartmental deterministic mathematical model describing HIV transmission and ART use was constructed. The basic structure of the model is illustrated in Figure 1 and described in more detail in Protocol S1. The model tracks two HIV strains, one resistant to ART and one sensitive. Each compartment of infected individuals has a defined infectiousness determined by treatment status and viral resistance type. Superinfection is incorporated only for individuals undergoing successful treatment for an ART-sensitive strain, where superinfection with an ART-resistant strain can occur. It is assumed that treatment failure (defined as viral rebound or failure to achieve viral suppression) precedes resistance evolution.

ART. We assumed a single, standard triple-combination therapy regimen, with no second-line or salvage therapy available for those who experience treatment failure. The World Health Organisation guidelines for ART use in resource-poor settings recommend at least one combination salvage therapy option [8], which may be feasible and could be investigated by extending this model. However, as this may not be realistic in all regions, especially where access to first-line therapy must be rationed, we believe that the assumption of one ART regimen only is an appropriate starting point.

HIV and AIDS. In the model, an ART-resistant strain is resistant to the triple regimen rather than to individual drugs within that regimen. It is assumed that there is no pre-existing background level of resistance in the population generated by ART drug use outside the modelled ART programme.

The model was solved numerically using the Runge-Kutte 4 algorithm in Berkeley Madonna version 8.0.1, but programmed concurrently using C for validation.

The model was stratified into four distinct HIV infection stages with different associated infectiousness: primary

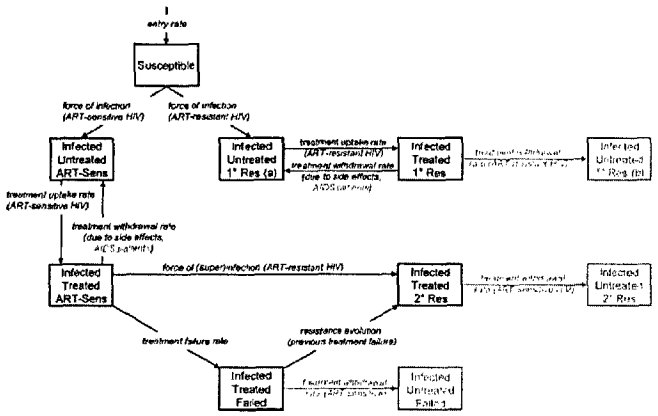


Figure 1. Schematic Illustration of the Structure of the HIV Transmission Model

For clarity, stages of infection (primary infection, incubation, pre-AIDS, and AIDS) and death rates are not shown. "1° Res" denotes those with primary (transmitted) resistance, while "2° Res" denotes those with secondary (acquired) resistance. "ART-Sens" denotes people infected with ART-sensitive virus. Treatment withdrawal, used in some scenarios, is shown in grey.

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infection, incubation, pre-AIDS, and AIDS. The incubation period is further divided into eight compartments, with an average duration in each of one year, in order to approximate the average time spent in this stage more accurately than by using an exponential distribution.

Sexual behaviour and treatment outcomes. Sexual partnerships in this type of model have no duration—they form (and implicitly end) instantaneously, accompanied by infection transmission, if this has been determined to occur. The model assumes that all partnerships are heterosexual. It does not distinguish between the sexes, but includes four sexual activity classes. A small proportion of the population (0.1%) is in the highest activity class; 26%, 59%, and 15% make up the respective lower-activity classes, with partner change rates of 153, 13.6, 0.5 and 0.2 partners per year, respectively. These form sexual activity groups 1 to 4, respectively. All individuals progressing to AIDS move to the least-active group because of their illness.

Patients starting ART spend an average of six months in an "initial" compartment. For AIDS patients in this "initial" period, the assumed effects of ART on sexual activity are not yet imposed—they have not yet sufficiently recovered to increase any risk-taking behaviour. For pre-AIDS patients, with milder disease, an immediate decrease in sexual activity (dropping to the next lowest sexual activity class) is assumed to follow diagnosis and effective counselling. The incorporation of these compartments allows for different treatment outcomes for AIDS and pre-AIDS patients initiating ART.

On leaving this "initial" phase, a fraction of patients are assumed to drop out (due to tolerability problems) and return to the "untreated" compartment at the same infection stage. The fraction that drops out is higher for AIDS patients than for pre-AIDS patients, because of immune reconstitution syndrome. A substantial proportion of treated AIDS patients die after leaving this stage, an assumption that reflects the high mortality observed in the first few months of treatment for those at late-stage infection [16]. All other patients move to "successfully treated" or "unsuccessfully treated" compartments, from which point patients initiating ART at AIDS and pre-AIDS have the same progression rates. A fraction (85%) of AIDS patients increase sexual activity after initiation of ART and move to the next higher sexual activity group. For simplicity, this effect does not wane with time. These are the baseline assumptions regarding changes in the risk-taking behaviour of HIV-infected patients upon initiating ART.

Resurgence of clinical symptoms was modelled as progression through eight treatment stages without symptoms before development of a new ADC upon entering the ninth compartment, when all patients revert back to the lowest sexual activity group. "Successful" treatment is defined as long-term viral suppression, while "unsuccessful" treatment is viral outgrowth (treatment failure). A fraction of patients fail treatment each year, from which point their progression through the stages to AIDS is faster. Patients may also develop resistance as a result of treatment failure or become superinfected with ART-resistant virus. In the case of primary resistance, there is also staged progression back to AIDS upon treatment initiation, but for simplicity, there is no "initial" period.

Parameter values. The majority of parameter values were selected after a review of literature and are presented in Table 1 and Table S1. The baseline values were used for model runs in Figures 2 and 3, and the ranges were used for the uncertainty analyses employed in Figures 4 and 5. Table 1 illustrates the range of parameter values used for Latin hypercube sampling (LHS) [17] and for the best- and worst-case scenarios for ART, both used in Figures 4 and 5. LHS parameters were varied independently of one another. "Best-" and "worst-case" scenarios in Table 1 refer to the effectiveness of ART provision in terms of mortality and

Table 1. Descriptions and Baseline Values of Some Key Model Parameters, with Sources

Parameter Type	Parameter Description	Value	Sources
Biological parameters	Duration of pre-AIDS stage	1 y	[29–31]
	Duration before death with AIDS (all infection categories)	9 mo	[32,33]
Treatment parameters	Fraction of treated patients with viral rebound developing resistance at each treatment stage	40%; LHS range: 20%–60%	[34–36]
	Fraction of treated patients who drop out after each treatment stage due to side effects	2%; LHS range: 1%–5%	[35,36]
	Fraction of AIDS patients initiating ART who drop out due to side effects during the "initial" phase	5%, best-case scenario; 15%, worst-case scenario	[37,38]
	Fraction of treated patients who suffer viral rebound at each treatment stage	10%, best-case scenario; 30%, worst-case scenario	[31,39]
	Fraction of AIDS patients initiating ART who develop viral rebound or failure to suppress during the "initial" phase	30%, best-case scenario; 50%, worst-case scenario	[21,40]
	Exit rate from "initial" phase for patients first starting ART	2 per year (average duration: 6 mo)	[41,42]
	Fraction of AIDS patients initiating ART who die during the "initial" phase	10%, best-case scenario; 20%, worst-case scenario	[22,43,44]
	Baseline rate of withdrawal of failing therapy (primary or secondary resistance or other viral rebound)	0	—
	Rate of transfer to next treatment stage, successful viral suppression	1 per year (average duration before progression to AIDS: 8 y)	[45]
	Factor increase in rate of transfer to next treatment stage, patients with viral rebound and/or resistance (duration before AIDS 80% of that for patients with viral suppression)	1.25	[22,45]
	Factor increase in rate of transfer to next treatment stage after removal of ART (duration before AIDS 20% of that for patients with viral suppression)	5	[46,47]
	Relative transmission probability per partnership for patients with viral suppression on ART, compared with untreated individuals	2%; LHS range: 1%–10%	[41,42]
	Relative transmission probability per partnership for patients with viral rebound and/or resistance receiving ART, compared with untreated individuals	75%; LHS range: 50%–100%	[38,43]
	Relative transmission probability per partnership for patients with viral rebound and/or resistance and not on ART, compared with untreated individuals	100%	[43]
	Probability that an untreated individual with secondary resistance transmits resistant rather than sensitive virus	5%; LHS range: 0%–10%	[48,49]
	Probability that a treated individual with secondary resistance transmits resistant rather than sensitive virus	30%; LHS range: 20%–40%	[43]
	Probability that an untreated individual with primary resistance transmits resistant rather than sensitive virus during primary (acute) infection	100%; LHS range: 75%–100%	[45,50]
	Probability that an untreated individual with primary resistance transmits resistant virus, all other stages of infection	5%; LHS range: 0%–10%	[45,50]
	Probability that a treated individual with primary resistance transmits resistant virus rather than sensitive virus	100%	Model assumption

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drop-out rates of AIDS patients in the initial treatment period and treatment failure for all ART recipients. This is to reflect the success of the programme in promoting adherence, ensuring adequate drug supplies, managing complications, and providing other medications and nutritional supplements where necessary. A best-case scenario would have low rates of treatment failure, because patient adherence is high and drop-out low. A full listing of all model parameters and additional reference sources is provided in Table S1.

Reliable estimates for partner change rates and HIV infectiousness are difficult to obtain [18,19]. Parameter values were chosen to represent the HIV epidemic in Malawi as closely as possible, using data on HIV prevalence from antenatal clinics in major urban areas [20]. Malawi was chosen as an example of a country with a mature, high-prevalence HIV epidemic and limited resources with which to provide ART for all those in need. These values also reflect the situation in resource-poor settings more generally. Partner change rates, distributions of individuals between sexual activity groups, and degree of assortative mixing between these groups were parameterised by fitting the model to the prevalence data using the curve fit function in Berkeley Madonna, having seeded the population with five infected individuals, with primary infection in the highest sexual activity class (we consider a hypothetical ART programme in a population of one million). The partner change rate for individuals in the highest-risk group is set very high, at 153 partners per year, while that of the lowest-risk group is just 0.23 partners per year, in order to mimic the timing and scale of the Malawi epidemic as closely as possible, with a peak prevalence of 27%. There are large differences in HIV prevalence between major urban and non-urban areas in Malawi [20]. We calibrated the model to urban prevalence, as

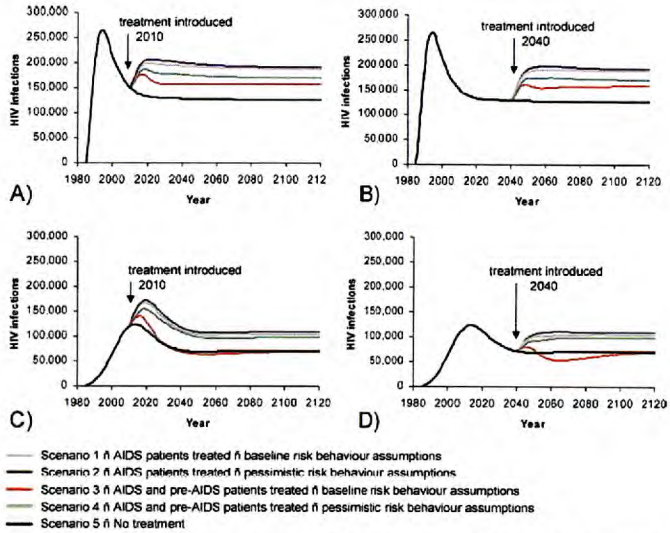


Figure 2. Total Number of HIV Infections through Time for Various HIV Epidemics and under Different Assumptions regarding Behaviour Change of Treated Patients

(A) and (B) illustrate a high prevalence, mature epidemic, similar to that of Malawi; (C) and (D) a smaller-scale epidemic (partner change rates one-third of those for the Malawi simulation). (A) and (C) introduce ART in 2010, before equilibrium for (A) and early in the epidemic for (C); (B) and (D) introduce ART in 2040, once equilibrium is reached for (B) and after the peak of the epidemic for (D). For each HIV epidemic scenario graph, two treatment options and two behaviour change scenarios are illustrated: (1) treatment of AIDS patients only, baseline behaviour change assumptions (Table 3); (2) treatment of AIDS patients only, pessimistic behaviour change assumptions (Table 3); (3) treatment of AIDS and pre-AIDS patients, baseline behaviour change assumptions; (4) treatment of AIDS and pre-AIDS patients, pessimistic behaviour change assumptions.

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it is likely that ART will be introduced in urban areas before gradual roll-out to other regions. A graph comparing the model simulation run using the parameters in Table 1 with the antenatal clinic prevalence data from Malawi is shown in Figure S1.

Life-years gained for each scenario were calculated by integrating the total number alive and comparing with the no-treatment scenario. Person-years of treatment were calculated by integrating the total number on treatment.

Analyses of ART Effect

Effect of ART on different HIV epidemics. In order to model different types of HIV epidemics, with different basic reproductive numbers and thus scales, the partner change rates across all activity groups were cut to one-third of their original value, generating an epidemic with a peak prevalence of 14.4%. ART was introduced in 2010 and 2040 to investigate the impact by maturity of each epidemic, with unlimited treatment of eligible individuals (details are provided in Table 2). HIV patients are recruited into the ART programme very quickly (an average of one month after qualifying for treatment due to reaching the appropriate HIV infection stage). This represents the most optimistic scenario, in which all individuals qualifying for ART are screened, identified, and treated virtually immediately, in order to investigate the maximum impact of ART. Results are investigated with baseline assumptions regarding behaviour change upon initiating ART, as described above, compared with more pessimistic assumptions, as described in Table 3.

Impact of ART—Levels of coverage. Using baseline values for all parameters (Table 1) and for baseline changes in risk-taking behaviour upon initiating ART, key outcome measures were recorded for ART programme capacities ranging from 5,000 to 60,000 patients. Best- and worst-case scenarios as well as scenarios in which AIDS patients only versus AIDS and pre-AIDS patients qualified for treatment were calculated. ART was introduced in 2010 with an uptake rate of 12, which equates to uptake of ART an average of one month after progressing to the eligible treatment stage, either AIDS or pre-AIDS.

Impact of ART—Treatment strategies. To represent the availability or absence of CD4 count testing and viral load monitoring, timing of treatment initiation, and withdrawal of failing treatment, parameters were varied as described in Table 4. The model assumes that without CD4 count or viral load testing, only AIDS patients (defined as those showing ADCs) can be identified and treated (scenarios A and D; Table 4). A programme that offers CD4 count testing can treat individuals at an earlier stage of immunologic decline, at the pre-AIDS stage (scenarios B and C, E–G; Table 4). Where drugs are rationed, we explored two possible approaches: treatment in the order in which patients present to the clinic (a "first come, first served" approach, scenario B; Table 4), or preferential treatment of patients most likely to benefit from ART and least likely to suffer complications such as immune

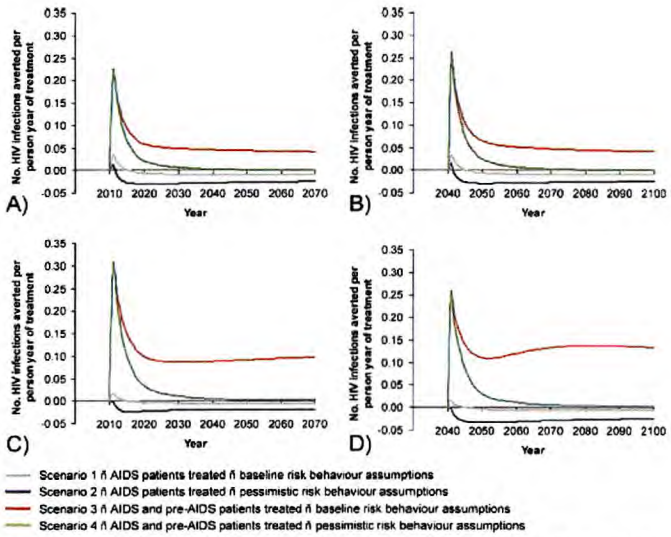


Figure 3. Total Number of HIV Infections Averted per Person-Year of Treatment for Various HIV Epidemics and under Different Assumptions regarding Behaviour Change of Treated Patients

Scenarios as for Figure 2.

DOI: 10.1371/journal.pmed.0030124.g003

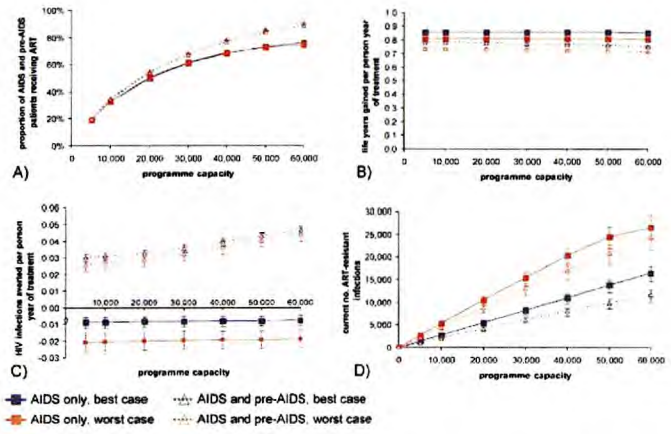


Figure 4. Effect of Programme Capacity

Outcome measures ten years after introduction of ART compared with no treatment, for various levels of coverage (ART programme capacities of 2,000 to 40,000) and for treating AIDS patients only or AIDS and pre-AIDS patients. Results are for the epidemic calibrated to Malawi prevalence data. Best- and worst-case scenarios refer to optimistic or pessimistic outcomes of ART use, respectively (see Table 1). Shown are coverage level, defined as proportion of those most in need (AIDS patients) receiving ART (A); cumulative number of life-years gained over ten years, per person-year of treatment (B); HIV infections averted per person year of treatment over ten years (C); and current number of ART-resistant infections ten years after ART introduction (D). Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range.

DOI: 10.1371/journal.pmed.0030124.g004

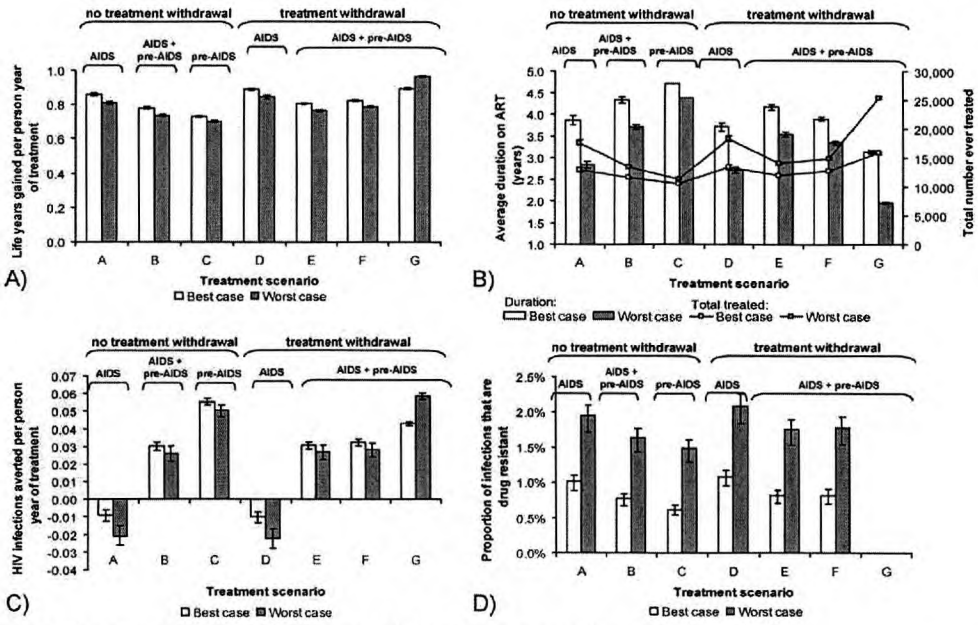


Figure 5. Description of Potential Treatment Strategies for ART Programmes in Resource-Limited Settings

Types of ART programme may vary by availability of laboratory tests (CD4 count and viral load testing) and approach to rationing (preferentially treating those at different stages of infection and possibly withdrawing failing treatment). Different strategies are simulated by varying which populations qualify for treatment, and withdrawal of therapy after viral rebound, immunologic, or clinical treatment failure. Outcome measures are ten years after introduction of ART compared with no treatment. The seven scenarios, labelled A–G on the *x*-axes of the bar graphs, refer to different levels of use of laboratory testing and prioritisation of different groups of patients (see Table 4). Best and worst cases refer to optimistic and pessimistic assumptions regarding ART (see Table 1). Shown are cumulative life-years gained per person-year of treatment compared to no treatment (A); average duration on ART per patient and cumulative number ever treated (B); HIV infections and deaths (all causes) averted per person-year of treatment compared to no treatment (C); and proportion of all infections in the population that are ART-resistant at ten years after ART introduction (D). Results are the median values of the LHS sensitivity analysis; error bars represent the interquartile range.

DOI: 10.1371/journal.pmed.0030124.g005

reconstitution syndrome and treatment failure (a "best-prognosis" approach, scenario C; Table 4).

Treatment failure in this case was defined as viral rebound, which can often precede immunologic treatment failure (decline in CD4 count) and clinical progression by a considerable period [15], with patients still able to respond well to ART [21,22]. Scenario D investigates clinical management, where patients having failed ART are removed from therapy an average of three months after developing AIDS. In scenario E, although CD4 testing would allow earlier detection of immunologic treatment failure, it is still assumed that ART is withdrawn only from those with AIDS, whereas the earlier

Table 2. Summary of Treatment Scenarios—Effect of ART on Various Epidemics: Changes in Size and Maturity of HIV Epidemic

Graph[a]	Partner Change Rate by Sexual Activity Class (per Year)				Proportion in Each Activity Class (%)				Year ART Introduced
	1	2	3	4	1	2	3	4	
A	152.8	13.6	0.5	0.2	0.1	26	59	15	2010
B	152.8	13.6	0.5	0.2	0.1	26	59	15	2040
C	50.9	4.5	0.2	0.1	0.1	26	59	15	2010
D	50.9	4.5	0.2	0.1	0.1	26	59	15	2040

Other parameters: All other parameters as in Table 1 using best case scenario values with unlimited treatment coverage.

[a]Graphs A–D refer to those described in Figures 2 and 3: A, high prevalence, mature epidemic with ART introduced in 2010 before epidemic equilibrium; B, high prevalence, mature epidemic with ART introduced in 2040 once epidemic equilibrium is reached; C, smaller scale epidemic with ART introduced in 2010 early in the epidemic; D, smaller scale epidemic with ART introduced in 2040 after the peak of the epidemic.

DOI: 10.1371/journal.pmed.0030124.t002

Table 3. Summary of Treatment Scenarios—Effect of ART on Various Epidemics: Changes in ART Patients' Risk-Taking Behaviours

Scenario	Treatment Uptake Rates (per Year)		Risk-Taking Behaviour Assumptions	
	AIDS	Pre-AIDS	AIDS	Pre-AIDS
1	12	0	Baseline—Patients stay in (lowest) sexual activity group 4 or move to group 3	No change (not treated)
2	12	0	Pessimistic—Patients stay in (lowest) sexual activity group 4 or move to groups 2 and 3	No change (not treated)
3	12	12	Baseline—Patients stay in (lowest) sexual activity group 4 or move to group 3	Baseline—Patients move to the next lowest (less active) sexual activity group
4	12	12	Baseline—Patients stay in (lowest) sexual activity group 4 or move to group 3	Pessimistic—No change in sexual activity group
5	0	0	No change	No change

Other parameters: All other parameters as in Table 1 using best case scenario values with unlimited treatment coverage.
DOI: 10.1371/journal.pmed.0030124.t003

withdrawal due to the detection of failure is used in scenario F. Scenario F involves withdrawal of ART at this detection stage, when immunologic decline is identified. ART is withdrawn from patients one treatment stage before progressing to AIDS, i.e., within a year of developing a new ADC.

Scenario G incorporates viral load testing and assumes the extreme measure of withdrawing all ART at the earliest definition of treatment failure, viral rebound, when patients are still benefiting from treatment. Viral load testing is assumed to identify treatment failure and facilitate withdrawal of individuals from therapy less than one year after treatment failure.

Results

Effect of ART on Various HIV Epidemics

The scenarios in Figures 2 and 3 illustrate the various long-term impacts that ART may have on HIV prevalence when its availability is not limited. The impact of widespread ART on the HIV epidemic (Figure 2) and cumulative HIV infections averted per person-year of treatment (Figure 3) is illustrated. All scenarios have high treatment uptake rates, requiring a rigorous screening programme in order to identify all patients eligible for ART, and the best-case scenarios are used. Therefore this result represents the best possible outcome of ART introduction.

The impacts of treating AIDS patients and pre-AIDS patients differed, partly because, in these unlimited-treatment scenarios, the numbers receiving ART differed substantially. Treating solely AIDS patients increased prevalence for all modelled epidemics by increasing life expectancy, while additionally treating pre-AIDS patients initially counteracted this increase to some extent by averting more infections (Figure 3). Changing the assumptions regarding behaviour change upon initiation of ART (see Table 3 for details) had little effect when ART eligibility was limited to AIDS patients. In contrast, the "pessimistic" assumption of an absence of behaviour change for treated pre-AIDS patients (scenario 4; Table 3) substantially increased prevalence for all scenarios, especially for the epidemic with the lower partner change rates and R_0 (Figure 2). The model suggests that the most "optimistic" impact that ART may have on an HIV

Table 4. Summary of Treatment Scenarios—Availability of Laboratory Facilities

Scenario		Entry Criterion	ART Uptake Rates (per Year)		Withdrawal of ART[a]
			AIDS	Pre-AIDS	
A	Clinical management or "most in need"	AIDS only	12	0	No withdrawal
B	CD4 testing and "first come, first served"	AIDS and pre-AIDS	12	12	No withdrawal
C	CD4 testing and "best prognosis"	Pre-Aids only	0	12	No withdrawal
D	Treatment withdrawal, clinical management	AIDS only	12	0	Rate of ART withdrawal upon progressing to AIDS − 4 (per year)
E	CD4 testing and "first come, first served" with treatment withdrawal	AIDS and pre-AIDS	12	12	Rate of ART withdrawal upon progressing to AIDS − 4 (per year)
F	Treatment withdrawal, CD4 count testing	AIDS and pre-AIDS	12	12	Patients removed from ART one treatment stage before progressing to AIDS for all treated compartments
G	Treatment withdrawal, CD4 count and viral load testing	AIDS and pre-AIDS	12	12	Patients removed from ART one treatment stage after developing viral rebound

[a]Withdrawal as a result of treatment failure (defined as viral rebound or failed viral suppression, with or without drug resistance). Treatment introduced at 2010. Other parameters: maximum number on treatment = 5,000. Best- and worst-case scenarios refer to optimistic and pessimistic selection of parameters regarding treatment failure rates (Table 1). Baseline assumptions regarding behaviour change upon initiating ART are assumed.
DOI: 10.1371/journal.pmed.0030124.t004

epidemic with no limitation on numbers treated is no change in number of infections; this scenario would require treatment of all AIDS and pre-AIDS patients, accompanied by significant change in risk-taking behaviour, and an epidemic with an intrinsically low R_0 (Figure 2C and 2D). Figure 3 suggests that, although treating pre-AIDS patients may prevent infections in the short term, over the long term the net gain is considerably reduced. This is not due to outgrowth of ART-resistant viruses; the constraint that wild-type is more transmissible than the resistant phenotype prevents substantial primary resistance under this choice of parameters. Rather, the immediate effect of decreased risk-taking behaviour among treated patients was negated by their increased life expectancy.

Impact of ART—Levels of Coverage

The effect when there are no constraints on the availability of ART drugs was compared with a limited number being treated at any one time, to reflect resource constraints (Figure 4). The implication for treatment coverage, in terms of proportion of individuals in need (AIDS and pre-AIDS patients) receiving ART for each programme capacity, is shown in Figure 4A.

Because of the limited effect of treatment on transmission, the benefits of ART to the community per person-year of treatment did not vary substantially with the capacity of a programme, as measured by life-years gained (Figure 4B). Each additional person treated produced the same benefit in terms of life-years gained and transmission and morbidity reduced—for a mature epidemic, there would be no herd effect producing a non-linear pattern of benefit of increasing access to ART in the short term. Paradoxically, treating both AIDS and pre-AIDS patients saved fewer life-years per person year of treatment than an AIDS-only approach, despite the fact that treating pre-AIDS averted more infections over this period (Figures 3A and 4C). The benefits of delaying imminent AIDS deaths were demonstrated immediately, while the prevention of future deaths by preventing infection was revealed more slowly. The number of life-years saved per person-year of treatment for pre-AIDS and AIDS treatment overtook that for AIDS-only treatment by 2029 when the model was run with a capacity of 30,000 ART patients and best-case scenario parameters (Figure S2).

A greater degree of coverage led to a greater degree of viral resistance evolution and potential spread (Figure 4D). Furthermore, the greater the coverage of a poorly run programme, where resistance evolution is frequent, the greater the opportunity for relatively fit ART-resistant mutants to evolve, which may compromise the entire programme in that area and possibly others.

Impact of ART—Treatment Strategies

Scenarios that may potentially be adopted by ART programmes in resource-constrained settings are described in Table 4 and Methods (section titled "Impact of ART—Treatment Strategies"), and relate not only to the availability of laboratory facilities but also to the priorities for treatment assigned by public health officials. We assumed that initiating treatment before extensive destruction of the cellular immune system, at pre-AIDS rather than AIDS, leads to less risk of mortality, treatment failure, and dropout due to drug intolerance. We also assumed that treatment failure leads to a decrease in treatment effectiveness, but that ART still has a substantial beneficial effect in the "failed patient" (see Table 1).

Figure 5A again shows that ten years after treatment introduction, the benefits of averting new infections by treating pre-AIDS patients are not evident, so treating only AIDS patients appears to confer more benefit in terms of life-years gained (scenario A versus scenario C). Figure 5B shows that without treatment withdrawal, pre-AIDS patients remained on ART substantially longer than did AIDS patients, because they have a better prognosis (lower mortality and likelihood of treatment failure). The influence of rates of treatment failure on duration of ART is shown by the large differences between best- and worst-case scenarios. Treatment withdrawal significantly decreased the average duration on ART, by over a year in some scenarios. Figure 5C shows that the earlier that individuals were placed on ART, the more infections were averted under these assumptions regarding behaviour change. Figure 5D shows population-level resistance prevalence, which appears relatively low, but was the result of relatively small coverage of the population (approximately 20% of all those in need at 2020).

For treatment withdrawal based on clinical management, there was little impact in terms of infections averted and resistance emergence (scenarios A versus D, and B versus E; Figure 5C and 5D). ART withdrawal was just a few months before death from AIDS, but in the context of rationing, this would free up treatment for others. Therefore, both life-years gained per person-year of treatment and the number of individuals that can be reached with ART increased slightly, because resources would be directed in a more "efficient" way (Figure 5). However, the difference in life-years gained for all scenarios was small; all patients must receive ART continuously to benefit, so this is not surprising. Assumptions regarding treatment withdrawal for scenario G (Figure 5) meant that ART was withdrawn from all patients after treatment failure but before emergence of drug resistance; this is unrealistic, but it illustrates the maximum impact that such a policy could have (Figure 5D). A substantial effect on preventing resistance is observed only for scenario G, with ART withdrawal after viral rebound. Viral rebound can occur shortly after initiating therapy, and potentially years before immunologic decline, while patients are free from symptoms, so risk-taking behaviour could be relatively high and thus there is considerable opportunity for transmission of resistant strains. If withdrawal is only after CD4 counts begin to drop, the chance of resistance transmission is substantially less. The impact on HIV transmission and life-years gained remained minimal (Figure 5C), and patients' duration on ART (a measure of life expectancy) was substantially reduced, although total numbers benefiting from therapy increased (Figure 5B).

Discussion

We have modelled the impact of ART on various types of HIV epidemics in resource-poor settings more realistically than hitherto, to investigate how the specific details of ART programme implementation might affect epidemiological and clinical impact. According to our modelling results, HIV epidemics in sub-Saharan Africa are not amenable to control through treatment, regardless of the extent of ART

roll-out, and must be integrated with prevention methods. In the absence of substantial behaviour change of treated patients through effective counselling, prevalence is likely to increase. Different coverage levels for ART would not affect benefits such as life-years gained per person-year of treatment because of the limited effect of treatment on transmission, but increasing coverage does increase the emergence and spread of drug resistance. Scenarios investigating withdrawal of failing treatment increased the numbers who could benefit from AIDS, but effectiveness per person was compromised. Only withdrawal at a very early stage of treatment failure, soon after viral rebound, would have a substantial impact on drug resistance emergence (Figure 5D), because the majority of transmission of resistant HIV strains would occur before immunologic treatment failure. While our model assumes conservative estimates for the fitness of resistant strains, substantial viral replication under continued treatment pressure could promote generation of even fitter strains, increasing the frequency of resistance transmission events.

While our model incorporated some behaviour change upon initiating ART, it did not consider the complex effects of voluntary counselling and testing on risk-taking behaviour. Both uptake of testing and risk-taking behaviour may vary substantially by scale of coverage and performance of ART programmes, and their impact is likely to have a large impact on prevalence. The model results suggest similar levels of benefit per person-year of treatment, regardless of the scale of ART provision, but in reality, scaling up programmes is likely to compromise quality, meaning higher dropout rates and mortality and treatment failure, negating the beneficial impacts of ART and increasing the rate of drug resistance emergence.

CD4 count testing allows the identification of pre-AIDS patients. Additionally, the implementation of laboratory facilities for viral load monitoring allows the identification of treatment failure earlier, increasing the sustainability of the programme, either by allowing switching to a salvage regimen, or perhaps (in the absence of alternative treatments) by halting therapy and giving the drugs to another patient whose prognosis is better, as is investigated here. The benefits of viral load testing will increase with higher levels of resistance in the population. The model does not incorporate background drug resistance levels due to uses of ART outside the modelled programme, but levels of resistance are likely to be higher in many areas due to prevention of mother-to-child transmission [23] and sporadic ART use [24], and because some programmes have used only double or single therapy [25,26]. For example, in the UNAIDS/Uganda Ministry of Health Drug Access Initiative pilot project, only 64% of patients were ART drug-naïve before enrolling in the initiative [26].

Withdrawal of failing treatment, where this is defined as viral rebound or immunologic failure, when the patient would still benefit from continuing ART, is unlikely to be acceptable to any ethics committee or government. However, the exploration of this strategy through modelling has shown the benefits in terms of increasing access to (albeit less effective) treatment to more individuals, and for withdrawal upon viral rebound, slowing the emergence of drug resistance. While the net health benefits in terms of life-years gained would be similar for each strategy, in a wider context, factors such as delaying orphanhood by even a short time for many patients' children, or by a longer time for fewer, make this comparison difficult to evaluate.

Results from this model suggest that counselling of patients to promote safe sexual practices is essential, and must aim to effect long-term change and prevent behavioural disinhibition (increase in risk-taking behaviour in response to perceptions of safety conferred by the use of ART), not only for ART patients, but for all individuals. Withdrawal of treatment at a potentially acceptable stage, that is, after immunologic deterioration when ART is no longer of benefit, would not have a substantial effect on containing resistance emergence, but would increase the number able to benefit from treatment where its availability is limited. As the pace of ART roll-out across southern Africa quickens, difficult decisions regarding the allocation of finite resources will have to be made. Mathematical models are increasingly being employed to explore optimal strategies for allocation of these funds [27,28]. Analysing the implications of different treatment strategies, using data from early programmes coupled with the types of modelling methods presented here, is needed to give AIDS treatment and prevention programmes the best possible chance of success.

Supporting Information

Figure S1. Comparison of Modelled Epidemic with Prevalence Data

Comparison of the projected epidemic using baseline parameter values, with UNAIDS prevalence estimates from antenatal clinics in Malawi [20].

Found at DOI: 10.1371/journal.pmed.0030124.sg001 (30 KB PPT).

Figure S2. Comparison of Life-Years Gained per Person-Year of Treatment over Time for AIDS Only and AIDS and Pre-AIDS Treatment Strategies

Model run with treatment capacity of 30,000 and best-case scenario parameters.

Found at DOI: 10.1371/journal.pmed.0030124.sg002 (39 KB PPT).

Protocol S1. Model Description

Detailed description of the model, including transmission equations and a full list of adopted parameter values.

Found at DOI: 10.1371/journal.pmed.0030124.sd001 (488 KB DOC).

Table S1. Descriptions and Adopted Values of All Model Parameters

Found at DOI: 10.1371/journal.pmed.0030124.st001 (396 KB DOC).

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Patient Summary

Background. Access to antiretroviral therapy (ART) is slowly increasing in resource-poor countries. Strategies for how to achieve the greatest health benefits with what will remain, at least in the near future, limited resources are necessary and being developed. How to distribute a limited amount of life-saving drugs in the face of a devastating pandemic—in other words, how to decide who will not get treatment—is a very difficult ethical question. Those who need to solve it must learn as much as possible from the experiences of others. In addition, theoretical predictions of the outcomes under different scenarios can help. To this end, public health scientists are using mathematical modelling of different scenarios of testing, treatment, and counselling. For the modelling data to be useful, they must be based as much as possible on realistic assumptions.

Why Was This Study Done? Sexual transmission of HIV is more likely if the HIV-positive partner has a higher viral load. Because ART not only slows AIDS progression but also reduces viral load in infected individuals, the drugs therefore not only improve the health and prolong the life of those who take the drugs but also make it less likely that they infect others. As a consequence, ART has been discussed not only as a treatment but also as a prevention tool in its own right. Mathematical modelling supports the notion that ART can reduce transmission rates, as long as the people receiving treatment do not change their sexual behaviour towards riskier sex (unprotected intercourse, more partners, etc.). So far, modelling the prevention effects has been based on experiences in the US and Australia, where most HIV-infected individuals get access to drugs during the early stages of infection, as soon as their CD4 counts drop (this is unlikely to be the case in resource-poor settings where many patients are diagnosed and treated only when they experience AIDS symptoms). These researchers used more relevant parameters to model the effects of ART on improving the health of those treated and on HIV prevalence, i.e., the rate of new infections.

What Did the Researchers Do and Find? They used a model to predict and compare the impacts of alternative strategies. Some of the strategies included the provision of diagnostic laboratories that could routinely measure CD4 counts and viral loads of HIV-infected individuals. Only if this is done could people be treated before they develop overt symptoms. They also took into account different ways that people might change their sexual behaviour if they get treatment (which might make them feel physically better and more likely to be sexually active) and counselling (which will hopefully increase safe sex practices). They found that providing ART to all individuals with AIDS symptoms (i.e., those at the late stages of the disease) was likely to increase the prevalence of HIV infection, as these people live longer and become sexually active again. If ART is also provided to people during the earlier stages of infection, the outcome on HIV prevalence depends on the behaviour of these individuals. If ART was more widely available, the risk of the emergence of drug-resistant strains of the virus increased.

What Does This Mean? These results suggest that provision of ART to symptomatic AIDS patients and/or those at the earlier stages of the disease is not likely to prevent many new infections. It could even increase transmission of the virus as patients live longer and are healthier. Counselling patients and the rest of society to promote safe sex practices must therefore be an essential part of any strategy if it is to contain and reverse the AIDS epidemic. The model presented here can support health policy makers in resource-poor settings in their difficult task of allocating limited amounts of antiretroviral drugs for the greatest benefit of their populations.

Where Can I Find More Information Online? WHO pages on HIV/AIDS:
http://www.who.int/hiv/en
Report from a Consultation on Anti-Retroviral Therapy for HIV Prevention:
http://www.nih.gov/od/oar/public/pubs/art_12_00.htm
Report from a Consultation on Studies of HIV Disease in Developing Countries:
http://www.nih.gov/od/oar/public/pubs/hivdeveloping.htm
Joint United Nations Programme on HIV/AIDS, World Health Organization. AIDS epidemic update 2004:
http://www.unaids.org/wad2004/report.html
Global HIV Prevention Working Group report, HIV Prevention in the Era of Expanded Treatment Access:
http://www.gatesfoundation.org/nr/downloads/globalhealth/aids/PWG2004Report.pdf

Appendix B

Table B1 FDA approved anti-HIV medications

Brand Name	Generic Name	Manufacturer	FDA Approval Date
1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Combivir	lamivudine and zidovudine	GlaxoSmithKline	27/09/1997
Emtriva	FTC, emtricitabine	Gilead Sciences	02/07/2003
Epivir	Lamivudine, 3TC	GlaxoSmithKline	17/11/1995
Epzicom	abacavir/lamivudine	GlaxoSmithKline	02/08/2004
Hivid	zalcitabine, ddC, dideoxycytidine	Hoffman-La Roche	19/06/1992
Retrovir	zidovudine, ZDV, azidothymidine, AZT	GlaxoSmithKline	19/03/1987
Trizivir	abacavir, lamivudine and zidovudine	GlaxoSmithKline	14/11/2000
Truvada	tenofovir, disoproxil/emtricitabine	Gilead Sciences	02/08/2004
Videx EC	enteric coated didanosine	Bristol Myers-Squibb	31/10/2000
Videx	didanosine, ddI, dideoxyinosine	Bristol Myers-Squibb	09/10/2000
(generic version)	didanoside (ddI) delayed release capsules	-	03/12/2004
Viread	tenofovir disoproxil fumarate	Gilead Sciences	26/10/2001
Zerit	Stavudine, d4T	Bristol Myers-Squibb	24/06/1994
Ziagen	Abacavir	GlaxoSmithKline	17/12/1998
2. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Rescriptor	delavirdine, DLV	Pfizer	04/04/1997
Sustiva	Efavirenz	Bristol Myers-Squibb	17/09/1998
Viramune	nevirapine, BI-RG-587	Boehringer Ingelheim	21/06/1996
3. Protease Inhibitors (PIs)			
Agenerase	amprenavir	GlaxoSmithKline	15/04/1999
Aptivus	Tipranavir	Boehringer Ingelheim	22/06/2005
Crixivan	indinavir, IDV, MK-639	Merck	13/03/1996
Fortovase	saquinavir	Hoffman-La Roche	07/11/1997
Invirase	saquinavir mesylate, SQV	Hoffman-La Roche	06/12/1995
Kaletra	lopinavir and ritonavir	Abbott Laboratories	15/09/2000
Lexiva	fosamprenavir, calcium	GlaxoSmithKline	20/10/2003
Norvir	Ritonavir, ABT-538	Abbott Laboratories	01/03/1996
Reyataz	atazanavir sulfate	Bristol Myers-Squibb	20/06/2003
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14/03/1997
4. Fusion Inhibitors			
Fuzeon	enfuvirtide, T-20	Hoffman-La Roche & Trimeris	13/03/2003

Adapted from U.S. Food and Drug Administration's Drugs Used in the Treatment of HIV Infection (available at http://www.fda.gov/oashi/aids/virals.html, accessed 4th October 2005)

Table B2 Estimated number of people receiving ART and percentage coverage in 20 countries with the unmet need, June 2005.

WHO region/country	Treated	Coverage (%)	Unmet need
African region			
South Africa	97,000 – 138,000	10 – 14	866,000
Nigeria	28,000 – 48,000	4 – 8	598,000
Zimbabwe	9,500 – 16,000	3 – 5	308,000
United Republic of Tanzania	5,500 – 9,500	2 – 3	307,000
Kenya	33,000 – 46,000	12 – 17	233,000
Ethiopia	15,000 – 19,000	5 – 7	261,000
Mozambique	11,000 – 13,000	5 – 6	204,000
Democratic Republic of Congo	5,000 – 6,000	2 – 3	203,000
Zambia	26,000 – 33,000	14 – 18	153,000
Malawi	18,000 – 23,000	11 – 14	150,000
Uganda	52,000 – 64,000	35 – 43	90,000
Cameroon	12,000 – 20,000	11 – 19	92,000
Côte d'Ivoire	11,000 – 19,000	10 – 17	96,000
Ghana	2,500 – 3,000	4 – 5	58,000
Lesotho	2,500 – 3,000	4 – 5	55,000
South-east Asia region			
India	33,000 – 67,000	4 – 9	735,000
Thailand	67,000 – 82,000	50 – 61	60,000
Western Pacific region			
China	11,000 – 14,000	14 – 18	65,000
European Region			
Russian Federation	4,000 – 6,000	4 – 7	94,000

The 20 countries with the highest number of people needing therapy are shown.
[a] Best coverage estimate based on the midpoints of the number of people receiving ARVs.
Adapted from the WHO "3 by 5" Progress Report, June 2005 [494].

Appendix C – Model Descriptions

Descriptions of models used in Chapter 2 to illustrate the effect of model structure on output:

C.1 ART Model 3 – staged HIV progression

State Variables

S_1 = susceptible individuals, "at risk"

S_2 = susceptible individuals, "no risk"

I_{Si}^{U} = ART-sensitive HIV infected individuals, untreated

I_{Si}^{T} = ART-sensitive HIV infected individuals, treated

I_{Si}^{TF} = ART-sensitive HIV infected individuals, treated but viral rebound

I_{Si}^{UF} = ART-sensitive HIV infected individuals, suffered viral rebound, withdrawn from treatment

I_{R2i}^{T} = ART-resistant HIV infected individuals (acquired, secondary resistance), treated

I_{R2i}^{U} = ART-resistant HIV infected individuals (acquired, secondary resistance), untreated

I_{R1ai}^{U} = ART-resistant HIV infected individuals (transmitted, primary resistance), untreated

I_{R1i}^{T} = ART-resistant HIV infected individuals (transmitted, primary resistance), treated

I_{R1bi}^{U} = ART-resistant HIV infected individuals (transmitted, primary resistance), withdrawn from treatment

where i refers to the stage of infection, $i = 1..11$.

Other values

λ_S = force of infection for ARV-susceptible virus phenotype

λ_R = force of infection for ARV-resistant virus phenotype

N = total model population

Transmission equations

(1) $S_1' = \sigma N_0 \varpi - S_1\left(\lambda_S + \lambda_R + \mu\right)$

(2) $S_2' = \sigma N_0\left(1-\varpi\right) - \mu S_2$

(3) $I_{Si}^{U'} = \lambda_S S + Z I_{Si}^{T} - I_{Si}^{U}\left(\mu + \nu_{Si}^{U} + \gamma_{Si} + \phi_{Si}^{U}\right) \qquad \{i=1\}$

(4) $I_{Si}^{U'} = \phi_{Si-1}^{U} I_{Si-1}^{U} + Z I_{Si}^{T} - I_{Si}^{U}\left(\mu + \nu_{Si}^{U} + \gamma_{Si} + \phi_{Si}^{U}\right) \qquad \{i=2..11\}$

(5) $I_{Si}^{T\prime} = \gamma_{Si} I_{Si}^{U} - I_{Si}^{T}\left(\mu + \nu_{Si}^{T} + f + \kappa + \lambda_{R} + \phi_{Si}^{T} + Z\right) \quad \{i = 1\}$

(6) $I_{Si}^{T\prime} = \gamma_{Si} I_{Si}^{U} + \phi_{Si-1}^{T} I_{Si-1}^{T} - I_{Si}^{T}\left(\mu + \nu_{Si}^{T} + f + \kappa + \lambda_{R} + \phi_{Si}^{T} + Z\right) \quad \{i = 2..11\}$

(7) $I_{Si}^{TF\prime} = fI_{Si}^{T} - I_{Si}^{TF}\left(\mu + \nu_{Si}^{U} + \alpha_{Si} + \kappa_{F} + \phi_{Si}^{TF}\right) \quad \{i = 1\}$

(8) $I_{Si}^{TF\prime} = fI_{Si}^{T} + \phi_{Si-1}^{TF} I_{Si-1}^{TF} - I_{Si}^{TF}\left(\mu + \nu_{Si}^{U} + \alpha_{Si} + \kappa_{F} + \phi_{Si}^{TF}\right) \quad \{i = 2..11\}$

(9) $I_{Si}^{UF\prime} = \alpha_{Si} I_{Si}^{TF} - I_{Si}^{UF}\left(\mu + \nu_{Si}^{U} + \phi_{Si}^{U}\right) \quad \{i = 1\}$

(10) $I_{Si}^{UF\prime} = \alpha_{Si} I_{Si}^{TF} + \phi_{Si-1}^{U} I_{Si-1}^{UF} - I_{Si}^{UF}\left(\mu + \nu_{Si}^{U} + \phi_{Si}^{U}\right) \quad \{i = 2..11\}$

(11) $I_{R2i}^{T}{}' = \left(\kappa + \lambda_{R}\right) I_{Si}^{T} + \kappa_{F} I_{Si}^{TF} - I_{R2i}^{T}\left(\mu + \nu_{Ri}^{T} + \alpha_{Si} + \phi_{Ri}^{T}\right) \quad \{i = 1\}$

(12) $I_{R2i}^{T}{}' = \left(\kappa + \lambda_{R}\right) I_{Si}^{T} + \kappa_{F} I_{Si}^{TF} + \phi_{Ri-1}^{T} I_{R2i-1}^{T} - I_{R2i}^{T}\left(\mu + \nu_{Ri}^{T} + \alpha_{Si} + \phi_{Ri}^{T}\right) \quad \{i = 2..11\}$

(13) $I_{R2i}^{U}{}' = \alpha_{Si} I_{R2i}^{T} - I_{R2i}^{U}\left(\mu + \nu_{Ri}^{U} + \phi_{Ri}^{U}\right) \quad \{i = 1\}$

(14) $I_{R2i}^{U}{}' = \alpha_{Si} I_{R2i}^{T} + \phi_{Ri-1}^{U} I_{R2i-1}^{U} - I_{R2i}^{U}\left(\mu + \nu_{Ri}^{U} + \phi_{Ri}^{U}\right) \quad \{i = 2..11\}$

(15) $I_{R1ai}^{U}{}' = \lambda_{R} S - I_{R1ai}^{U}\left(\mu + \nu_{Ri}^{U} + \gamma_{Ri} + \phi_{Ri}^{U}\right) \quad \{i = 1\}$

(16) $I_{R1ai}^{U}{}' = \phi_{Ri-1}^{U} I_{R1ai-1}^{U} - I_{R1ai}^{U}\left(\mu + \nu_{Ri}^{U} + \gamma_{Ri} + \phi_{Ri}^{U}\right) \quad \{i = 2..11\}$

(17) $I_{R1i}^{T}{}' = \gamma_{Ri} I_{R1ai}^{U} - I_{R1i}^{T}\left(\mu + \nu_{Ri}^{T} + \alpha_{Ri} + \phi_{Ri}^{T}\right) \quad \{i = 1\}$

(18) $I_{R1i}^{T}{}' = \gamma_{Ri} I_{R1ai}^{U} + \phi_{Ri-1}^{T} I_{R1i-1}^{T} - I_{R1i}^{T}\left(\mu + \nu_{Ri}^{T} + \alpha_{Ri} + \phi_{Ri}^{T}\right) \quad \{i = 2..11\}$

(19) $I_{R1bi}^{U}{}' = \alpha_{Ri} I_{R1i}^{T} - I_{R1bi}^{U}\left(\mu + \nu_{Ri}^{U} + \phi_{Ri}^{U}\right) \quad \{i = 1\}$

(20) $I_{R1bi}^{U}{}' = \alpha_{Ri} I_{R1i}^{T} + \phi_{Ri-1}^{U} I_{R1bi-1}^{U} - I_{R1bi}^{U}\left(\mu + \nu_{Ri}^{U} + \phi_{Ri}^{U}\right) \quad \{i = 2..11\}$

where:

$\phi_{x,11}^{y} = 0$

$$\lambda_S = \frac{c_H c_H}{c_H\left(S_1 + I_H\right) + c_A I_A}\left(\sum_{i=1}^{10}\begin{pmatrix}\beta_{Si}^U\left(I_{Si}^U + \iota I_{Si}^{TF} + I_{Si}^{UF}\right) + \\ \beta_{Ri}^U\left[\left(1-\omega_U^2\right)I_{R2i}^U + \left(1-\omega_U^1\right)\left(I_{R1ai}^U + I_{R1bi}^U\right)\right] \\ + \beta_{Ri}^T\left[\left(1-\omega_T^2\right)I_{R2i}^T + \left(1-\omega_T^1\right)I_{R1i}^T\right]\end{pmatrix} + \sum_{i=1}^{11}\beta_{Si}^T I_{Si}^T\right)$$

(21)

$$+\frac{c_A c_H}{c_H\left(S_1 + I_H\right) + c_A I_A}\begin{pmatrix}\beta_{S11}^U\left(I_{S11}^U + \iota I_{S11}^{TF} + I_{S11}^{UF}\right) \\ + \beta_{R11}^U\left[\left(1-\omega_U^2\right)I_{R2,11}^U + \left(1-\omega_U^1\right)\left(I_{R1a11}^U + I_{R1b11}^U\right)\right] \\ + \beta_{R11}^T\left[\left(1-\omega_T^2\right)I_{R2,11}^T + \left(1-\omega_T^1\right)I_{R1,11}^T\right]\end{pmatrix}$$

$$\lambda_R = \frac{c_H c_H}{c_H\left(S_1 + I_H\right) + c_A I_A}\sum_{i=1}^{10}\left(\beta_{Ri}^U\left[\omega_U^2 I_{R2i}^U + \omega_U^1\left(I_{R1ai}^U + I_{R1bi}^U\right)\right] + \beta_{Ri}^T\left(\omega_T^2 I_{R2i}^T + \omega_T^1 I_{R1i}^T\right)\right)$$

(22)

$$+\frac{c_A c_H}{c_H\left(S_1 + I_H\right) + c_A I_A}\left(\beta_{R11}^U\left[\omega_U^2 I_{R2,11}^U + \omega_U^1\left(I_{R1a11}^U + I_{R1b11}^U\right)\right] + \beta_{R11}^T\left(\omega_T^2 I_{R2,11}^T + \omega_T^1 I_{R1,11}^T\right)\right)$$

(23) $I_H = \sum_{i=1}^{10}\left(I_{Si}^U + I_{Si}^{TF} + I_{Si}^{UF} + I_{R2i}^U + I_{R1ai}^U + I_{R1bi}^U + I_{R2i}^T + I_{R1i}^T\right) + \sum_{i=1}^{11} I_{Si}^T$

(24) $I_A = I_{S11}^U + I_{S11}^{TF} + I_{S11}^{UF} + I_{R2,11}^U + I_{R1a11}^U + I_{R1b11}^U + I_{R2,11}^T + I_{R1,11}^T$

I_H is all asymptomatic infected individuals and I_A is all symptomatic infected individuals (i.e. with AIDS). It is assumed that individuals in stage $i = 11$ successfully receiving ART do not have symptoms of AIDS. The forces of infection λ_S and λ_R must balance the number of sexual partnerships within the population because the decrease in sexual activity of AIDS patients mean that there are essentially two sexual activity groups incorporated in the model.

Infectiousness of individuals varies with stage of infection. The model assumes that individuals with primary infection and AIDS (stages 1 and 11, respectively) have a higher degree of infectiousness than individuals in the incubation period (stages 2 to 9) by factor a. For individuals with pre-AIDS (stage 10), it is by factor $a/2$:

$$\beta_{x,i}^y = a\beta_x^y \quad \{i = 1, 11\}$$

$$\beta_{x,i}^y = \beta_x^y \quad \{i = 2..9\}$$

$$\beta_{x,i}^y = \frac{a}{2}\beta_x^y \quad \{i = 10\}$$

$$\beta_{S,i}^T \le \beta_{R,i}^T \le \beta_{R,i}^U \le \beta_{S,i}^U$$

$$\nu_{S,i}^T \le \nu_{R,i}^T \le \nu_{R,i}^U \le \nu_{S,i}^U$$

$$\phi_{S,i}^{T} \le \phi_{R,i}^{T} \le \phi_{R,i}^{U} \le \phi_{S,i}^{U}$$

Table C1 Baseline parameter values used in ART Model 3

Parameter	Definition	Default Value
c_H	Partner change rate for asymptomatic individuals	7 partners per year (increased from 5 partners used in ART Model 1)
c_A	Partner change rate for individuals with AIDS	0.5 partners per year
Z	Rate of withdrawal of ART due to side effects	0.1 year^{-1}
f	Rate of treatment failure (without resistance evolution)	0.1 year^{-1}
μ	Natural death rate	1/35 year^{-1}
β_{S1}^{U}	Transmission probability per partnership from an untreated ART-sensitive HIV infected individual during primary infection	50%
$\beta_{S2..9}^{U}$	Transmission probability per partnership from an untreated ART-sensitive HIV infected individual during the incubation period	2.5%
β_{S10}^{U}	Transmission probability per partnership from an untreated ART-sensitive HIV infected individual during pre-AIDS	25%
β_{S11}^{U}	Transmission probability per partnership from an untreated ART-sensitive HIV infected individual during AIDS	50%
$1/\phi_{S1}^{U}$	Duration of primary infection stage for an untreated ART-sensitive HIV infected individual	1.5 months
$1/\phi_{S2..9}^{U}$	Duration of incubation stage (8 years in total, from stages 2 to 9) for an untreated ART-sensitive HIV infected individual	1 year
$1/\phi_{S10}^{U}$	Duration of pre-AIDS stage for an untreated ART-sensitive HIV infected individual	1 year
$\nu_{x1..9}^{y}$	HIV death rate for individuals in primary infection or incubation stages, virus type x = S or R and treatment status y = U or T	0 year^{-1}
ν_{S10}^{U}	HIV death rate for an untreated ART-sensitive HIV infected individual during pre-AIDS	0.02 year^{-1}
ν_{S11}^{U}	HIV death rate for an untreated ART-sensitive HIV infected individual during AIDS	1 year^{-1}
$\alpha_{S,10}$, $\alpha_{S,11}$ $\alpha_{R,10}$	Rate of withdrawal of ineffective treatment (primary resistance or other treatment failure), pre-AIDS and AIDS	0.5 year^{-1}
$\alpha_{R,11}$	Rate of withdrawal of ineffective treatment (primary resistance), AIDS patients	2 year^{-1}
$\phi_{S1..11}^{T}$	Infection progression rate for treated individuals without treatment failure (=0.25 $\phi_{S1..11}^{U}$)	ϕ_{S1}^{U} = 2 year^{-1} $\phi_{S2..10}^{U}$ = 0.25 year^{-1} ϕ_{S11}^{U} = 0 year^{-1}
$\phi_{R1..11}^{T}$	Infection progression rate for treated individuals infected with ART-resistant HIV (=0.50 $\phi_{S1..11}^{U}$)	ϕ_{R1}^{T} = 4 year^{-1} $\phi_{R2..10}^{T}$ = 0.50 year^{-1} ϕ_{R11}^{T} = 0 year^{-1}
$\phi_{R1..11}^{U}$	Infection progression rate for untreated individuals infected with ART-resistant HIV (=0.95 $\phi_{S1..11}^{U}$)	ϕ_{R1}^{U} = 7.6 year^{-1} $\phi_{R2..10}^{U}$ = 0.95 year^{-1} ϕ_{R11}^{U} = 0 year^{-1}
$\beta_{S1..11}^{T}$	Transmission probability per partnership for treated individuals without treatment failure (=0.02 $\beta_{S1..11}^{U}$)	β_{S1}^{T}=1%, $\beta_{S2..9}^{T}$=0.05% β_{S10}^{T} 0.5%, β_{S11}^{T}=1%

Parameter	Definition	Default Value
$\beta^{T}_{R1..11}$	Transmission probability per partnership for treated individuals infected with ART-resistant HIV (=0.90 $\beta^{U}_{S1..11}$)	β^{T}_{R1}=45%, $\beta^{T}_{R2..9}$=2.3% β^{T}_{R10} 22.5%, β^{T}_{R11}=45%
$\beta^{U}_{R1..11}$	Transmission probability per partnership for untreated individuals infected with ART-resistant HIV (=0.95 $\beta^{U}_{S1..11}$)	β^{U}_{R1}=47.5%, $\beta^{U}_{R2..9}$=2.4% β^{U}_{R10} 23.8%, β^{U}_{R11}=47.5%
ν^{T}_{S10}	HIV death rate for treated individuals without treatment failure (=0.25 ν^{U}_{S10})	0.005 year^{-1}
ν^{T}_{S11}	HIV death rate for treated individuals without treatment failure (=0.25 ν^{U}_{S11})	0.25 year^{-1}
ν^{T}_{R10}	HIV death rate for treated individuals infected with ART-resistant HIV (=0.50 ν^{U}_{S10})	0.01 year^{-1}
ν^{T}_{R11}	HIV death rate for treated individuals infected with ART-resistant HIV (=0.50 ν^{U}_{S11})	0.50 year^{-1}
ν^{U}_{R10}	HIV death rate for untreated individuals infected with ART-resistant HIV (=0.95 ν^{U}_{S10})	0.019 year^{-1}
ν^{U}_{R11}	HIV death rate for untreated individuals infected with ART-resistant HIV (=0.95 ν^{U}_{S11})	0.95 year^{-1}
γ_{S1}, γ_{R1}	Treatment uptake rate for individuals with primary infection	0 year^{-1} (but varied in model analysis)
$\gamma_{S2..9}$, $\gamma_{R2..9}$	Treatment uptake rate for individuals in HIV incubation stage	0 year^{-1} (but varied in model analysis)
γ_{S10}, γ_{R10}	Treatment uptake rate for individuals with pre-AIDS	12 year^{-1} (but varied in model analysis)
γ_{S11}, γ_{R11}	Treatment uptake rate for individuals with AIDS	12 year^{-1} (but varied in model analysis)

C.2 ART Model 4 – heterogeneous sexual activity

ART Model 4 incorporates several sexual activity classes and therefore the cruder distinction of "at risk" and "no risk" susceptibles individuals used in previous models is no longer required.

State Variables

For individuals in sexual activity class i where $\{i = 1..4\}$:

S_i = susceptible individuals

I^{U}_{Si} = ART-sensitive HIV infected individuals, untreated

I^{T}_{Si} = ART-sensitive HIV infected individuals, treated

I^{TF}_{Si} = ART-sensitive HIV infected individuals, treated but viral rebound

I^{UF}_{Si} = ART-sensitive HIV infected individuals, suffered viral rebound, withdrawn from treatment

I^{T}_{R2i} = ART-resistant HIV infected individuals, treated

I^{U}_{R2i} = ART-resistant HIV infected individuals, untreated

I^{U}_{R1ai} = ART-resistant HIV infected individuals (transmitted resistance), untreated

I^{T}_{R1i} = ART-resistant HIV infected individuals (transmitted resistance), treated

I^{U}_{R1bi} = ART-resistant HIV infected individuals (transmitted resistance), withdrawn from treatment

λ_S = force of infection for ART-sensitive virus phenotype

λ_R = force of infection for ART-resistant virus phenotype (and force of (super)infection for ART-resistant virus phenotype, infecting an HIV wild type infected individual under treatment pressure)

Other values

λ_{Si} = force of infection for ART-sensitive virus phenotype

λ_{Ri} = force of infection for ART-resistant virus phenotype

N_i = total in sexual activity group i

Transmission equations

(25) $S_i' = \theta_i \sigma N_0 - S_i\left(\lambda_{Si} + \lambda_{Ri} + \mu\right)$

(26) $I^{U\prime}_{Si} = \lambda_{Si} S_i - I^{U}_{Si}(\mu + \nu^{U}_{S} + \gamma_S)$

(27) $I^{T\prime}_{Si} = \gamma_S I^{U}_{Si} - I^{T}_{Si}\left(\mu + \nu^{T}_{S} + f + \kappa + \lambda_{Ri}\right)$

(28) $I^{TF\prime}_{Si} = f I^{T}_{Si} - I^{TF}_{Si}\left(\mu + \nu^{U}_{S} + \alpha_S + \kappa_F\right)$

(29) $I^{UF\prime}_{Si} = \alpha_S I^{TF}_{Si} - I^{UF}_{Si}\left(\mu + \nu^{U}_{S}\right)$

(30) $I^{T}_{R2i}{}' = I^{T}_{Si}\left(\kappa + \lambda_{Ri}\right) + \kappa_F I^{TF}_{Si} - I^{T}_{R2i}\left(\mu + \nu^{T}_{R} + \alpha_S\right)$

(31) $I^{U}_{R2i}{}' = \alpha_S I^{T}_{R2i} - I^{U}_{R2i}\left(\mu + \nu^{U}_{R}\right)$

(32) $I^{Ua\prime}_{R1i} = \lambda_{Ri} S_i - I^{Ua}_{R1i}\left(\mu + \nu^{U}_{R} + \gamma_R\right)$

(33) $I^{T}_{R1i}{}' = \gamma_R I^{U}_{R1ai} - I^{T}_{R1i}\left(\mu + \nu^{T}_{R} + \alpha_R\right)$

(34) $I^{Ub\prime}_{R1i} = \alpha_R I^{T}_{R1i} - I^{Ub}_{R1i}\left(\mu + \nu^{U}_{R}\right)$

(35) $N_i = S_i + I^{U}_{Si} + I^{T}_{Si} + I^{TF}_{Si} + I^{UF}_{Si} + I^{T}_{R2i} + I^{U}_{R2i} + I^{Ua}_{R1i} + I^{T}_{R1i} + I^{Ub}_{R1i}$

$$(36)\ \lambda_{Si} = c_i \sum_i \frac{\rho_{ik}}{N_k} \begin{pmatrix} \beta_S^U \left(I_{Si}^U + I_{Si}^{UF} + \iota I_{Si}^{TF}\right) + \beta_S^T I_{Si}^T + \beta_R^T \left(\left(1-\omega_2^T\right) I_{R2i}^T + \left(1-\omega_1^U\right) I_{R1i}^T\right) \\ + \beta_R^U \left(\left(1-\omega_2^U\right) I_{R2i}^U + \left(1-\omega_1^U\right)\left(I_{R1i}^{Ua} + I_{R1i}^{Ub}\right)\right) \end{pmatrix}$$

$$(37)\ \lambda_{Ri} = c_i \sum_i \frac{\rho_{ik}}{N_k} \left(\beta_R^T \left(\omega_2^T I_{R2i}^T + \omega_1^T I_{R1i}^T\right) + \beta_R^U \left(\omega_2^U I_{R2i}^U + \omega_1^U \left(I_{R1i}^{Ua} + I_{R1i}^{Ub}\right)\right)\right)$$

Mixing matrix definition

ρ_{ik} is a mixing matrix, the elements ik of which are the probability that an individual in sexual activity class i will form a partnership with a member of sexual activity class k. The value of ρ_{ik} depends on the pattern of mixing which could vary from fully assortative, where partnerships only form within the same activity class, to random, where partnerships form randomly between different activity classes (equation 37). This is determined by the value of ε. $\varepsilon = 0$ denotes random mixing whereas $\varepsilon = 1$ denotes fully assortative mixing.

$$(38)\ \rho_{ik} = \varepsilon \delta_{lm} + (1-\varepsilon) \frac{c_k N_k}{\sum_k c_k N_k}$$

where $\delta_{lm} = 1$ when $i = j$ and $\delta_{lm} = 0$ when $i \neq j$.

Table C2 Baseline parameter values used in ART Model 4.

Parameter	Definition	Default Value
c_i	Rate of partner change per year for individuals in sexual activity class i	40,10,2,0.5 partners per year (i = 1,2,3,4 respectively)
θ_i	Proportion recruited into sexual activity class i	8%,10%,26%,56% (i = 1,2,3,4 respectively)
ε	Pattern of mixing (0= fully assortative, 1= random)	0.0 or 0.5

All other parameter values are the same as Table 2.1, Chapter 2.

Table C3 Parameter values varied for relative fitness of ART-resistant variants, ART Model 4.

Relative fitness	Relative transmission probability of ART-resistant compared to ART-sensitive untreated infections	Probability that untreated individuals with mixed infections transmit ART-resistant virus, ω_2^U
99%	$\beta_R^U = 0.99\beta_S^U$	49.5%
100%	$\beta_R^U = \beta_S^U$	50.0%
101%	$\beta_R^U = 1.01\beta_S^U$	50.5%

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