

MATHEMATICAL MODELLING IN THE RESPONSE TO THE HIV/AIDS EPIDEMIC IN SOUTHERN AFRICA

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Declaration

I hereby declare that, notwithstanding specific comments on contributions made in each chapter, the work in this thesis submitted for examination for the Doctor of Philosophy degree is my own work.

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Abstract

In the third decade of the HIV/AIDS pandemic, ten thousand people are estimated to be infected every day, mostly in southern Africa. An international response has gained momentum in recent years and billions of dollars have been donated to a wide range of interventions aimed at changing sexual behaviour and delivering life-preserving treatment for those already infected. In this thesis, mathematical models are developed to: (i) help monitor the epidemic and recognise where reductions in risk behaviour have led to downturns in HIV prevalence; and (ii), provide insights on how interventions – both to change sexual behaviour and deliver treatment – can be optimised. Throughout, the aim is to formulate specific recommendations for decision-makers and health professionals planning the next phase of struggle against HIV.

By comparing observed and model epidemic trends, it was found that recent reductions in prevalence in Zimbabwe, parts of urban Kenya and Haiti, could be associated with changes in sexual behaviour. A method was developed and tested that could be used in the future to estimate incidence using serial measures of prevalence in general population surveys.

The effect of interventions focussed on delaying first sex and reducing contact between young women and older men is dependent on the way in which these changes are accommodated by existing behavioural patterns. The impact of voluntary testing services relies upon high uptake and effective counselling leading to long-lasting behavioural changes among the young, the uninfected and those most at risk. Although a recent trial did not find evidence for an intervention aimed at high-risk group having a large population level impact, modelling suggests that insufficient time was allowed for the effect to develop. Analysis of a model of treatment delivery in Africa highlights the importance of frequent HIV testing, efficient referral and intensive monitoring in determining the success of such programmes.

Dedication

For Katharine and Elian, and everything after zero.

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Chapter 1: Introduction

1.1 Background

In the summer of 1981, the first signs of Acquired Immunodeficiency Syndrome (AIDS) among homosexual men came to light [1]. The case report then was of five young men in California. By 2006 [2], 39.5 million people around the world were estimated to be living with the causative Human Immunodeficiency Virus (HIV) infection [3-5], with 4.3 million newly infected that year. It follows that a crude estimate of the number of new infections arising from each prevalent case is approximately 1.1, indicating that at the global level, the epidemic could still be expanding.

However, international agencies and epidemiologists remain convinced that if the few regional successes were repeated on a wider scale, the pandemic could be brought under control [6, 7]. In 2002, it was predicted that, with seemingly realistic levels of intervention success, and assuming that the required \$27bn would be forthcoming, the number of new infections between 2001 and 2010 could be reduced by two-thirds, equivalent to 30 million infections averted. In 2006, new models indicated that half of the potential infections between 2005 and 2015 could be averted with an expanded response, at a cost of \$122bn [7]. Whilst providing a cause for optimism, these two studies also tell another story – that for each days delay in fully implementing prevention interventions many more people unfortunately acquire the infection and the cost of turning back the epidemic increases.

In the last years, combination antiretroviral therapy, which is capable of greatly prolonging survival of those infected with HIV [8], has started to become widely available through public health services in most parts of the world [9]. However, relying on this measure – reducing mortality in the short-term, but accumulating demand for therapy in the future – does not constitute a sufficient response [10]. Preventing new infections will have to be at the centre of all regional, national and international responses to the epidemic if the demand on the frailest health-care systems and economies is not going to rise inexorably. Yet finding effective and feasible mechanisms through which individuals will put themselves and others in the community at less risk of infection has been difficult. Although the history of the epidemic is dotted with isolated success stories, no ‘magic bullet’ has been found, and, most would agree, behaviour change programmes are failing in the battle to persuade many people to change their behaviours.

This thesis is about the recent developments in the HIV epidemic and our response to it. Specifically, how to monitor the course the epidemic, projecting the impact of interventions and identifying ways in which programmes could be optimised to alleviate further infection and mortality. Data from a wide variety of sources are

collated and synthesised in mathematical models representing the complicated epidemiological processes to provide new methods and insights, as well as to identify areas of uncertainty and for further research. Throughout, the emphasis is on Africa, which has so far borne the brunt of the epidemic.

In this introduction I describe the conditions that have allowed Africa to be so heavily affected by HIV, and the methods used to monitor the trends in the epidemic. I then describe some of the success stories in reducing HIV spread within communities. The epidemic has also been greatly altered by the international community's support of antiretroviral treatments, which I discuss. This has opened up the way to new interventions such as expanded testing and counselling which are described along with the prospects for new biomedical intervention technologies. Throughout the HIV epidemic mathematical models have been used to inform our understanding and guide policy. Mathematical models are a central tool within this thesis and the history of their use in the HIV field is briefly described. Lastly, the Manicaland HIV Prevention Study, which has been a major source of detailed information on patterns of behaviour and HIV, is detailed.

1.2 HIV in Africa

The global prevalence of HIV is 0.8% (37.2 million adults infected divided by world adult population 4700 million [11]), but there is great heterogeneity in the distribution of infection. Sub-Saharan Africa, with only 10% of the global population, is home to 63% of all those infected and 72% of the children infected. It is also where 72% of AIDS deaths occur and where 80% of AIDS-orphans are left [2, 12]. In Africa, the HIV epidemic is thought to have claimed more than twenty million lives so far, including two million in the last year [2]. After an initial focus on men, most new infections are now among women [2], with the further consequence that more children than ever are being maternally orphaned; currently 25-30 million children are estimated to be orphans of the HIV/AIDS epidemic [2, 13].

In February 2000, the situation in Africa was considered so severe that it was raised at the United Nations Security Council [14], the part of the organisation charged with surveillance of international peace and security. The recognition that, in the years preceding that meeting, HIV/AIDS had killed ten times as many people as all the on-going conflicts in Africa, prompted the council, led by Al Gore (then US vice President) to state that the epidemic was itself a serious threat to peace and stability [14].

Within Africa, the furthest developed epidemic is in the east (including Uganda and Kenya) with an estimated average prevalence of between 15 and 20% in 1990, reducing slightly to between 10 and 15% by 2002 [15]. Countries in central and western Africa have supported lower prevalence epidemics, in most cases less than 5% [2, 15]. However, the worst epidemic has been observed in southern Africa, where HIV prevalence rose from 5% in 1990 to 25% ten years later [15]. Zimbabwe, a country that had typified this region with 30% HIV prevalence in 2000, now stands apart, showing a decline in prevalence to 24% [16, 17].

An important scientific research question has been why there is such heterogeneity in the prevalence of HIV globally and across Africa.

1.3 A Perfect Storm

There are thought to be two main reasons for the much greater spread of HIV in southern and eastern Africa that have combined to create a 'perfect storm' [18]; extra-marital sexual practices and low rates of male circumcision.

In Africa it is common for men to have several sexual partners at the same time, that may either be called wives or classified as extra-marital partners [19-21]. This so-called concurrency allows faster transmission of HIV than serial monogamy (where the same number of partnerships are formed over time, but such that they do not overlap) because, from the point of view of the virus, it can spread between contacts without waiting for the partner to change. This subtle difference in sexual behaviour means that broad indicators of sexual behaviour such as the average number of partners, while being important variables in the spread of infection, do not explain the differences in the global distribution of infection [21, 22]. Mathematical modelling confirms the importance of this effect, with one model estimating that when half of the partnerships in a population are concurrent, the size of the epidemic after five years is ten-times as large as when everyone practices sequential monogamy [23]. This effect will probably be augmented by the chance of transmission being highest immediately after infection. If partnerships did not overlap, this most dangerous period would normally pass whilst the newly infected individual remains in the partnership with someone already infected. The 'zero-grazing' policy in Uganda, which sought specifically to discourage this practice of concurrent partnerships, has been credited for the dramatic downturn in prevalence in the early 1990s [24].

When examined in this way, reports of sexual behaviour from a wide range of countries help explain why the epidemic rages in Africa and not (so far) in Asia [20]. For instance, in Lesotho, 55% of men reported having more than one regular sexual

partner at the same time (including spouses) compared to 3% of men in Thailand, and 2% of men in Sri Lanka and Singapore [19].

In contrast, differences in sexual behaviour do not seem to explain why Western Africa has been saved from the worst epidemics in the continent [25]. Instead, the key factor for the lower epidemic levels in these parts may be the high rates of male circumcision [26, 27]. A large body of literature has built up that suggests that circumcision can decrease the chance that a man is infected with HIV by about 40-60% [28, 29]. Recently, three randomised control trials in South Africa, Kenya and Uganda reported a c.60% reduction in the risk of HIV acquisition for men [30-32]. The effect of circumcision on the probability of transmission is not clear and another trial in Uganda seeking to examine this was stopped early because of a higher rate of acquisition in the partners of those circumcised, seemingly due to men resuming sexual activity before their wound had fully healed [33]. Nonetheless, observational studies that find partners of circumcised men to be less likely infected than others [34-36] are consistent with a reduction in transmission after the wound has healed.

1.4 Why is HIV still spreading?

Some diseases, like small pox and SARS have been successfully controlled, so why has the global spread of HIV not been curbed since it first appeared almost thirty years ago? It has been suggested that there could be a range of epidemiological and socio-cultural reasons why HIV has proved particularly difficult to control:

- 1- Asymptomatic transmission. Without regular testing of everyone in the population, public health interventions to prevent transmission of an infectious agent rely on the appearance of symptoms to identify those infected. With symptoms, individuals may tend naturally to mix less in the population, or public health programmes could quarantine such individuals until the chance that they infect someone passes. The timing of symptoms and the timing of infectiousness may overlap considerably, so that an efficient quarantine programme can isolate individuals for most of the time for which they are infectious. The degree of overlap, together with the basic reproductive number R_0 (a measure of the tendency for an infectious agent to spread in a particular population [37]), characterise the chance that infections can be controlled [38]. For example, individuals with SARS typically developed symptoms as soon as they became infectious so that (together with a low tendency for epidemic spread) the epidemic could be successfully controlled with quarantining measures. HIV, by contrast, leaves individuals transmitting

the virus for on average ten years, unaware that they are infected. When symptoms develop, there may be a “self-quarantining” effect, whereby ill individuals become less likely to form new sexual partnerships, but by this time, it is probably too late. Thus, even though HIV and SARS have comparably low basic reproductive numbers (approximately 2-7 [38]), the way that transmission of HIV is ‘silent’ has helped it to evade control.

- 2- Community-level risk. Sexual contact is the major route of transmission for most new infections in the regions worst hit by the epidemic [2]. Unlike the forms of contact that mediate transmission of other diseases (such as casual contact, or living in the same building), or for HIV (such as injecting drug users sharing needles [39]), sexual contact is determined by a large number of cultural and social practices that can be resistant to change. A sexual contact also (normally) requires a specific partner to consent [40, 41] so that a successful intervention has not only to change the intentions of individuals, but the social norms that prevail across the community. In addition, the continuing spread of HIV may be supported by only a small fraction of the population [42] and the epidemic will persist even if most other individuals reduce their sexual risk behaviour. This makes it likely that programmes with insufficient coverage or capacity will fail to make a substantial impact.
- 3- Poverty and priorities. Although there are other proximate biological and behavioural reasons why the spread of HIV has gone as far as it has in Africa, a key underlying factor must be poverty. Poverty, or at least disparity in wealth, is thought to support sex work and transactional relationships, which are recognised to play such an important role in facilitating HIV spread [40, 41]. However, poverty may also make individuals resistant to changing their sexual behaviour, because other issues are more pressing. As the President of Uganda has written, “In countries like ours, where a mother often has to walk 20 miles to get an aspirin for her sick child or five miles to get any water at all, the question of getting a constant supply of condoms may never be resolved” [43].

1.5 How is the HIV epidemic monitored?

It was clear from early in the epidemic that relying on reported AIDS deaths to monitor the epidemic could be misleading. The coverage of death-reporting systems were not complete, it was possible that the cause of death could be given as the proximate condition instead of HIV/AIDS, the long incubation period from infection to death would obscure recent trends in the epidemic, and there would be danger that

identifying cases would lead to the stigmatisation of their families [44, 45]. Prevalence of infection (fraction of population living with the virus) is a better measure because it relates to the current scale of the epidemic, but it requires HIV testing in a chosen population. Women attending ante-natal clinics (ANCs) were chosen as a convenient sample in which to measure HIV prevalence (blood was already taken to test for syphilis). Routine testing minimises selection biases [45] and anonymity was retained by unlinking test results from other personal data.

There are several issues to consider when using such data to make estimates and projections for the course of the epidemic. First, the sample is only of women and it is not always clear how this relates to prevalence among men. Second, the women being tested are pregnant and have been able and chosen to attend an ANC, which could introduce several conflicting biases. On the one hand, the women who get pregnant may have been having more unprotected sex, and may therefore be more likely to be infected than others. This bias probably operates most at young ages, with pregnancy indicating early sexual activity, but it could also act at older ages, with the women that are able to use modern methods of contraception being the most likely to adopt practices to avoid the risk of infection. On the other hand, bacterial sexually transmitted infections (STIs) and HIV lead to sub-fertility [46], so pregnancy at older ages could be a marker for women that have not been at high risk for acquiring infection. This bias could increase over time, as more women reach advanced stages of HIV-related diseases when fertility is lowest [47]. But if AIDS progressively removes those individuals that spread bacterial STI, the overall change in fertility over time may be small [48]. Depending on which of these factors is the most powerful, the estimate of prevalence could either be too high or too low relative to prevalence among women of reproductive ages in the general population. The balance is likely to depend on the background fertility level in the population and change over time as the epidemic reaches women with lower risk behaviour [48]. Changes in age at first sex could also introduce artificial changes in prevalence seen at the ANC [49] and the fertility transition, which is ongoing in some parts of sub-Saharan Africa, could add further layers of shifting biases which are hard to determine.

It has been possible to directly compare prevalence at ANCs and prevalence in the general population in a few settings, which has been used to assess the usefulness of ANC in sentinel surveillance. Generally, ANC estimates of prevalence are lower than comparable estimates among women in the general population, but, given that men generally have a lower prevalence in established epidemics [50], ANC estimates may be taken as representative of the general population. In high-

fertility populations, where most women are exposed to unprotected sexual contact, it seems that sub-fertility due to HIV infection depresses prevalence in ANC clinics, by, on average, 25% [46]. In populations where contraceptive use is higher, such as Zambia [51] and Zimbabwe [52], the bias is smaller, possibly because the sub-fertility effects are counteracted by pregnancy correlating with riskier sexual behaviour.

A further problem in interpreting ANC data is that there is no definite catchment population. Given the strong urban-rural gradient in infection, there is a danger that mobile individuals could contaminate estimates, if, for example, urban-living women go their rural home during pregnancy [52]. Also, as the surveillance system has been extended, more remote sites have been added in rural areas, which have had the result of bringing down average prevalence estimates in recent years [53]. When examining trends in prevalence over time, it is essential to only consider data from sites that have been sampled continuously.

Another important disadvantage in using prevalence data to monitor the course of the epidemic is that secular trends in prevalence can be generated without any change in individual risk behaviour. Those at most risk of acquiring HIV will be infected first so that HIV incidence will quickly increase, but it will then decrease as new infections occur more slowly among those at lower risk. This means that prevalence, which is determined by the balance between new infections and mortality among those infected, can decrease in a mature epidemic as part of the internal “natural dynamics” [54]. Thus, when prevalence declines are observed, apart from checking that the trend is valid in a statistical sense, it should also be checked whether it is valid in an epidemiological sense. One way to do this is to use a model of HIV transmission model to test whether the observed decline could be consistent with behaviour staying constant [54, 55]. In Chapter 2, this method is extended and applied to recently reported prevalence declines in Zimbabwe, Kenya and Haiti.

Given the potential biases in the data and the way in which trends can be spuriously generated by endogenous epidemiological processes, it is important to simultaneously monitor trends in behaviour, especially when there is a suggestion that prevalence has declined. This has been advocated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), as “second generation surveillance” [56]. Serial measures of a range of behaviour indicators also allows changes in incidence to be attributed to particular types of behaviour change, but probably not to distinct intervention [57, 58].

For the official UNAIDS estimates, time-series of prevalence at ANCs are used to fit four-parameters of an epidemic model that estimates the associated changes in incidence [59]. The model is usually fit to data aggregated by urban or

rural parts of one country. Although the model is semi-mechanistic (meaning that its description of the epidemic is partly based on realistic assumptions, and partly on features chosen for analytic convenience), the model can also be used to make short-term predictions. The Epidemic Projection Package (EPP) implements this model and is distributed to national level surveillance experts. From the model fit, the number of people currently infected and the number newly infected each year can be calculated but estimates of past and future mortality rates and other key demographic and economic indicators are estimated using an additional piece of software called the Spectrum Projection Package (Futures Group) [60]. This program imports the EPP epidemic curve (prevalence over time) and sets it against its own demographic cohort model, distributing the number of cases by age and gender according to fixed templates based on aggregated observational data [60].

In recent years, demographic and health surveys (DHS) have been extended to incorporate HIV testing ('DHS+') [61]. The key advantages to such a measurement, compared to ANC estimates, are that they have better geographical representation and they include non-pregnant women and men. Prevalence estimates from the DHS+ have tended to be substantially lower than the UNAIDS estimates based on ANC data [62] but this does not necessarily mean that the scale of the epidemic has been over-stated. The disadvantage of the DHS+ prevalence estimates, and the probable reason why the derived estimates are lower, is that for people to be included in the survey they have to be found and agree to participate. For instance, mobile people and those with unusual living arrangements (e.g. live in hostels or army posts) are not typically included in the DHS+ sample, although it is expected that prevalence amongst them would be higher than average. Non-response in the DHS surveys is also substantial, with 25-40% of those eligible not being tested [62]. Although it is impossible to know how HIV prevalence is correlated with non-response, early studies have indicated that those who chose not to respond were more likely to be infected than others [44]. In contrast, ANCs in Africa are attended by the vast majority of women (including those who are mobile or in unusual living arrangements), and HIV testing is routine so there is very little non-response. There is no gold standard for population level estimates with which to compare these alternative methods. However, given the extreme difficulties in interpreting ANC prevalence data, the DHS+ is probably more useful for assessing the current scale of the epidemic. Future studies will better inform how non-response might be related to infection and then correction procedures can be adopted. In the next rounds of the DHS+, new efforts could be also be made to improve coverage of high-risk populations and improve response rates. Despite the usefulness of the DHS+ data,

ANC data should continue to be collected because long time-series will be the most important source of information for measuring epidemic trends.

In the last few years, assays have been developed that can discriminate recently acquired prevalent infections from older ones, which could be used to make an estimate of HIV incidence [63]. Incidence (the rate at which new infections arise among uninfected individuals) would be more useful for monitoring epidemic trends, identifying risk groups and making comparisons between populations. The assay which has so far received the greatest attention and been tested in a variety of settings is the BED capture enzyme immunoassay [64], which identifies new infections by measuring the proportion of a type of immunoglobulin that is HIV antibody, which increases with time since seroconversion. This relies on good knowledge of how fast that proportion changes over time since infection [65]. In a validation exercise, BED-derived incidence estimates were in close agreement with cohort estimates, indicating that this method could be a useful surveillance tool [65]. However, that test was for a population in Europe; in developing countries where similar studies have been done, BED-derived estimates of incidence are substantially higher than other estimates of incidence [66]. The reason for the error is probably to do with old infections being incorrectly classified as new infections by the test, because in African populations, the proportion of HIV antibody can get very low at advanced stages of infection [66]. Nonetheless, calibration may be possible with high quality clinical data.

In Chapter 3, other methods for estimating HIV incidence are developed and tested. These methods could take advantage of the DHS+ sero-surveys, which will be repeated in the same population every five years. By decomposing the observed changes in prevalence between the sero-surveys into the contribution of new infections and mortality [67-69], HIV incidence can be estimated. By validating these methods with data simulated in a mathematical model and actual data collected in African cohort studies, it is hoped that these methods could confidently be used with data from future rounds of DHS+ surveys to supplement the existing surveillance tools.

HIV surveillance has equipped public health professionals with the information required to mount a response to the epidemic. Surveillance data has also been used to monitor the effects of interventions [70]. This has provided powerful evidence of a number of intervention "success stories", which have been influential in setting the international agenda for action against HIV/AIDS.

1.6 The First Success Story – Thailand

In Thailand, surveillance systems were quickly set up after pockets of infection among injecting drug users were discovered in 1988. They recorded a sharp rise in prevalence among sex workers from 3.1% in 1989 to 15.2% in 1991 and a simultaneous increase in prevalence among young men recruited to the military, from 0.5% to 3% [71]. Men who have sex with sex workers and also have steady girlfriends or wives form a bridge between the small high prevalence sex worker population and the large low-risk general population [72]. Targeting sex worker and their clients was therefore a quickly recognised priority.

Almost as soon as the epidemic in brothel-based sex workers was detected, a programme to enforce condom use was piloted in one region (Ratchaburi) [71]. The rationale was that brothels that required condom use would lose business to others that did not, generating an economic disincentive to safer sex practices. The plan was to make all brothels require condoms with financial penalties for those that failed to do so, tipping the economic scale in the opposite direction. The pilot study successfully reduced local rates of sexually transmitted infections (STIs) and the programme was unrolled nationally in 1991 together with a package of measures that promoted and distributed condoms and legislature to maintain high production standards for condoms. A year later, the fraction of female sex workers that report using a condom with the most recent partner exceeded 90% (and has since increased to more than 95%) [71]. At the national level, the number of men reporting sexually transmitted diseases dropped substantially between 1989 and 1994.

Further evidence came from monitoring recruitment to the army, which occurs via a lottery of healthy twenty-one year-old men and involves an HIV test and a face-to-face interview. This provides regularly-spaced random samples of young men, which are likely to be directly comparable over time and representative of the population from which they came. Since prevalence among young people is a good proxy for incidence, changes in these samples can be confidently attributed to regional trends in risk. Among recruits from northern regions, between 1991 and 1995, prevalence reduced by about half (from 10.4 – 12.5% in 1991 to 6.7-6.8% in 1994) [73], and by 1998, prevalence fell by more than half again, to 2.4% [74]. Reporting of the most significant risk behaviours also declined sharply; the fraction that said they had visited a sex worker in the previous year fell from 57% in 1991 to 24% in 1994, and the fraction that reported using a condom on the last visit to a sex worker increased from 61% to 93%. Interestingly, although there remained an excess risk of infection associated with unprotected sex with a sex worker, this differential

reduced over time, indicating that contact with sex workers got less risky, potentially as prevalence amongst them declined.

A programme in Cambodia, following in Thailand's footsteps, may also have been successful, although the evidence is much less clear [75].

1.7 The Ugandan Success Story

The first story of behaviour change turning the tide on a generalised epidemic came from Uganda. At the start of the 1990s, HIV prevalence in most African countries was low [2], but almost one in three women attending ante-natal clinics in Kampala, the capital of Uganda, were infected [76]. The situation was almost as bad in the country's other urban centres, where prevalence peaked in 1991 and 1992 at 18% (median) and was rather less severe in rural areas where the highest prevalence was 12% in 1994 [76]. For many years a civil war had disrupted normal life, exacerbated poverty and driven migration that has scattered families around the country, often separating children from their families [77].

The president, then and now, Mr Yoweri Museveni, is widely credited with acting promptly and responsibly in the face of this new humanitarian crisis. In 1986 he established the National AIDS Control Program (NACP), which was the first of its kind in Africa, and began a national response to the epidemic that is thought to have been open, multilateral and resourced with strong political leaders at all levels [77, 78]. The 'zero-grazing' campaign is widely regarded as the most significant action of NACP [77]. In the form of advertisements on the radio and on poster bill-boards, the message was relayed that men should not have more than one sexual partner at the same time. The unusual choice of wording was intentionally humorous, recalling how an efficient farmer should graze his livestock exclusively in one paddock, and designed to catch the eye of this largely agricultural population. The practice of sustaining long-term extra-marital partnerships had been wide-spread, with 36% of men in 1989 reporting having had such a partner in the last year [24]. Other initiatives focussed on persuading young people to delay sexual debut, and creating magazines such as *Straight Talk* and *Young Talk*. Condom distribution was not initially a focus of the NACP approach, but in 1991 a policy of "quiet promotion and responsible use of condoms" was begun [77]. The distributions of condoms thereafter rocketed, from 10 million procured in 1994 to 30 million in 1997 and then 120 million in 2003 [79].

By the 1995 demographic and health survey, a dramatic change in sexual behaviour was apparent [24, 80]. Three types of behaviour change stood out:

1. Young people reported that they had, on average, started sex two years later;
2. 60% fewer men reported that they had had a casual partner in the last year (apparently, this was incorrectly reported as 9% in the first analysis [80]);
3. More men (from 5% to 28%) and women (from 0% to 20%) reported having used condoms with a non-regular partner in the last year.

These three elements have come to be summarised as 'ABC', for Abstinence, Being faithful and using Condoms.

Throughout the 1990's, ANC prevalence estimates show a sustained decline [76] and by the year 2000, prevalence in Kampala was just over 10%. In urban and rural centres, average prevalence had reduced by more than half. Despite the large prevalence reductions, there remained some doubt as to whether it could be due to the rising toll of AIDS deaths rather than to a reduction in incidence. Mathematical simulations confirmed that the prevalence decline was unlikely to completely attributable to AIDS deaths and that it could be associated with changes in sexual behaviour [54, 55]. Direct incidence measures in a rural community-based cohort between 1989 and 1999 confirm a sustained decline in incidence throughout this period [81]. Further modelling work has compared the total effect of the behavioural changes to that of an HIV vaccine that was 80% effective [24].

Identifying the behavioural changes that underlie the reduction in risk is essential if the success of Uganda is to be repeated elsewhere [24, 78] and the relative contributions of the three types of behaviour change has been hotly debated [82]. Re-analyses have suggested that the contribution of increased condom use may be low, on the basis that incidence probably decreased before condom use distribution increased, and that the level of condom use after the prevalence decline is comparable with levels in other countries with growing or stable epidemics [24]. The number of men and women with a casual partner and the fraction of young men who have started sex, on the other hand, dropped to much lower levels than observed in neighbouring countries. The stable fertility rate since the 1980s [77] indicates that women are exposed to the same number of unprotected sexual acts, which also suggests that condom use did not change substantially, even though condom distribution and reports of condom use did. However, even if increased condom use did not underlie the initial change in risk, it may have played a substantial role in sustaining and augmenting other types of risk reduction. After all, demand for condoms drove the massive ten-fold increase in supply, and it seems unlikely that no more were used or averted any infections. My own simulation studies suggest that the reduction in partner acquisition would have to be substantial

to reproduce the observed decline in prevalence without a simultaneous increase in condom use [70]. It can also be argued that comparing prevalence and a crude indicator of condom use across neighbouring countries is invalid because the frequency of other types of behaviour and the overall pattern of transmission could vary, so that condom use in a particular type of partnership could have more or less epidemiological significance in other places. Reports between different countries may also be subject to differing degree of reporting biases.

1.8 Uganda and PEPFAR

Although efforts to control the spread of HIV have been co-ordinated by governments, WHO and UNAIDS, substantial funding has been sourced from charities, non-governmental organisations, international agencies and philanthropists. At the international level, a major funder of intervention activities is The Global Fund for AIDS, TB and Malaria [83]. This organisation collects money from states and individuals all over the world and distributes it to many local projects.

Latterly, in his state of the union address in 2003, George W Bush announced a new American initiative that would take a rather different approach. The President's Emergency Plan for AIDS Relief (PEPFAR) [84] committed \$15bn over five years, with a focus on fifteen chosen countries. The plan was to use the best science available to guide the response to the epidemic on the three fronts – prevention, care and treatment. For prevention, the conclusion taken by PEPFAR from the Uganda story was that condom use should be restricted to the minority engaging in high risk behaviours, and that the primary tools for avoiding infection should be delaying first sex and then remaining faithful to one sexual partner.

1.9 The Controversy of the American Initiative

To many, PEPFAR is an extension of the 'strings attached' model of foreign aid that America has followed since the Second World War. It has been alleged that the selection of focus countries, which have received special attention in the programme, was made on the basis of American interests and domestic pressure and not epidemiological need [85]. Stories abound of how funding opportunities in PEPFAR have been directed away from those involved in family planning, or supporting abortion practices or women in sex work [85].

Epidemiologists have objected to PEPFAR for the way in which it promotes its own science for application to many different countries. They argue that a 'one-size fits all' approach is unlikely to maximise the intervention effect when the practices and customs in countries with severe HIV epidemics vary so widely. The relative

contributions of the 'ABC' components (in particular the role of condoms, versus abstinence and faithfulness) of an intervention will need to vary according to epidemiological context [86], especially the age-range and current behaviours of the target population. Although, it is expected (and acceptable) for implementing agencies to be more comfortable promoting some elements of ABC than others, it is not right for information and scientific evidence on the effectiveness of the alternatives to be withheld [87] or for the information to be coloured with ideological moralising. However, there has been suspicion that exactly this has happened in the first years of PEPFAR [85].

Randall Tobias, the first Global AIDS co-ordinator in charge of PEPFAR, signalled his scepticism on the usefulness of condoms in preventing new infections by noting that although condoms had been the principal intervention tool over the last decades, the HIV epidemic had continued to spread [88]. One third of US state funding is directed toward 'abstinence-only' programs, which do not mention condoms as an alternative to abstinence for avoiding the risk of HIV infection. Human Rights Watch [88] allege that information on the safe use of condoms was removed from a CDC fact sheet in 2002, although I have not been able to verify this claim. The American Foundation for AIDS Research [89] has responded to these trends with a statement that, "the scientific evidence does not support the recent shift in U.S. government policy that stresses lack of condom efficacy" and has conducted research showing that the efficacy at reducing HIV transmission is 80-95% (the scientific evidence on the use of condoms is discussed in greater detail below). The position of the new Global AIDS co-ordinator, Mark Dybal, may be slightly less antagonistic, at least in rhetoric. However, in Uganda, where the ABC programme had its first success, condoms sales have declined over recent years, as links between Washington and Kampala have strengthened [85]. And worryingly, this has been accompanied by a stabilization or slight upward trend in HIV prevalence and incidence rates in some parts [90].

The evidence from Uganda is that the declines in incidence were not driven by a change in a single dimension of sexual behaviour. The distortion of evidence is unfortunate and unlikely to assist in generating an adequate response elsewhere.

1.10 A New Story – Zimbabwe

Zimbabwe makes an unlikely candidate for a success story with HIV rates declining. Land redistribution, increased migration, a failing economy and increasingly brutal state conduct, have combined to considerably increase the hardship of the average

Zimbabwean in the last decade. However, during this time, HIV prevalence has declined substantially [17].

Median prevalence across twelve national surveillance locations exceeded 30% in the year 2000, making Zimbabwe one of the worst affected countries in the world. However, 2001, 2002 and 2004 saw successively lower prevalence estimates and the estimate for 2004 was 22%. That is to say, over five years, the number of people living with HIV reduced by more than a quarter. Naturally in the face of such a striking result, important questions have been raised about its validity. In 2005, UNAIDS sought to address these concerns with a comprehensive scientific review of the epidemiological data [17].

The HIV test ('Genscreen') used in the surveillance protocol has a lower specificity than had been presumed, meaning that prevalence could be slightly overestimated. However, since the same protocol has been used throughout these surveys, this could not contribute to the observed trend. An unusual feature of the data is that the reduction in prevalence is approximately equal in all age-groups, whereas one might predict that a change in incidence in a mature epidemic would lead to greater declines in prevalence at younger ages. However, this assumes that the change in risk is the same in each age-group, and greater changes in behaviour in older age-groups could generate the observed pattern of prevalence decline. Alternatively, average fertility rates in older infected women may have decreased further over time, leaving the sample progressively more dominated by uninfected women, contributing to the observed prevalence decline at older ages. There has also been a lot of emigration from Zimbabwe, which could drive the decline in prevalence if those infected are more likely to leave than others. This could be the case, for instance, if they were leaving for South Africa in search of treatment, which was not available in Zimbabwe. This issue can be taken up with mathematical modelling, by exploring the degree of emigration needed to generate the observed prevalence decline (see chapter 2).

Further weight is lent to the national-level studies by parallel observations in a cohort of postnatal women in Harare [17] and an open cohort in the rural Manicaland region in the eastern highlands [91]. Among the Harare women, prevalence rose and fell through November 1997 to January 2000. Taken together with comparable ANC data, this period seems to capture the point of incipient prevalence decline. It would be expected that changing risk behaviour would develop first in more educated urban populations [92], and this pattern of prevalence decline does slightly precede the changes seen at the national level. In the rural cohort, a significant prevalence decline was detected between 1998 and 2003 from 21% to

19%. Prevalence declined by almost two-thirds among men and women aged under twenty years, conforming to the expectation that changes are greatest at young ages.

During the period of prevalence decline, available data also indicate substantial changes in sexual behaviour. A clear trend from nationally [17] and locally-collected data [91] is that, in more recent surveys, fewer men report having a casual partnership in the last year. At the national level, there has been little change in number of partnerships formed by women, but in Manicaland, they also report engaging in fewer sexual partnerships and having fewer sexual partnerships at the same time. Recent measures of condom use at the national level have not changed in the last five years, although reported use with casual partners is quite high and the changes in risk associated with the current prevalence decline probably precede the period for which there are data. In fact, the number of condoms distributed increased by nearly ten fold during the 1990s, with a particular surge after 1997, when social marketing of condoms began, so it is credible that condom use increased as well. There is evidence from Manicaland that young men and women are starting sex later, although there is little suggestion of this in the national level data.

The standard of evidence for the prevalence decline in the Manicaland study is much higher than that from national level studies in either Zimbabwe or Uganda because it refers to the same general population sample at two time-points. In this way, changes in the composition of the sample or biases in those attending clinics do not contribute to observed trends. Because this study also collects detailed sexual behaviour in the same population, changes in risk can be confidently associated with changes in prevalence. Future rounds of the Manicaland cohort study will furnish successive incidence measurements, which could provide an even greater level of evidence for the ongoing epidemic changes.

In common with Uganda and contrary to popular opinion, Zimbabwe benefited from strong political leadership and openness about the epidemic from early on. Zimbabwe was the first country in the region to start an AIDS levy, a tax stream dedicated to funding the national response to the HIV/AIDS epidemic [93]. There was also a successful STI control program in the early 1990s [17, 94] which may have directly contributed to reducing transmission. The documented changes in Zimbabwe and Uganda share particularly strong evidence for reductions in the number of casual partnerships. That might be because reducing the number of casual partners is the most feasible and effective change, or because it is the simple indicator that most closely measures general risk behaviour or is most susceptible to social desirability bias.

In order to better identify the interventions (or other factors) that contributed to the epidemic changes in Zimbabwe, the timing of the risk reduction is investigated in Chapter 2. In Uganda, the change in risk behaviour may have begun in the phase of the epidemic when mortality grew in lower risk groups [24] and it has been hypothesised that the motivation could have been attending funerals of close friends, neighbours and family members [95]. The average Zimbabwean citizen may have gone through this sad process about ten years after his peers in Uganda, but the effects may have been the same.

These successes, in Thailand, Uganda and Zimbabwe, are the exception not the rule for the result of interventions against the HIV epidemic. Moreover, in the case of Uganda and Zimbabwe, it is unclear how much of the “success” was a consequence of specific planned interventions and policies, if the true motivational force was AIDS mortality and funerals. Must other countries wait for their epidemics to spread further before the death toll is sufficient to inspire more effective action? There has been extensive research into the best way to prevent infection in limited resource settings. The opportunity cost of other interventions has created tensions between proponents of alternative strategies, and the evidence has not always been assessed objectively. The first major intervention activity was the distribution of male condoms, about which controversies have already been mentioned.

1.11 Trends in Interventions – First, Condoms

In the 1990s, when the magnitude of the HIV epidemic and its potential for devastation was first realised, condom distribution increased significantly, by about ten to one hundred fold in some places [75]. It has been suggested that the lack of evidence for the success of this approach in turning back the generalised epidemics is conspicuous. One example is illustrative; in Botswana between 1993 and 2001, condom distribution tripled while prevalence leaped from 27% to 45%.

However, one cannot know how much faster the epidemics would have grown if these efforts in condom promotion had not been made. There are also some important reasons why distributing condoms has not had the hoped for effect.

First, condoms are not perfectly effective. Their efficacy (use under idealised conditions) can never be measured because this would require randomising serodiscordant couples to use condoms or not (ethically unacceptable) and demand perfect adherence throughout the trial (which could not be verified). Effectiveness (use “in the real world”) has been estimated in many studies [96], and a meta-analysis indicates a 90-95% reduction in the chance of transmission per sex act,

which is roughly the same as their contraceptive effect [97]. Probable reasons for the imperfect effectiveness are improper use and poor storage conditions.

Second, condom distribution is not an indicator of condom use. For the millions of condom distributed, many contacts will be unprotected even if everyone wanted to use a condom. In Zimbabwe, for example, the 80 million distributed in 2004 [17] amounts to 25 per man, or approximately one condom for every six sex acts. Although most sex acts will remain unprotected even with high levels of condom distribution, this does not necessarily argue that the limiting factor has been insufficient distribution. The number of condoms currently distributed would probably be more than enough if they were selectively used in sero-discordant partnerships, so a confounding problem is lack of knowledge of infection status. Condom use in many countries is much higher with a 'casual' (or non-cohabiting) partner than with a regular partner [75]. Mathematical models have highlighted the particular importance of condom use in such high-risk partnerships, particularly if either partner has an STI [98]. For example, for the same reduction in women's lifetime risk of infection, one sixth as many condoms are required if they are used when a partner has an STI, as when they are used 50% of the time irrespective of STI symptoms. However, it is also now recognised that partnerships perceived as stable and low risk, and in which condom use is low [98], tend to run concurrently so that the chance of transmission between them is high [72]. In summary, the lack of association between increased condom distribution and declines in incidence could be due to an insufficient number of condoms, or insufficient knowledge about the risk of getting infected with HIV and when to use a condom.

Third, occasional condom use is not enough. Consider an infected man and an uninfected woman forming a five year relationship; assume that there are three sex acts per week (780 sex acts in total), that the chance of male-to-female transmission is 0.001 [99] and that the effectiveness of condoms in preventing transmission is 95% [97]. What is the chance there is a transmission event sometime in the partnership? Without any condom use, the chance she gets infected is 54%, whereas if condoms are used in every act, the chance is 4%. However, compared to using condoms in all sex acts, the chance of infection is five time higher if condoms are used in 75% of sex acts, and nine times higher if condoms are used in 50% of sex acts (still perceived as a "high" value). In fact, the overall risk of infection when condoms are used in half of all sex acts is 37% less than if condoms were not used at all, illustrating the faster-than-linear payoff of using condoms in more sex acts.

The sensitivity to infrequent use of condoms is greater for longer partnerships, because the absolute number of unprotected acts increases. Models suggest that with the same average condom use, a small number of people using condoms consistently can have more effect than a larger number using them inconsistently [98, 100]. It is notable that in those instances where condoms can be credited with leading to a substantial population-level effect, condom use was strictly enforced and high levels of compliance recorded – in Thailand (see above), and Nevada [101], for instance. For the general population, it is one thing to supply some condoms and encourage people to use them sometimes, but quite another to stimulate demand for consistent use and develop the supply chain to support it. It also means that studies showing that high but incomplete usage of condoms is not associated with lower incidence should not be interpreted as condoms being unable to provide a high level of protection against infection when they are used properly.

Given that the protection afforded by condoms is jeopardised by infrequent use, there is a genuine danger that a focus on condoms could lead to deleterious interactions with other interventions activities. For instance, there has been concern that promoting condoms to young people will lead to starting sex earlier and having more sex but with inconsistent condom use. However, the limited data available do not support this [102] and, in some settings, the opposite is true. For example, condom promotion has been associated with other forms of behaviour change, including less visits to sex workers in Thailand [103] and fewer casual sex partners in Brazil [104].

If alternative types of behaviour change intervention are not antagonistic then another important argument for a multi-pronged approach is that risk-reducing behaviour changes are more powerful in combination than in isolation. This arises because the association between risk behaviour and the chance of infection is not linear, but a multiplicative function of both risk behaviour and the level of infection already in circulation [37]. Thus, using condoms could decrease an individual's chance of infection by a certain amount, but the reduction in incidence at the population level could be greater if accompanied by other behaviour changes in other parts of the population, such as reduced partner change or "zero-grazing". This effect means that attributing Uganda's success, for instance, to one particular aspect, though tempting, is prone to understate the role of certain behaviours (such as condom use) which may have been mostly restricted to marginalised parts of society.

1.12 Treatment of STIs

With clear evidence that curable STIs (such as gonorrhoea, Chlamydia and syphilis) increase the chance that HIV is acquired and transmitted [105], treating STIs with cheap drugs (antibiotics) at basic clinics seemed like a promising way to tackle HIV epidemics [106]. To test whether controlling STIs could have an effect on HIV incidence, it was necessary to conduct randomised control trials but the unit of study was the community because the intervention (treating STIs) and the outcome (HIV incidence) both relate to the community, not the individual. Treating STIs is expected to reduce STI prevalence, which will impact on both the acquisition and transmission of HIV and lead to lower HIV prevalence in the community, so that even people who are not directly involved with the intervention itself stand to benefit.

Ten years ago the first positive trial result for this approach came from the rural Mwanza area in southern Tanzania [107]. This was the first time an HIV intervention was shown to work and many countries started to adopt STI treatment as part of epidemic control programmes [108]. In the trial, twelve communities were organised into pairs on the basis of HIV prevalence, STI prevalence and other environmental factors. One community in each pair was randomly assigned to the treatment arm, which provided improved syndromic management of STIs, and the other to the control arm, where basic health care services were continued. The effect of the community-wide interventions was gauged in 1000 adults, randomly chosen from each community. In fully adjusted analyses, over two years the HIV incidence rate in the intervention communities was about 40% lower than in the control communities.

This strikingly successful trial led others to be set up, all based on the idea of treating STIs, but aiming to deal with asymptomatic reservoirs in the Rakai trial [109], and combining STI treatment with behaviour change interventions in the Masaka [110] and Manicaland trials [94]. In the Rakai trial, one group of communities were offered antibiotics every 10 months, as a 'mass treatment' of STIs, for those with or without symptoms. In the Masaka trial, communities were either given behavioural counselling services, or behavioural counselling services in addition to a Mwanza-style syndromic STI management service, whilst the existing health care services were maintained in other comparison communities. In Manicaland, the approach was slightly different again; in addition to improving syndromic management of STIs, peer-led behaviour change counselling was directed to sex workers and their clients.

However, none of these more recent trials has been able to reproduce a positive result. The apparently contradictory results of the Mwanza, Rakai and Masaka trials have been explained by differences in the epidemiological contexts in which the trials were run and difficulties in implementing the mass treatment

intervention. Essentially, the Mwanza trial was a special case; curable STIs were unusually prevalent and existing STI services were unusually poor [111, 112]. In Rakai, genital herpes, an STI that has been shown to potentially be an important cofactor enhancing HIV transmission [113] but which cannot be treated with antibiotics, was very common and probably supported much HIV transmission [108, 114]. Also, in the Mwanza trial, the STI treatment services were provided continuously, so that STI prevalence remained low, but, in the Rakai trial, infections could have been reintroduced between rounds of mass treatment [108]. Lower coverage of treatment services among those most at risk could also undermine the impact of treatment on HIV incidence [115]. It has been suggested that providing a syndromic management service (but not a mass treatment service) also acts as a behaviour change intervention because with STI symptoms, patients would be advised to be temporarily abstinent [116]. In this way, new STI symptoms will tend to coincide with the individual having had a risky exposure, through which they may also have acquired HIV; by avoiding sex in the period immediately after, the chance of transmitting the HIV infection is then substantially reduced.

Another well accepted reason for the success in Mwanza and not elsewhere is that, in contrast to the contexts of the other trials, the epidemic in Mwanza was younger, at a lower prevalence, and growing during the trial. In such a phase, the HIV epidemic remains largely in those with the riskiest sexual behaviour who are most likely to have STIs, so that the fraction of HIV infections attributed to curable STIs is high [117]. Later, when most new infections occur within lower risk, long-term partnerships, amplification in the transmission probability has a relatively smaller effect on the overall chance of transmission in the partnership, because of the greater number of sexual acts.

Taken together in a detailed mathematical model, these effects can explain the differences between the trial outcomes in Mwanza, Rakai and Masaka [118, 119]. However, further issues surround the Manicaland trial, where a reduction in HIV incidence was detected in the immediate male target group, but not in the wider community [94]. This raises the question of whether a positive result would have been recorded if the trial had run for longer. However, the incidence rate ratio showed no trend to decrease in the intervention communities; indeed the trend was in the opposite direction. In the mature Zimbabwean epidemic, the prevalence of STIs was already low [17], the contribution to transmission of high-risk behaviours may have been small, or high-risk behaviours may not have been effectively targeted. It also seems possible that the effect of the intervention and the chance of detecting a statistically significant result could have been influenced by the large

epidemiological changes that occurred in Zimbabwe over the course of the trial [91]. These questions are the subject of chapter 6.

In summary, STIs can be successfully controlled with inexpensive treatments, which should be a goal in its own right, since such disease are amongst the leading cause of morbidity among prime-aged men and women [108]. In addition, syndromic management of STIs has been shown in one study to reduce HIV incidence, but in a particular set of circumstances i.e. in growing epidemics, where curable STIs are common. Although the effect of treating STIs on HIV has not been shown in trials in other contexts, it may still make a important contribution to limiting HIV incidence rates, and is likely to remain a cost-effective option given the cheapness of treatment and the size of the mature epidemics [120]. The conditions for STI treatment to have a major impact may no longer apply in most African countries, but it could still be a promising intervention in south and central America, India and many other parts of Asia [2, 108].

Amid the many and varied approaches to behaviour change intervention currently being advocated and implemented, two themes seem particularly prominent. These are: a focus on young women's sexual behaviour, especially their sexual partnerships with older men; and, voluntary counselling and testing.

1.13 Current Trends in Interventions - Young Women's Sexual Behaviour

Observational studies show that HIV prevalence among young women usually far exceeds that among young men [121], which has prompted some to stress the importance of protecting young women in particular from infection [121-125]. Statistical analyses of individual behaviour data show that the risk of HIV infection is lower amongst women that avoid older sexual partners [40, 126] and begin sexual activity later [40, 127, 128]. In Manicaland, women whose last partner was at least ten years older were twice as likely to have a prevalent infection than women whose last partner was less than five years older [40]. Young women (15-24 years) who began sex younger than seventeen were 30% more likely to be infected than those who started after their twenty-first birthday [40, 129]. For these reasons, it has been suggested that behaviour interventions should focus on reducing cross-generational sex and delaying sexual debut [121, 130, 131]. However, further analysis on timing of sexual debut reveals that the apparent protective effect of delaying first sex is short-term [127] and is mostly driven by the association between early first sex and riskier sexual behaviour later in life [127, 129, 132]. The impact of delaying sex and

changing the pattern of age mixing on transmission at the population-level has been presumed but not scientifically investigated and quantified [41, 121, 125, 126, 130, 131, 133-135]. Mathematical models can provide insight into how individual behaviour changes relate to epidemic patterns and this is taken up in Chapter 4.

1.14 Current Trends in Interventions – Voluntary Counselling and Testing

As mentioned above, one of the limiting factors to challenging the spread of the epidemic is that most of those transmitting infection do not know that they are infected. The reducing price and increasing speed and ease of HIV testing has made it possible to offer a testing service so that individuals that want to find out if they are infected can do so and get the result immediately. Before and after the test, there is an opportunity for counselling and a randomised control trial in the United States of America demonstrated the extra power of counselling to enable behaviour change when it is integrated with an HIV test result [136]. In low-income countries, other trials have shown that voluntary counselling and testing (VCT) is an effective and cost-efficient means of reducing HIV risk behaviours [137-139]. However, in a recent cluster-randomised trial for VCT delivered at the workplace [140], there was no net reduction in HIV incidence associated with VCT and, in another study, where VCT was conducted outside of a formal trial [141], only small behaviour changes were detected after VCT, and some individuals that found they were not infected went on to increase their risk behaviour. Another potential problem with VCT is that serodiscordant couples with an infected woman may be more likely to end the relationship after VCT [142], which could lead the infected women to form more new partnerships, increasing the potential for onward transmission.

VCT is also used as an entry-point to the health-care system [143] so that those found to be infected can be referred for treatment of opportunistic infections, prevention of mother-to-child transmission services and ART, if it is available.

In many countries there is a drive to roll-out VCT facilities. Some of the earliest approaches were led by the commercial sector, with Population Services International aiming to stimulate demand for VCT with social marketing techniques [144]. Television and print media advertisement were used to target specific population sub-groups (adolescents, young couples and mobile workers, in particular) and the pilot 'New Start' centres in Zimbabwe have now tested 660,000 individuals [144]. However, many of these tests were delivered to the same people attending multiple times, and the coverage of the adult population may be much less than 10%. Uptake is thought to be much lower in most other settings, where as few as 8-25% of people living with HIV are estimated to know they are infected [145]. It

has been presumed that the major barriers to testing are stigma and lack of convenience. To combat both of these, on-site VCT services have been proposed and a study in Zimbabwe found that uptake of VCT of on-site services was much greater than comparable off-site services [146]. In Botswana, although ART has been available for many years, relatively few were receiving therapy because most people have not been tested and do not know they are infected with HIV. In 2004 the government made testing routine, so that at each visit to a doctor, the patient is tested for HIV unless they “opt-out” [147]. This had been met with mixed feelings, with many respondents reporting that it would have been difficult to decline the test, and with lower testing coverage remaining in important groups, such as those with only basic education and those with stigmatising attitudes [147].

Although there is political and commercial support for VCT, the potential impact of the services at the population level has not been quantified. VCT also raises the possibility of new types of behaviour change, such as sero-sorting and selectively using condoms in ‘known’ serodiscordant partnerships, the impact and relative advantage of which may depend on certain elements of the VCT service. Other programmatic questions, such as whether to frequently repeat test individuals, the effect of targeting services to particular groups and the potential antagonism between the two roles of VCT (promoting behaviour change and entry to health care services) are relevant for public health officials and decision-makers in charge of delivering these services [148, 149]. With limited service coverage and data on these issues, mathematical modelling can provide a useful investigative tool and VCT is the subject of Chapter 5.

1.15 Anti-retroviral Therapy

Although it took time for the political community to accept that a new lethal retrovirus was spreading beyond marginalised groups in the early 1980s, efforts to alleviate infection and mortality have since been exceptionally well funded [150]. In the United States, the National Institute of Health established the AIDS Clinical Trials group (ACTG) in 1986, which has tested hundreds of suggested compounds. AZT (Zidovudine) was the first to be licensed after initially promising results, although it was considered costly, toxic and ultimately not very successful at slowing the onset of AIDS [150]. The break-through that became known as (Highly Active) Antiretroviral Therapy ((HA)ART) came a decade later [151, 152].

The success of ART in the US is evidenced by the sharp and sustained decline in AIDS deaths from a peak of 50,000 in 1994, to slightly more than 10,000 a

year in 1999. The therapy is really a package of three distinct treatments that interrupt different phases of viral replication. Managing these three types of drug and coping with their toxicities and associated metabolic disorders can be difficult [153]. The best-practice guidelines for delivering ART in western populations have shifted in the time that therapy has been available [154, 155]. Initially, a “hit hard, hit early” approach was advocated [156], whereby ART was given almost as soon as the patient was found to be infected with HIV. A meta-analysis of western cohorts suggests great advantages of starting therapy earlier: a young patient starting therapy before any symptoms of immune-suppression have started (that is, with 350 or more CD4 cells/ μ L and a viral load below 100,000 copies/mL) has a 3.4% chance of dying of AIDS within three years, whereas a patient starting therapy in the very advanced stages of disease (that is, with fewer than 50 CD4 cells/ μ L and a viral load greater than 100,000 copies/mL), has a 50% chance [157]. However, the toxicity [153] of the drugs and the associated issues of low adherence and the emergence of drug resistance [158] have lead some to recommend starting therapy later [159].

Another benefit of ART is that by reducing viral load, it probably reduces the chance of HIV transmission [160]. Many mathematical models have been used to investigate whether this would lead to HIV incidence being reduced at the population level, with conflicting results [161]. However, the consensus is that is very unlikely that ART alone could bring the epidemic under control [10, 161].

1.16 Universal Access to Anti-retrovirals in Africa

Until 2001, the price of ART was too high for almost anyone in the developing world to afford but, in response to growing international pressure, the pharmaceutical companies made two commercial concessions. First, they agreed to sell the drugs at a lower price in the developing world, and second, they agreed to let other companies produce the same drugs without their branding (i.e. ‘generic’ copies) [85, 150]. This brought the price of ART crashing down, by approximately 90-99%. For example, 30 days of triple therapy (with branded drugs) in Uganda cost \$479–\$556 in 1998, but about \$70 (down 86%) in 2002 and about \$30 (down 93%) for unbranded products [162].

Two programs have led the increase in access to anti-retrovirals since 2003. The first was PEPFAR, which set itself the goal of putting two million on treatment over its five year run [163]. At the half way mark, they are slightly behind schedule - as of September, 2006, it was estimated that 822,000 people were receiving therapy from PEPFAR in the 15 focus countries [164].

Later that year, on World AIDS day (1st December), the WHO and UNAIDS launched the “3 by 5” initiative, a plan to provide therapy to three million by 2005. When it was announced, about 400,000 were on therapy (mostly in Latin America, where cheap drugs had been widely available for some time already), representing about 5% of those in need. The ambitious target of three million was estimated to equate to about 50% of those in need [165]. A review in 2006 indicated that progress had been slower than hoped for, suggesting that, by the middle of 2005, about one million were on therapy – about 15% of those in need – only a third of the way to the target [9].

A new commitment was made at the G8 summit of the world’s richest industrialised countries in 2005, hosted by the British government in Gleneagles, Scotland. By 2010, they agreed, there should be ‘as close as possible to universal access to treatment’ [166]. This new target goes much further than the WHO dared in 2003 and would require an incredible surge in finance and roll-out of services, little evidence for which can be found two years on.

How well does therapy work in the developing world? There was scepticism that therapy could be as effective in poorer settings, where maintaining good adherence and precisely timing doses was thought by some to be impractical [167]. However, a recent meta-analysis indicates that adherence to therapy is actually better in Africa than in north America [168]. On the other hand, a meta-analysis of survival on ART has found that many more individuals in lower-income countries die in the first year of treatment than in high-income countries [8]. However, this is partly because patients in low-income countries tend to start therapy later and the chance of death while on ART is higher in low-income countries only during the first months and by the ninth month the survival outcomes for patients in low-income and high-income countries are statistically indistinguishable [8].

The question of when to start ART has taken on a new dimension in poorer countries. Whilst in western countries the decision to initiate ART can be informed by a range of high-technology tools [169, 170], in poorer countries a more pragmatic public-health approach has been adopted [171]. The decision to start therapy may be taken without any laboratory support at all, using instead standard symptom staging criteria. Studies from India and Africa show that, although early signs of disease can be apparent within a few years of infection [172, 173], advanced immune depletion is not always associated with severe clinical symptoms [174-176]. To better identify those in need of treatment, the WHO has recommended using CD4 counts [177] and, in the “3 by 5” program, almost all the focus countries used CD4 counts to help judge when ART should be initiated [178]. CD4 cells are the principle target of the virus and

their numbers are steadily depleted with time since infection, so that a count of the number of CD4 cells in a sample of peripheral blood indicates the degree of immune-suppression and the immediacy of the need for therapy [179].

It has been argued that such is the priority for delivering these life-saving drugs, there is no time for a more sophisticated medical infrastructure to be developed [180]. However, given that the prognosis on ART is linked so closely with the state of the immune-system when therapy is started, it seems that the CD4 counting technology could provide a useful “early warning system” for the need for therapy, and substantially increase the life-years saved. Other aspects of the health-care system could also play a role in maximising the impact of ART programmes, such as enabling earlier diagnosis of infection through increased uptake of VCT, and regular observation of patients not yet in need of ART. These issues are examined in Chapter 7.

1.17 The Future

It has been said that a quarter of a century into the epidemic, we now stand at a cross-roads [181]. Without doubt, momentum and political agitation for success in the global response to the epidemic has grown in recent years. Since 2000, commitments for HIV/AIDS have increased; the Global Fund has distributed \$5.2billion, PEPFAR has committed \$15billion; the UN has discussed AIDS as an international security issue; the World Bank has become much more active in AIDS-related lending, increasing its commitments from \$500million in 1998 to \$2.7billion in 2006; UNAIDS has successfully drawn support from its international partners and member states and mounted a coherent response strategy [181].

These grand multilateral or ideologically driven ventures can place a concern in the spot light and mobilise substantial resources, but they can also fall short of high expectations and distract focus other methods of effective action. Competition and antagonism between programmes could undermine their total eventual contribution. There may also be a case that numerical targets for treatment – though of pressing importance – could distract from the priority of preventing new infections. The line of least resistance might be to rely on familiar supply-chain and programme management skills to distribute a product or service (condoms or ART) in Africa to meet specific targets, rather than to engage with the more complex issues of sexual behaviour and behaviour change. The successes that there have been (in Uganda and Thailand) are characterised by properties that PEPFAR, the Global Fund and the UN cannot buy; strong political leadership at all levels and a simple behavioural response developed from the beginning by the people working at the frontline.

However, the “next generation” of interventions offer ways of reducing the risk of infection without individuals changing (by very much) their sexual behaviour.

In the short-term, male circumcision and acyclovir treatment for genital herpes look like promising options. After having encouraged countries to make preparations for many months [182, 183], this spring, UNAIDS and WHO officially endorsed male circumcision as an intervention [184]. The evidence for male circumcision reducing the risk of HIV acquisition (among men) is now overwhelming and includes three randomised control trials in three different countries [30-32]. Given the cheapness of the operation and the high cost of treating opportunistic infection and providing ART, it is no surprise that such an intervention is likely to be cost-effective [185]. There are concerns, though, that a man would tend to use condoms less after being circumcised (behavioural ‘disinhibition’), potentially overturning any protective effects at the population level, and that “back-street surgeons” could offer the operation cheaply but with sub-standard practices, expose individuals to the risk of serious bacterial infections. As discussed above, circumcising infected men may lead also to an increased chance of transmission, at least in the short-term [33].

Genital herpes, mainly associated with Herpes simplex virus type 2 (HSV-2), an incurable viral infection [186], is known to increase the chance of HIV infection and onward transmission [113, 187]. Although, disappointingly, a trial recently reported that treating HSV infection with acyclovir in suppressive therapy failed to reduce the risk of HIV acquisition [188], there is some evidence that suppressive or episodic treatment could reduce HIV viral shedding and therefore reduce the rate of transmission [189, 190]. There are many reasons why this is not the same as treatment of bacterial STIs, which, as discussed, has not worked in a number of African trials. The co-factor effect of HSV when ulcers are themselves present is greater than bacterial STIs; the prevalence of HSV is often much higher and is more common in lower risk couples, making the contribution of HSV to HIV spread increase over time [114, 117, 191]; and, the effect of HSV could be greater in mature epidemics because advanced immune-suppression makes episodes, when infectiousness is highest, more frequent.

On the horizon, there are two more medical-type interventions. The result of efficacy and safety trials of topical microbicides are expected in 2008 [192]. These are chemical agents used topically within the vagina by women prior to sex. Many have been developed and several are currently in phase III clinical trials. They work by destroying the viral envelope, preventing binding, or by blocking transcription by the virus [192, 193]. Critically, they could provide a prevention tool that is under the control of women. Although they are unlikely to be completely effective (probably

reducing rates of infection by between 30 and 60% [192]), they could nonetheless lead to substantial reductions in infection, especially if combined with condom use. Since microbicides are less effective than using condoms, there is a risk that “condom migration” could put some women at increased risk [194]. Other modelling studies suggest that within the range of efficacies expected, adherence will be a stronger determinant of effectiveness than biological efficacy [195]. New technologies aim to improve adherence by, for instance, using resident vaginal rings that maintain a slow release of the active agent over a period of weeks or months [192].

In the long-term, there is also the prospect of a pre-exposure prophylactic vaccine [196]. A result seems as distant as ever and we are told not to expect a vaccine any time in the next decade [196]. Yet work is encouraged by modelling projections that suggest that even a partially effective vaccine could have a significant impact, provided that it does not lead to increases in risk behaviour [197, 198]; for instance, it is estimated that achieving 30% coverage with a 50% efficacious vaccine could reduce the number of new infections worldwide by about a half [199].

For the foreseeable future, there will be no magic bullet which can in isolation eradicate HIV infection. But, there is cause for optimism that, in combination, the multiplying number of tools could send the epidemic into decline. The Achilles heel of each approach, though, is behavioural disinhibition [200]; encouraging volitional behaviour change will have to remain at the centre of all HIV/AIDS intervention projects.

1.18 Mathematical Modelling in HIV epidemiology

The methods used in this thesis involve the application of mathematical models to data analysis, informing the interpretation of surveillance data or the design of interventions. Mathematical models are a precise way of describing assumptions about the transmission dynamics of an infectious disease and can be used to generate predictions for the course of an epidemic and can provide insights into how it can be monitored and controlled [201].

Models of infectious disease epidemiology have a long history, beginning with the work of Daniel Bernoulli in 1760 investigating the impact of small pox on life-expectancy [202]. The architecture of most mathematical models used today was established a century ago, when a “mass-action” assumption was first used to characterise net transmission as the rate of random contact between infectious and susceptible individuals [203, 204]. With the simplest of such random-mixing models (where individuals are only classified as either susceptible or infectious), the important finding emerges that incidence can decline over time as the number of

susceptible individuals diminishes [201]. This means that the contribution of epidemiological dynamics must be considered when interpreting observed epidemiological trends [54, 55]. With such a model, it can also be shown that, for infections with long generations times, prevalence lags any changes in incidence, which has the implication that the impact of successful interventions may not be apparent for many years after they start. These basic findings are the starting point for the work in Chapters 2, 3 and 6, where methods for monitoring epidemics and evaluating trials are developed.

Over time, as greater biological knowledge about the natural history of HIV and data on sexual behaviour has accumulated, models have been progressively adapted to incorporate further complexities. Important modifications include: variation in risk behaviour in the population [205] and patterns of mixing [42, 206, 207], variable patterns of infectiousness and disease over time [208, 209], the temporal relationship of partnerships [23, 210] and many other important details of the sexual behaviour network [211, 212]. These additions have contributed to better understanding the course of HIV epidemics, the global variation in epidemic profiles and the distribution of infection within communities. In particular, simple homogenous random-mixing models of HIV cannot readily reconcile the low transmission probability of the virus [160], the quick initial epidemic spread, and the relatively low endemic prevalence.

Under the random-mixing assumption, the potential for epidemic spread is greatly enhanced by variation in the rate of forming sexual partnerships [210]. This provided one of the first solutions to the paradox whereby behavioural surveys reveal superficially similar levels of (mean) risk factors in communities with high and low HIV endemic levels [21, 25]. The extent of contact between those at most risk with others can also determine the extent to which the infection can spread. HIV will be restricted to only those with the highest risk if they mostly form partnerships with one another, whereas prevalence can reach higher levels over the whole population if those at most risk often form partnerships with others [42, 213, 214]. When the finite duration of partnerships is incorporated in models (in many other models it is assumed that contact is instantaneous), is it clear that the potential for epidemic spread (R_0) depends on both the average partnership duration and the inter-partnership gap, with transmission promoted when individuals are released from partnerships and are able to re-form more partnerships before the period of infectiousness runs out [215]. (R_0 is the basic reproductive number, defined as the number of secondary infections arising from one infection in entirely susceptible population [37]). As already discussed, it has further been shown that communities in which partnerships tend to temporally

overlap can support faster epidemic growth [23, 216]. Other diseases can also act as co-factors for HIV transmission, including malaria [217], tuberculosis [218] and classical STIs [105], thereby shaping the pattern of HIV spread. Ulcerative STIs (in particular chancroid) are thought to have played a particularly important role in the early phases of the HIV epidemic, when the transmission was concentrated amongst those at the highest risk and before improved STI management helped reduce STI prevalence [119, 219]. The contribution of HSV to HIV transmission (which is chronic and untreated [186]), on the other hand, may increase over time, as the infection spreads to lower risk groups [114]. By increasing (HIV) viral load, malaria makes infected individuals more likely to transmit the virus, and in addition, malaria-infected individuals are more likely to acquire HIV [217]. Co-infection with tuberculosis (TB), however, tends to reduce survival with HIV, potentially contributing negatively to R_0 [218].

Models have also been developed to explore specific questions such as the impact of HIV on demography [220], the epidemiological changes associated with using HAART [198, 221, 222], and the impact of particular interventions like hypothetical vaccines [223, 224], STI management [119] and proposed/actual behaviour change interventions [24, 75], which have been described in this chapter. The range of mathematical models used varies greatly in complexity, usually trading analytic tractability against biological realism and specificity. For example, the potential impact of interventions that offer male circumcision has been the focus of several recent studies. In some, the general case was considered analytically by considering expected changes in the basic reproductive number, R_0 [27, 225], whereas others explored various scenarios in stochastic (micro-)simulation models, incorporating many details of sexual behaviour measured in particular African communities [226, 227].

Models are best developed in a step-wise fashion, testing the importance of each particular assumption [201]. In tackling each of the questions posed in this thesis, mathematical models were developed that included only sufficient complexity to tackle the problem at hand. In each chapter, the choices for the model structure are justified and the issue of whether this was adequate is taken up in the conclusion chapter (chapter 8).

1.19 A Note on the Manicaland Study

Although most of the chapters do not relate specifically to Zimbabwe or the Eastern Highlands area of Manicaland, it has been useful to ground analyses in a specific setting rather than a hypothetical “typical” southern African population. Data collected

in the *Manicaland HIV/STD Prevention Project* have been used extensively to parameterise models in all chapters and a summary of the study is provided here. Other data sources are identified as they are used.

The Manicaland Project collects behavioural and biomedical data in a stratified community-based open cohort. Data from two rounds are used in this thesis; the first round was between July 1998 and February 2000, and the second was between July 2001 to February 2003 [40, 91, 94]. The population strata comprised twelve distinct communities: two forestry plantations, two tea and coffee estates, four subsistence farming areas, two small towns and two roadside trading centres. A preliminary household census enumerated 8233 of 8386 (98%) known households in the study areas. One man or woman from each marital grouping in a household was invited to participate in the survey. In total, 4331 men aged 17-54 years and 5149 women aged 15-44 years agreed to participate (77% of those eligible). In the closed cohort, the follow-up rate between the first and second survey was 55% (75% of those from the baseline survey that were still alive and resident at time of second survey).

Structured interviews were conducted face-to-face by trained social science graduates familiar with the local culture but from outside the study area. Some personal questions came after there had been a time for informal discussion to build up rapport between the interviewer and subject. Response to other sensitive questions about sexual behaviour were recorded using an informal confidential voting interview (ICVI) method in three-quarters of the interviews with literate respondents (selected at random) [228]. This method entails the participant writing his or her response to certain questions on a card so that the interviewer cannot read them and then depositing them in a locked box. It has been found that in the interviews using the ICVI, the respondent tended to report more sexual partners, suggesting that data collected in this way may be less subject to socially desirability bias.

Midway through the interview, a sample of blood was taken on filter paper and tested for HIV with a standard dipstick test [94].

Written informed consent was sought as a condition of enrolment and both free voluntary HIV counselling and testing and free STI treatment was made available in each study area. Prior ethical approval for the study was obtained from the Research Council of Zimbabwe (Number 02187) and from the Applied and Qualitative Research Ethics Committee, Oxford, UK, N97.039. Custom-made forms in SPSS-PC version 5.0 were used for data entry and validation.

1.20 Organisation of Chapters

This thesis aims to tackle some of the questions that have been current and pressing in the last three years, in the fields of surveillance, behaviour change intervention and delivering ART.

Chapter 2 addresses how to use the available biological and behavioural surveillance data to ascertain whether detected trends in HIV prevalence can be related to changes in risk behaviour. The first part of that chapter analyses national level data from eight countries. The second part analyses regional data from Zimbabwe to estimate the timing of the change in risk behaviour. Chapter 3 presents and tests methods that can use the new DHS+ surveillance data to estimate incidence in the general population. Chapters 4 and 5 explore the population level impact of two types of behaviour change intervention that have received attention in recent years; reducing cross-generational mixing and delaying first sex (Chapter 4) and effective testing and counselling for behaviour change (Chapter 5). In chapter 6, the obstacles to measuring the effectiveness of such interventions are considered in relation to the recent community randomised trial in Manicaland. The role that the healthcare system plays in determining the effectiveness of ART programmes is addressed in Chapter 7. Overall conclusions are discussed in Chapter 8.

A different mathematical model was used in each of the six results chapters but there are substantial similarities between the ones used in Chapters 2 and 4 and 6. A full description of that model is given in Chapter 2 and details of pertinent modifications are given in subsequent chapters.

1.21 Publications

Each of the six results chapters has been submitted as an original research article and published manuscripts are given in the appendix [Appendices A and B]. Six other papers and letters have been published during the period of study that generated this thesis; the two original articles for which I am the first author are also included in the appendix.

1. Hallett, T.B., White, P.J. & Garnett, G.P. The appropriate evaluation of HIV prevention interventions: from experiment to full scale implementation. *Sex Transm Infect* (2007). [Appendix C]
2. Hallett, T.B. et al. Age at First Sex and HIV Infection in Rural Zimbabwe *Stud Fam Plann* 38, 1-10 (2007). [Appendix D]
3. Hallett, T.B. and G.P. Garnett, Has global HIV incidence peaked? *Lancet*, 2006. 368(9530): p. 116-7.

4. Looker, K.J. and T.B. Hallett, Individual freedom versus collective responsibility: too many rights make a wrong? *Emerg Themes Epidemiol*, 2006. 3(1): p. 14.
5. Lopman, B. A., Barnabas, R., Hallett, T. B., Nyamukapa, C., Mundandi, C., Mushati, P., Garnett, G. P. & Gregson, S. (2006) Assessing adult mortality in HIV-1-afflicted Zimbabwe (1998 -2003). *Bull World Health Organ*, 84, 189-97.
6. Gregson, S., Garnett, G. P., Nyamukapa, C. A., Hallett, T. B., Lewis, J. J., Mason, P. R., Chandiwana, s. K. & Anderson, R. M. (2006) HIV decline associated with behavior change in eastern zimbabwe. *Science*, 311, 664-6.

1.22 Contributions

All of the work presented in the thesis has relied on data collected by others and has been shaped by useful guidance and discussion with my supervisors, collaborators and, in some cases, the comments of anonymous referees. These specific contributions are indicated in each chapter and the sources of the data are cited where they are first used. Notwithstanding these remarks, it may be assumed that all other content is my own work.

Chapter 2: Natural Dynamics and Behaviour **Change in Mature Generalised HIV Epidemics**

2.1 Introduction

Heterogeneity in the risk of acquisition and transmission of an infectious disease can have consequences for the pattern of spread of the infection, the evolution of the pathogen, and the chance of bringing an epidemic under control [37]. Patterns of unprotected sex, the risk behaviour for acquiring and transmitting a sexually transmitted infection, varies greatly from person to person which can lead to temporal changes in incidence, even if individual risk behaviour stays constant [37, 42, 229]. Incidence will rise quickly at first as the infection spreads among those with the riskiest sexual behaviour but it will then decline as further infections will be among those at lower risk (Figure 2.1(a)). For HIV, which leads to AIDS and death after a decade [230], there may be a longer-term reduction in incidence because the individuals with the riskiest sexual behaviour are selectively removed from the population. This can have a direct effect on incidence, because there will be fewer high-risk individuals to spread the infection, and an indirect effect, because low-risk individuals will have less opportunity to form risky sexual partnerships [231]. The overall effect is that incidence rises quickly early in the epidemic and falls to a lower level later on. However, in most settings, sentinel surveillance is based on monitoring prevalence [56], which is determined by the balance between incidence and mortality (and migration). The long interval between HIV infection and AIDS deaths means that the surge in mortality caused by the early spike in incidence will not occur until after incidence has settled at a lower level. This means that for a short time in a mature epidemic, AIDS deaths can exceed current incidence levels and lead to a decline in prevalence (Figure 2.1(b)). After that wave of mortality, and in the absence of further changes in incidence, prevalence will remain constant.

When declines in prevalence are recorded, it is tempting to conclude that risk behaviour must have changed and that interventions are working. However, since there are conditions when HIV prevalence could decline without changes in individual risk behaviour, a check should be made as to whether the observed decline could be generated by the natural dynamics alone. Mathematical models are a precise way of describing assumptions about the transmission dynamics of an infectious disease and can be used to generate predictions [232]. It is possible to generate predictions of HIV prevalence over time with and without behaviour change, and test which predictions are consistent with observed patterns of prevalence. In the 1990's, a downturn in prevalence was detected in Uganda and the belief that behaviour change was responsible was strengthened through comparing observed prevalence trends with those generated by mathematical models with and without changes in risk behaviour [55]. This national success story has been extensively re-analysed to

try to identify the root cause the reduction in the individual risk of infection. By estimating that incidence started to reduce before large-scale condom distribution was underway, it has been possible to attribute at least some of the prevalence decline to reductions in casual sexual partnerships [24]. This has had profound implications for global policy on HIV control leading to the development of prevention strategies and substantial investment in programmes promoting such behavioural change [124, 163].

In 2004, declines in prevalence were reported in a number of African countries [15] and the UNAIDS Reference Group on Modelling, Estimates and Projections convened a meeting to analyse prevalence and behavioural data from a number of countries experiencing severe generalised maturing epidemics [233]. A number of countries reported declines in prevalence for the first time. In addition, for Zimbabwe there is a relatively long time-series of prevalence estimates, a recently compiled comprehensive review of behavioural changes [17] and an analysis of trends in sexually transmitted infections is underway. This provides an opportunity to estimate the timing of risk reduction and generate hypotheses about the changes that have driven the Zimbabwean prevalence decline, contributing to the current debate over the best way to prevent infections in sub-Saharan Africa.

In the first part of this chapter, a method for creating null epidemic projections with the steepest decline in prevalence generated by natural dynamics alone, to test whether the observed declines could be consistent with behaviour not having changed. In the second part, data from Zimbabwe is analysed further to help identify the processes that may have led to change in individual's risk of infection.

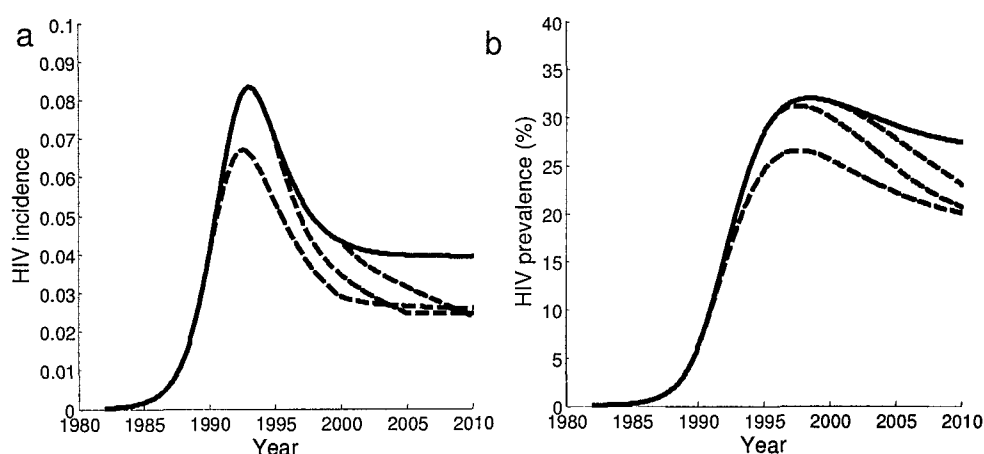


Figure 2.1 Model projections of (a) incidence (b) prevalence for a generalised HIV epidemic in the absence of behaviour change (solid lines) and with behaviour change (50% reduction in partner change rate) starting in 1990, 1995 and 2000.

2.2 Methods

2.2.1 Mathematical Model for Country-level Analyses – Summary

A deterministic mathematical model of the heterosexual transmission of HIV in a sex, age and sexual activity (defined according the rate of sexual partner change) stratified population, based on earlier published models [48] was developed. To focus on trends in prevalence in young women attending antenatal clinics, the model included a detailed yearly age structure of young adults allowing changes in ages of sexual debut and rates of partner change in those recently entering the sexually active population.

HIV is assumed to be transmitted through sexual partnerships or at the time of birth from an infected mother to her child. The population is divided into five sexual activity groups, characterised by the number of sexual partnerships formed per year. On sexual debut most individuals enter the group with the lowest sexual activity, but a minority enter groups with much higher sexual activity. In response to differential mortality in these groups two assumptions are possible: first, the highest sexual activity groups can be depleted if those with high risk suffer greater mortality; second, the relative sizes of the groups are maintained by recruiting individuals from other sexual activity groups into the higher activity groups. An individual of a particular sex, age and sexual activity forms a number of sexual partnerships each year with partnerships preferentially directed between older men and younger women and with individuals of the corresponding sexual activity class of the opposite gender. Transmission of HIV is assumed to be prevented by correct and consistent condom use throughout the partnership and the probability of consistent use depends on the age of both partners. To represent the long and variable incubation period of HIV and the higher transmission probability associated with initial and later stages of infection, those infected progress through three stages of asymptomatic infection prior to AIDS: a first stage lasting 3 months with a high transmission probability; a second stage lasting several years with the lowest transmission probability; and a third stage lasting 6 months with a high transmission probability.

The growth of the model epidemic was roughly matched to the earliest available ANC prevalence data by adjusting the transmission probability per sexual partnership and the assortativeness of mixing between the high and low sexual activity groups. The date of the start of the epidemic was chosen in consultation with local epidemiologists. Other model parameters values were chosen to maximise the natural decline in HIV prevalence and create a robust 'null model' of trends without extrinsic behaviour change. These assumptions are outlined in the results. A model

scenario with no exogenous behaviour change was compared with one where behaviour change was assumed. Where behaviour change data were available (using the same indicator in successive surveys) these were used to estimate the change in parameter values for the alternative model run. If no such data were available a stepwise change in the transmission probability per partnership was used instead.

2.2.2 Mathematical Model for Country-level Analyses– Full definition

The model is defined by a set of partial differential equations with respect to time and age that are solved numerically with a four-stage Runge-Kutta algorithm (time-step = 0.02 years). The population is stratified by sex ($k=1$ for males, $k=2$ for females) and sexual activity ($m=0$ (lowest) to 4 (highest)). The model treats HIV infection status as either HIV negative (X), HIV acute infection (Y^1), latent infection (Y^2), pre-AIDS (Y^3) or full blown AIDS (Z). The model is run for 100 years to establish a stable population structure before the introduction of infection with 0.01% of males aged 25-29 years in the highest sexual activity group moving from X to Y^1 . The partial differential equations are:

$$\begin{aligned}\frac{\partial X_{k,m}}{\partial t} + \frac{\partial X_{k,m}}{\partial a} &= -X_{k,m}(\mu_k(a) + \lambda_{k,m}(a,t)) \\ \frac{\partial Y_{k,m}^1}{\partial t} + \frac{\partial Y_{k,m}^1}{\partial a} &= \lambda_{k,m}(a,t) \cdot X_{k,m} - Y_{k,m}^1(\mu_k(a) + v_1) \\ \frac{\partial Y_{k,m}^2}{\partial t} + \frac{\partial Y_{k,m}^2}{\partial a} &= v_1(a) \cdot Y_{k,m}^1 - Y_{k,m}^2(\mu_k(a) + v_2(a)) \dots (2.1) \\ \frac{\partial Y_{k,m}^3}{\partial t} + \frac{\partial Y_{k,m}^3}{\partial a} &= v_2(a) \cdot Y_{k,m}^2 - Y_{k,m}^3(\mu_k(a) + v_3) \\ \frac{\partial Z_{k,m}}{\partial t} + \frac{\partial Z_{k,m}}{\partial a} &= v_3 Y_{k,m}^3 - Z_{k,m}(\mu_k(a) + \alpha)\end{aligned}$$

$\mu_k(a)$ is the gender and age-specific per-capita death rate; $\lambda_{k,m}(a,t)$ is the force of infection to individual of that gender, age and activity-group at time t ; $\frac{1}{v_1}$, $\frac{1}{v_2(a)}$ and $\frac{1}{v_3}$ are the mean number of years spent with acute infection, latent infection and pre-AIDS, respectively; α is the mortality rate for those with AIDS.

At each moment, the number of new-borns introduced into each gender and sexual activity-group in the population is:

$$\begin{aligned}
X_{k,m}(0,t) &= \varpi_k \gamma_m \left\{ \int \varphi(a) \sum_m X_{2,m}(a,t) da \right. \\
&\quad \left. + (1-\sigma) \int \varphi(a) \sum_m [f_1 Y_{2,m}^1(a,t) + f_2 Y_{2,m}^2(a,t) + f_3 Y_{2,m}^3(a,t)] da \right\} \\
Y_{k,m}^1(0,t) &= \varpi_k \gamma_m \sigma \int \varphi(a) \sum_m [f_1 Y_{2,m}^1(a,t) + f_2 Y_{2,m}^2(a,t) + f_3 Y_{2,m}^3(a,t)] da \\
&\dots (2.2)
\end{aligned}$$

where $\varphi(a)$ is the age-specific fertility and f_1, f_2 and f_3 are the reduction in fertility associated with acute infection, latent infection and pre-AIDS, respectively; σ is the probability of mother-to-child transmission, ϖ_k is the fraction of babies born that gender and γ_m is the fraction entering that sexual activity-group. For simplicity, entering into a sexual activity class is assumed to be at birth but that sexual activity does not occur until they individuals reach older age groups.

The risk of a susceptible individual becoming infected is a function of the yearly age group rather than a continuous function of age such that $\lambda_{k,m}(i-0.5 \leq i < i+0.5, t) = F_{k,i,m}(t)$. We define the pattern of contact within the population through a matrix determining the age and activity group-specific rates of partnerships formation with the age and activity groups of the opposite gender. Here one's own age and activity category is denoted i and m , respectively, and those of members of the opposite gender are distinguished with a prime (i' and m').

The force of infection is calculated as:

$$\begin{aligned}
F_{k,i,m}(t) &= \sum_{m'} \sum_{i'} (c_{k,i,m,i',m'}(t) \cdot P_{k,i',m'}(t) \cdot (1 - \psi_{i,i'})) \quad \} A^1 \leq i \leq A^2 \\
F_{k,i,m}(t) &= 0 \quad \} \text{otherwise} \\
&\dots (2.3)
\end{aligned}$$

where $c_{k,i,m,i',m'}$ is the number of partnerships formed with individuals of the opposite gender by age and activity group, $P_{k,i',m'}$ is the risk of acquiring infection when forming partnerships with individuals of the opposite gender by age and sexual activity, and $\psi_{i,i'}$ is the chance that condoms are used consistently in partnerships formed between individuals of age i and i' , and A^1 and A^2 are the ages at which sexual activity begins and ends, respectively. The definition of these terms follows.

$C_{k,i,m}$ is the total number of partnerships formed each year and they are shared amongst the age and activity groups of the opposite gender according to the matrix $c_{k,i,m,i',m'}$:

$$c_{k,i,m,i',m'} = C_{k,i,m} \left[(1-\varepsilon) \delta_{m,m'} + \varepsilon \frac{N_{k,i',m} C_{k',i',m'}}{\sum_{m'} N_{k',i',m} C_{k',i',m'}} \right] \Delta_{k,i,i'} \dots (2.4)$$

$$N_{k,i,m} = \int_{i-0.5}^{i+0.5} X_{k,m}(a,t) + Y_{k,m}^1(a,t) + Y_{k,m}^2(a,t) + Y_{k,m}^3(a,t) da \dots (2.5)$$

where $N_{k,i',m'}$ is the number of sexually-active individuals and $\delta_{m,m'}$ is the identity matrix. Thus the pattern of mixing with respect to activity ranges from assortative (like-with-like, $\varepsilon=0$) to random ($\varepsilon=1$) and the pattern of mixing with respect to age is determined by the distribution $\Delta_{k,i,i'}$ - the fraction of partnerships that are formed between individuals age i and i' . Here we assume that $\Delta_{k,i,i'}$ depends only on the age difference between partners: (age of male minus age of female); which for females is:

$$\Delta_{2,i,i'} = \frac{\kappa \rho^\kappa (i' - i + r)^{\kappa-1}}{(1 + (\rho(i' - i + r))^\kappa)^2} \text{ if } i' \geq i \dots (2.6)$$

$$\Delta_{2,i,i'} = 0 \text{ otherwise}$$

And for males is:

$$\Delta_{1,i,i'} = \sum_{i'} \Delta_{2,i',i} \dots (2.7)$$

$\Delta_{k,i,i'}$ is scaled so that $\sum_{i'=A^1}^{A^2} \Delta_{i,i'} = 1$. Here κ , ρ and r are the shape parameters for log-

logistic distribution. This distribution allows most partnerships to be formed between women and men a few years older but a few partnerships to involve women and men many more years their senior.

The difference in rate of partnership formation between the sexual activity groups is defined as:

$$C_{k,i,m} = \frac{M_{k,i}}{\tau^{\sum m \gamma_m}} \tau^m \dots (2.8)$$

Here $M_{k,i}$ is the gender and age-specific geometric mean of partnership formation rate and τ independently determines the common ratio of the partner change rates between the sexual-activity categories. For example, for a mean partner change rate of 1.6, the number of sexual partners per year for each group (and percent of population in that group) would be: 0.79 (59%), 2.38 (25%), 7.13 (10%), 21.39 (5%) and 64.16 (1%).

At each moment, the pattern of partnership formation ($c_{k,i,m,i',m'}$) is constrained such that the total number of sexual partnerships formed by males of type i,m with females type i',m' must equal the total number of partnerships formed by females of type i',m' with males of type i,m . That is:

$$N_{1,i,m} c_{1,i,m,i',m'} = N_{2,i',m'} c_{2,i',m',i,m}$$

If this does not hold the following adjustment is made:

$$\begin{aligned} D_{i,m,i',m'} &= \frac{N_{1,i,m} c_{1,i,m,i',m'}}{N_{2,i',m'} c_{2,i',m',i,m}} \\ c_{1,i,m,i',m'} &\rightarrow \frac{c_{1,i,m,i',m'}}{\sqrt{D_{i,m,i',m'}}} \dots (2.9) \\ c_{2,i',m',i,m} &\rightarrow c_{2,i',m',i,m} \sqrt{D_{i',m',i,m}} \end{aligned}$$

In this way, equal proportionate changes are made for males and females in the overall partner change rate and mixing pattern.

The other two components of $F_{k,i,m}(t)$ are the chance of infection per partnership and the probability that condoms are used correctly and consistently throughout those sexual partnerships. The probability of getting infected through a sexual partnership in which condoms are not used with individuals of the opposite gender aged i and in sexual activity group m , is:

$$P_{k',i',m'}(t) = \frac{\int_{i'-0.5}^{i'+0.5} (\beta^1 Y_{k',m'}^1(a,t) + \beta^2 Y_{k',m'}^2(a,t) + \beta^3 Y_{k',m'}^3(a,t)) da}{\int_{i'-0.5}^{i'+0.5} X_{k',m'}(a,t) + Y_{k',m'}(a,t) + Y_{k',m'}^2(a,t) + Y_{k',m'}^3(a,t) da} \dots (2.10)$$

where β^1 , β^2 and β^3 are the probabilities of transmission of HIV during acute infection, latent infection, pre-AIDS and AIDS respectively.

The chance that condoms are used correctly and consistently in sexual partnerships between individuals aged i and i' is $\psi_{i,i'}$. We write $\psi_{i,i'} = \Theta \chi_{i,i'}$ so that the pattern of condom use reported in cross-sectional data collected in rural Zimbabwe [40] $\chi_{i,i'}$, is scaled by Θ to match the age-specific levels of condom use reported in each country's behavioural surveys.

If the relative sizes of each sexual activity group are to be kept constant (with respect to time and age) individuals may need to move between sexual activity groups to compensate for the greater AIDS mortality the higher sexual activity groups may suffer:

$$\Omega_i = \left(\gamma_m N_{k,\bullet}(a) - \frac{N_{k,m}(a)}{N_{k,\bullet}(a)} \right) \dots (2.11)$$

Then iterating for $m=4,3,2,1$:

$$\begin{aligned} S_{k,i,m} &\rightarrow S_{k,i,m} + \frac{S_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i & S_{k,i,m-1} &\rightarrow S_{k,i,m-1} - \frac{S_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i \\ Y^1_{k,i,m} &\rightarrow Y^1_{k,i,m} + \frac{Y^1_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i & Y^1_{k,i,m-1} &\rightarrow Y^1_{k,i,m-1} - \frac{Y^1_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i \\ Y^2_{k,i,m} &\rightarrow Y^2_{k,i,m} + \frac{Y^2_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i & Y^2_{k,i,m-1} &\rightarrow Y^2_{k,i,m-1} - \frac{Y^2_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i \dots (2.12) \\ Y^3_{k,i,m} &\rightarrow Y^3_{k,i,m} + \frac{Y^3_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i & Y^3_{k,i,m-1} &\rightarrow Y^3_{k,i,m-1} - \frac{Y^3_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i \\ Z_{k,i,m} &\rightarrow Z_{k,i,m} + \frac{Z_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i & Z_{k,i,m-1} &\rightarrow Z_{k,i,m-1} - \frac{Z_{k,i,m-1}}{N_{k,i,m-1}} \Omega_i \end{aligned}$$

The modelled HIV prevalence among women attending clinics can be weighted to take into account the potential under-representation of those with advanced disease [47] or less risky behaviour:

$$y = \frac{\int_{15}^{50} \left\{ \int f_1 w_m Y_{2,m}^1(a,t) dm + \int f_2 w_m Y_{2,m}^2(a,t) dm \right.}{\int_{15}^{50} \left\{ \int f_1 w_m X_{2,m}(a,t) dm + \int f_1 w_m Y_{2,m}^1(a,t) dm + \int f_2 w_m Y_{2,m}^2(a,t) dm \right.} \\ \left. + \int f_3 w_m Y_{2,m}^3(a,t) dm + \int f_4 w_m Y_{2,m}^4(a,t) dm \right\} da}{\int_{15}^{50} \left\{ \int f_3 w_m Y_{2,m}^3(a,t) dm + \int f_4 w_m Y_{2,m}^4(a,t) dm \right\} da}$$

where w_m is the relative chance of women in that sexual activity group attending clinic, and f_1, f_2, f_3 and f_4 are the relative chance (with respect to uninfected women) of women with acute, latent, pre-AIDS and AIDS attending clinic.

Default model parameters are listed in Tables 2.1, 2.2, 2.3, 2.4, 2.5 and 2.6.

Parameter Value	Symbol	Default Value	Source
Mortality rate	$\mu_k(a)$	Table 2.2	[200]
Fertility rate	$\phi(a)$	Table 2.2	[200]
Mean time in acute infection stage	$1/\nu_1$	3 months	[47]
Mean time in latent infection stage	$1/\nu_2(a)$	Table 2.3**	[47]
Mean time in pre-AIDS stage	$1/\nu_3$	6 months	[47]
Mean time with full blown AIDS before dying	$1/\alpha$	6 months	[47]
Transmission probability (latent infection stage)	β	(0.01 – 0.06)**	[97]
Transmission probability (primary stage, tertiary stage and full blown AIDS)	10β	(0.1 – 0.6)**	[97]
Probability of vertical transmission	σ	0.35	[47]
Fraction of contacts made randomly with respect to sexual activity class	ε	(0.3-0.6)**	[47]
Age-difference between sexual partners (shape parameters for log-logistic distribution)	r κ ρ	0.15* 2 0.25	Behavioural survey in rural Zimbabwe [39]
Number of partnerships formed per year: Common ratio between sexual activity groups Age and gender-specific geometric mean	τ $M_{k,i}$	(3-4)** Table 2.4	DHS survey from Cote D'Ivoire (1994) [225].
Probability of consistent condom use: Age-specific pattern Scalar	$\chi_{a,a'}$ Θ	Table 2.5 1.00*	Behavioural survey in rural Zimbabwe [39]
Age at first sex	A^1_k	16*	
Age at last sex	A^2_k	55*	
Proportion of population born into each activity group	γ_1		
	γ_2	0.59	
	γ_3	0.25	
	γ_4	0.10	
	γ_5	0.05 0.01	
Relative chance of appearing in ANC sample:			
acute stage relative to HIV negative	f_1	0.58	[46]
latent stage relative to HIV negative	f_2	0.47	
pre-AIDS stage relative to HIV negative	f_3	0.43	
full blown AIDS relative to HIV negative	f	0.14	
Relative chance of women in that sexual activity group attending ANC.	w_m	1.00**	

Table 2.1 Default parameter values for the country-level analyses model. * indicates that this parameter was used to fit to the model to country-specific data. ** indicates that the effect of this parameter on trends in prevalence was investigated and a value was chosen so as to maximise the drop in prevalence (Table 2.7).

Age-range	Deaths per person-year ($\mu(a)$)		Births per female person-year ($\phi(a)$)
	Male	Female	
<1	0.117	0.100	0
1-4	0.019	0.019	0
5-9	0.007	0.006	0
10-14	0.004	0.004	0
15-19	0.004	0.004	0.175
20-24	0.006	0.005	0.313
25-29	0.007	0.006	0.324
30-34	0.007	0.006	0.271
35-39	0.008	0.007	0.201
40-44	0.010	0.008	0.125
45-49	0.012	0.009	0.053
50-54	0.016	0.012	0
55-59	0.021	0.016	0
60-64	0.030	0.024	0
65-69	0.044	0.038	0
70-74	0.068	0.060	0
75-79	0.105	0.094	0
80+	0.189	0.174	0

Table 2.2 Demographic data for the country-level analyses model. Per-capita mortality rate for males and females, and per-capita fertility rate for females (data from [207]). These data generate population growth of approximately 4% per year and a life expectancy at birth of 52.1 for males and 54.7 for females.

Age-range	Mean years spent in secondary stage of infection $Y^2 (v_{23}(a)^{-1})$
0-9	0.75
10-24	6.0
25-29	4.8
30-34	4.0
35-39	3.4
40-44	3.0
45-49	2.7
50-59	2.4
60+	2.2

Table 2.3 Mean time spent in secondary stage of infection in the country-level analyses model. Older individuals remain in the secondary stage of infection for less time giving an overall faster progression from infection to AIDS (values based on data from [234]).

Mean number of partnerships formed per year ($M_{k,i}$)		
Age-range	Males	Females
15-19	1.6	1.2
20-24	1.6	1.2
25-29	1.6	1.1
30-39	1.7	1.5
40-49	1.6	1.1
50+	1	1*

Table 2.4 Mean rate of partnership formation by gender and age. Mean number of sexual partners in last twelve months, by age and gender (Cote d'Ivoire DHS 1994 [235]). *this value was not available from the survey – the value used for females was set equal to that for males.

	Probability condom used in partnerships ($\chi_{i,i'}$)	
	Female aged <25	Female aged 25+
Male aged <25	0.32	0.29
Male aged 25+	0.10	0.07

Table 2.5 Probability of correct and consistent condom use. The fraction of sexual partnerships (by male and female age) in which a condom was used last time, as reported by either male or female (data from rural Zimbabwe [40]).

2.2.3 Data Sources for Country-level Analyses

To avoid trends in prevalence reflecting changes in the sampled population, only data collected from the same ANC sites over time were included in the analysis. Where sample sizes were available we could construct 95% confidence intervals around the prevalence estimates. If such data were not available we include a $\pm 3\%$ uncertainty interval, which approximates the width of 95% confidence intervals if the sample was of ~ 300 individuals.

A brief summary of the HIV prevalence data used follows: *Haiti* Five urban Ante-natal clinic (ANC) sites from 1993 to 2003 [236]; *Kenya* Thirteen urban ANC sites from 1990 to 2003 [237]; *Zimbabwe* Nationwide ANC sites from 2000 to 2004 (Genscreen test) [16]; *Cote d'Ivoire* Ten urban sites from 1997 to 2002 [233]; *Malawi* Nineteen nationwide sites from 1996 to 2003 [238]; *Rwanda* Twenty-four nationwide ANC sites in 2002 and 2003 [239]; *Uganda* Five ANC sites from 1992 to 2002 (St Marys Hospital, Lacor, Gulu (northern Uganda), St Francis Hospital, Kampala (central Uganda), Mbarara Hospital (south western Uganda), Jinja Hospital (eastern Uganda) and Mbale Hospital (eastern Uganda) [240]; *Ethiopia* Urban sites from 2001 to 2003 [241].

From each of these counties the following data were sought for model parameterisation: median age at first sex for males and females, age-specific use of condoms (at last sex and with last non-regular partner), age-specific mean number of

sexual partners in last year and age of spouse or last partner. A brief summary of the sexual behaviour data that were received and that were used follows: *Haiti* Mean number of different sexual partners per year, age at first sex for males and females and condom use (at last sexual intercourse) for 1994/5 [236]; *Kenya* Age at first sex from the Kenyan Demographic and Health Survey (KDHS) 1993, condom use (at last sex with any partner) from KDHS 1998 and difference in median age at marriage from KDHS 2003 [237]; *Zimbabwe* Condom usage (with any partner in last four weeks) taken from the Zimbabwe Demographic and Health Survey 1994 [16]; *Cote d'Ivoire* Total number of different sexual partners in last year, condom usage (with any partner in last two months), age of spouse and females' age at first sex from the Cote d'Ivoire Demographic and Health Survey (CDHS) 1994 and males' age at first sex from CDHS 1998/9; *Malawi* Condom use (at last sex with non-marital/non-cohabitating partners) from Knowledge, Attitudes and Practices in Health Survey 1996, percent married by age from Malawi Demographic and Health Survey (MDHS) 1992 and age at first sex from MDHS, 2000 [238]; *Rwanda* Median age at first sex from Enquête Démographique et de Santé (2000) [239]; *Uganda* Condom use (at last sex with any partner) from Ugandan Demographic and Health Survey (UDHS) (2000) and median age at first sex from UDHS (1995) [240]; *Ethiopia* Condom use (at last sex with any partner) and age at first sex from the Ethiopian Demographic and Health Survey (2000) [241]. These data are given in Table 2.6.

These population averages fail to specify some of the details of individual behaviour required to fully parameterise the model. To overcome this lack of detail in country-wide data we used detailed sexual behaviour data from a household-based population survey in rural Zimbabwe [40] to specify the heterogeneity in sexual partner change rates and the dependency of condom use on age of both partners. For each country all values were altered to generate the observed averages. The mean age difference between sexual partners was estimated by either the mean age difference between spouses or the difference in the median age of marriage between men and women. Where no data were available default model parameters were based on the rural Zimbabwe data, with the exception of partner acquisition rates as a function of age which were based instead on observed patterns reported in Cote D'Ivoire for 1994, which it was thought would be more representative of national averages. Parameter values for each country are given in Table 2.7. All simulations were run using a common demographic background rates [207] such that in the absence of infection the population would grow at approximately 4% per year and life expectancy at birth for males and females is 52.1 and 54.7 respectively.

	Haiti	Kenya	Zimbabwe	Uganda (N, C, W)*	Uganda (E)*	Ethiopia	Cote d'Ivoire	Malawi	Rwanda
Baseline settings									
Age at first sex (Males)	18	17	17	17	17	20	18	18	17 [†]
Age at first sex (Female)	19	17	17	17	17	16	16	17	17 [†]
Probability of consistent condom per partnership (male<24 with female<24)	0.09	0.29	0.06	0.42	0.42	0.11	0.27	0.32	0.32 [†]
Mean age difference between partners (male age minus female age)	6.4	5.4	7.3 [†]	7.3 [†]	7.3 [†]	7.3 [†]	8.6	5.8	7.3 [†]
Behavioural changes (year implemented)									
Probability of HIV transmission (<i>proportionate reduction</i>).	n/a	n/a	50% (2000)	75% (1990)	80% (1994)	n/a	n/a	n/a	n/a
Delay in age at first sex, males (<i>years</i>).	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Delay in age at first sex, females (<i>years</i>).	n/a	+1 (1999)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
		F [‡] 30% (1999)							
Number of sexual partnerships per year (<i>proportionate reduction</i>)	10% (1995)	M [‡] 26% (1999); 0.80 (2001)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Probability of consistent condom per partnership (<i>proportionate increase</i>)	100% (1995)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Table 2.6 Behavioural data used in parameterisation of the model. †denotes that the default parameter was used in place of country-specific data. ‡ F-Females, M-Males. *Uganda sites were provided separately as N-Northern (St Marys Hospital, Lacor, Gulu), C-Central (St Francis Hospital, Nsambya, Kampala), Western (Mbarara Hospital,), E-Eastern (Jinja Hospital and Mbale Hospital). Sources for behaviour data are listed in the supplementary material.

	Haiti	Kenya (Busia...) [†]	Kenya (Garissa,...) [‡]	Zimbabwe	Uganda (N, C, W) ^{**}	Uganda (E) ^{**}	Ethiopia	Cote d'Ivoire	Malawi	Rwanda
Transmission probability per partnership for secondary stage of infection (β)	0.01	0.02	0.02	0.03	0.05	0.04	0.04	0.04	0.08	0.03
Mean years from infection to death (aged<30years)*	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3	7.3
Common ratio in partner-change rate between sexual activity groups (τ)	3.3	2.7	3.3	2.7	2.2	2.7	2.7	2.1	3.0	4.0
Randomness of mixing between sexual activity groups (ϵ).	0.3	0.6	0.6	0.8	0.3	0.6	0.6	0.3	0.3	0.3
	1.0	0.1	0.5	0.1	0.1	1.0	1.0	1.0	1.0	1.0
Probability of adults being in ANC [†] sample by sexual activity group (ascending)	1.0	0.2	0.5	0.2	0.2	1.0	1.0	1.0	1.0	1.0
	1.0	0.5	0.5	0.5	0.5	1.0	1.0	1.0	1.0	1.0
	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table 2.7 Values of parameter used in the application of the model to specific countries. These parameters are the most influential on the trends in prevalence and were used to maximise the drop in prevalence and fit the model to data as closely as possible. Due to paucity of available data, the large number of parameters and the absence of uncertainty estimates for the recorded prevalence, statistical fitting could not be satisfactorily applied: a subjective graphical fitting method was used instead. [†]ANC stands ante-natal clinic. *see table 2.3 for full details of relationship between age and time spent in second stage of HIV infection. [†] Urban Kenya sites – Busia, Meru, Nakuru and Thika, [‡] Urban Kenya sites of Garissa, Kisii, Kitui and Nyeri. ^{**}Uganda sites were provided separately as N-Northern (St Marys Hospital, Lacor, Gulu), C-Central (St Francis Hospital, Nsambya, Kampala), Western (Mbarara Hospital, E-Eastern (Jinja Hospital and Mbale Hospital).

2.2.4 Data Sources for Further Analysis of Zimbabwe Epidemic Changes

The time at which incidence may have declined in Zimbabwe was estimated by fitting a simplified mathematical model to observed changes in prevalence from individual ANC sites. Since the pattern of prevalence decline in maturing epidemics is determined by the rate of growth earlier in the epidemic, ANC sites with the longest

time series were selected. In Zimbabwe, there are 12 sites with data from 1997 and some of these sites have collected data from as early as 1990. The estimates from before 1997 were made by the World Health Organization using slightly different methods from that used for estimates made later by the Centers for Disease Control. The fitting procedure was therefore repeated taking the earliest data into account ("Fit 1") and rejecting the data from before 1997 ("Fit 2"). The full dataset is shown in Table 2.8.

Location	Site	HIV Prevalence Estimates (Genscreen test)										
		Year: 1989	1991	1992	1993	1994	1995	1997	2000	2001	2002	2004
Urban	Bindura					40.0	27.0	29.3	32.1	25.9	34.3	26.1
	Nkulamane (Bulawayo)	10.0	17.1		25.8		30.0	24.0	31.1	27.9	26.4	18.8
	Chitungwiza (Harare)			29.0		41.7		23.3	33.5	30.7	33.9	22.5
	Gweru		28.1	24.0	21		22.9	24.0	36.4	28.5	27.7	26.9
	Kuwadzana (Harare)							28.1	27.8	30.5	26.9	20.3
	Chinotimba							42.6	55.7	45.3	36.3	35.8
	Median	10.0	22.6	26.5	23.4	40.9	27.0	26.1	32.8	29.5	30.8	24.3
Other	Beitbridge							46.0	41.2	28.9	36.2	28.0
	Chiredzi									32.1	37.3	20.4
	Gwanda							48.0	30.4	42.2	42.4	30.7
	Median (excl Chiredzi)							47.0	35.8	35.6	39.3	29.4
Rural	Binga			13.6		11.5		9.2	13.0	19.1	19.6	12.4
	Karanda							23.9	18.3	19.3	23.5	14.2
	Mutoko			20.7				13.4	33.7	33.2	22.7	22.0
	Sadza							22.0	42.7	31.6	34.2	26.4
	Median			17.2		11.5		17.7	26.0	25.5	23.1	18.1

Table 2.8 HIV prevalence estimates in Zimbabwe from consistently samples ANC sites.

2.2.5 Model for Further Analysis of Zimbabwe Data

The model used here is also a deterministic representation of the heterosexual transmission of HIV in a sex and sexual activity stratified population. In contrast to the previous model, there is no age-structure and the population is set to grow at a constant rate in the absence of HIV/AIDS. This makes the model much quicker to execute, which is an important consideration in model design when computationally-intensive fitting procedures are used. Since the data are not specified by age and patterns of sexual behaviour over age were not found to be influential in the process of epidemic maturation, this simplification should not interfere with the analysis.

The model is defined by the following set of ordinary differential equations, for which a numerical solution was found using Euler’s method (time-step 0.05 years).

The state variables are $X_{k,i}^s$, where k is gender ($k=1$ for males; $k=2$ for females), i is the sexual-activity group ($i=1$ (highest) to 3 (lowest)) and s is the disease-state ($s=1$ for susceptible; $s=2$ for acute infections; $s=3$ to 6 for latent

infection; $s=7$ for pre-AIDS; $s=8$ for AIDS). Where possible, the symbols chosen are the same as in the first model definition; a full list of parameter meanings and values is given in Table 2.9.

The ordinary differential equations are:

$$\begin{aligned}\frac{dX_{k,i}^1}{dt} &= \frac{\mu + \alpha}{2} \left(\sum_s \sum_i X_{k,i}^s \right) - \lambda_{k,i} X_{k,i}^1 \\ \frac{dX_{k,i}^2}{dt} &= \lambda_i X_i^1 - \sigma_2 X_i^2 \\ \frac{dX_{k,i}^s}{dt} &= \sigma_{s-1} X_{k,i}^{s-1} - \sigma_s X_{k,i}^s \quad \text{for } s = 2, 3, \dots, 8\end{aligned} \quad \dots(2.13)$$

The force of infection is calculated as the product of a scalar “risk” parameter $R(t)$ and, as above, the partner change rate for that group and a matrix describing the distribution of contact with respect to the sexual activity groups of the opposite gender.

$$\begin{aligned}\lambda_{k,i} &= R(t) c_{k,i} \sum_{i'} \left(\rho_{k,i,i'} \frac{X_{k',i'}^{s'} \sum_{s=2}^7 (1 - (1 - \kappa_k \beta_{s'})^{X_{\min(i,i')}^s})}{\sum_{s=1}^7 X_{k',i'}^{s'}} \right) \quad \dots(2.14) \\ \rho_{k,i,i'} &= (1 - \varepsilon) \partial_{i,i'} + \varepsilon \frac{c_{k',i'} \sum_{s=2}^7 X_{k',i'}^s}{\sum_{i'} \left(c_{k',i'} \sum_{s=2}^7 X_{k',i'}^s \right)}\end{aligned}$$

The problem of ‘balancing’ the supply and demand of sexual partnership by males and females is tackled in the same way as the previous model:

$$\begin{aligned}D_{u,v} &= \frac{\rho_{1,i,i'} \sum_{s=2}^7 X_{1,i}^s}{\rho_{2,i',i} \sum_{s=2}^7 X_{2,i'}^s} \\ \rho_{1,i,i'} &\rightarrow \rho_{1,i,i'} (D_{u,v})^{0.5} \quad \dots(2.15) \\ \rho_{2,i,i'} &\rightarrow \rho_{2,i',i} (D_{v,u})^{0.5}\end{aligned}$$

Unlike in the earlier model, the partner change rates in the different activity groups are parameterised by the arithmetic mean across all groups and proportional differences between each group and the group with the lowest rate:

$$c_{k,1} = \frac{\bar{c}_k}{\sum_i \omega_{k,i} \phi_{k,i}} \quad \dots(2.16)$$

$$c_{k,i} = c_{k,1} \phi_i \quad \text{for } i = 2, 3$$

The timing of the risk reduction is estimated by fitting the initial risk level, r_1 , the time of change T , and the eventual risk level, r_2 . At the time of change, the overall risk decreases linearly for three years:

$$R(t) = r_1 \quad \text{if } t < T$$

$$R(t) = r_1 - (r_1 - r_2) \frac{t - T}{3} \quad \dots(2.17)$$

$$R(t) = r_2 \quad \text{if } t > T + 3$$

The model output, to which the ANC prevalence data is fitted, is weighted HIV prevalence among females.

$$\text{Weighted prevalence} = \frac{\sum_{s=2}^7 \sum_i w_i X_{2,i}^s}{\sum_{s=1}^7 \sum_i w_i X_{2,i}^s} \quad \dots(2.18)$$

An important difference between this model and the one described earlier in the chapter is that the compartment for latent infection ($s=3$ to 7) is split into four compartments, so that the overall survival time from infection to death is gamma distributed, giving a better agreement with observed survival distributions [230, 234] (Figure 2.2). Whereas in the previous model, the decline in prevalence was to be exaggerated by assuming a fast progression to death, it is important in this application to have a more realistic temporal distribution of mortality so that the timing of changes in incidence can be accurately estimated from prevalence data.

Changes in all types of sexual risk behaviour (multiple sexual partners, concurrency of sexual partners, STIs, condom use, and so on) are subsumed into a single parameter, R , which describes overall “risk”. An initial match to the growth part of the epidemic is found manually by varying r_1 and w_i . The values of r_2 and T

are fitted using a general-purpose search algorithm, which implements a form of the Nelder-Mead simplex method [242]. Information on the sample sizes associated with each estimate was not available so goodness-of-fit was assessed using sum-of-squared errors assigning equal weighting to each data-point.

Estimates of prevalence at ANCs can be very high compared to models parameterised using reported behaviour data. This is because current reports of risk behaviour probably represent the lower bound of the range of risk behaviour that existed when the epidemic started, since some individuals will have changed their risk behaviour, some individuals with risky sexual behaviour will have died [231], and social desirability biases may tend to make reports of behaviour increasingly conservative over time [228]. In addition, ANC prevalence may over-estimate prevalence in the general population, since pregnant women may have been disproportionately exposed to unprotected sex, and because women not using modern methods of contraception may be least likely to take measures to protect themselves from HIV infection [52]. For the model to fit observed prevalence data, a high level of risk at the start of the epidemic is required (r_1), which suppresses the natural epidemiological dynamics later on, and potentially leads to over-estimating any estimate of the reduction in risk. To overcome this, observed ANC prevalence estimates are matched with model prevalence values weighted to favour the contribution of the higher risk sexual activity group. This negates the need for a high level of risk at the beginning of the epidemic and maximises the contribution of the natural epidemiological dynamics to the downturn in prevalence during maturation.

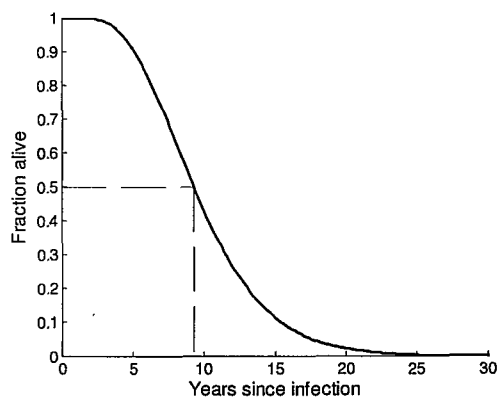


Figure 2.2 Distribution of time from infection to death in the simplified model used in the analysis of Zimbabwean ANC site data.

Interpretation	Symbol (or formula)	Default Value
Years spent sexually active	$1/\mu$	50
Population growth rate in the absence of HIV/AIDS	α	0.04
Mean time with acute infection	$1/\sigma_2$	2
Mean time with latent infection	$4/\sigma_3 = 4/\sigma_4$ $= 4/\sigma_5 = 4/\sigma_6$	8
Mean time with pre-AIDS	$1/\sigma_7$	1
Mean time with AIDS	$1/\sigma_8$	0.5
Per sex-act transmission probability from individuals with acute infection	β_2	0.01
Per sex-act transmission probability from individuals with latent infection	$\beta_3 = \beta_4 = \beta_5 = \beta_6$	0.001
Per sex-act transmission probability from individuals with pre-AIDS infection	β_7	0.01
Relative transmission probability from male-to-female compared with female-to-male ($\kappa_1=1$ by definition)	κ_2	2
Number of unprotected sex acts in partnerships with individuals in highest risk group	χ_1	4.8
Number of unprotected sex acts in partnerships with individuals in middle risk group	χ_2	45
Number of unprotected sex acts in partnerships with individuals in lowest risk group	χ_3	95
Mean partner change rate for males	$\bar{c}_1$	4
Mean partner change rate for females	$\bar{c}_2$	3.5
Relative partner change rate for individuals in highest sexual activity group compared with those in the lowest ($\omega_{k,3}=1$ by definition).	$\omega_{k,1}$	100
Relative partner change rate for individuals in middle sexual activity group compared with those in the lowest.	$\omega_{k,2}$	20
Fraction of individuals that start sex in highest sexual activity group.	$\phi_{k,1}$	0.1
Fraction of individuals that start sex in middle sexual activity group.	$\phi_{k,2}$	0.3
Fraction of individuals that start sex in lowest sexual activity group.	$\phi_{k,3}$	0.6

Table 2.9 Default parameter values for the simplified model used in the analysis of Zimbabwean ANC site data.

2.3 Contributions

I am grateful to a large number of people for providing access to the data used in this chapter - their names are listed at the end of this chapter. In addition to my supervisors, I received constructive comments from John Stover (Futures Group,

Washington D.C.) and an anonymous referee who both read initial versions of the paper on which this chapter is based.

2.4 Results

2.4.1 Maximising Natural Dynamics Prevalence Declines

The aim of modelling the transmission dynamics of HIV here was to predict the course of the epidemic in the absence of behaviour change. In order for the contribution of natural dynamics to be excluded when interpreting any observed reductions in prevalence. For a conservative analysis, assumptions were made that maximise the predicted declines in prevalence.

As HIV spreads first among those with the highest risk of acquiring infection, incidence increases sharply. This rapid local “saturation” of those at highest risk is a consequence of the extreme variance in sexual activity within the population with the majority forming few new sexual partnerships each year and a minority forming very many more. Incidence will increase more quickly if there is a high transmission probability of the virus in those recently infected. Subsequent infection mainly occurs in those with lower risk sexual behaviour and the number of new cases and the risk per susceptible decreases. A prevalence decline ten to twenty years into the epidemic could be the product of that historic reduction in incidence or a more recent reduction in incidence associated with the deliberate adoption of safer sexual behaviour. Understanding the determinants of that initial decline in incidence and how it influences later trends in prevalence is crucial in our analysis. Whether the initial decline in incidence generates a subsequent fall in prevalence is determined by how spread out deaths are and how closely incidence and prevalence are coupled, i.e. the interval between infection and death Figure 2.3(A). A long interval means that prevalence will record information about the risk experience accumulated over many years with the early reduction in incidence not manifest, but a shorter interval allows prevalence to follow the drop in incidence more closely. The relationship between prevalence and incidence is easier to interpret in young people because infections will have been acquired recently as they have only recently become at risk (as they begin sexual activity) and there will be few deaths to AIDS [49]. Thus, in young adults, prevalence is more a reflection of the current pattern of HIV transmission and changes in prevalence following the adoption of safer sexual behaviour should appear first and most clearly among young people Figure 2.3(B).

Following the initial growth of an HIV epidemic, and as those with riskiest sexual behaviour who are infected die or reduce their sexual activity due to illness, the structure of the sexual network could begin to change; both because the high risk

behaviour itself is lost, and because the opportunity for other individuals to form high risk partnerships is removed [231]. This depends upon how an individual's risk behaviour changes as they age and the change in risk behaviour of those that remain following the deaths of those most at risk. At one extreme, if individuals remain at the same level of risk throughout their life, average sexual behaviour naturally becomes safer as those with risky behaviour die Figure 2.3(C). For this reason, changes in average sexual behaviour should be interpreted with some caution, since any safer average behaviour may not be a consequence of the deliberate behaviour change. In the model it is possible to assume that as the number of high-risk individuals declines less risky individuals can adopt higher risk behaviour to keep constant average rate of partner acquisition. In this case, incidence remains high and may balance the surge in AIDS-related mortality, maintaining a steady prevalence of infection Figure 2.3(D).

In interpreting trends in HIV prevalence we also need to be concerned with changing biases in the ANC population as a sample of women [46]. First, reductions in fertility caused by the progression of HIV infection could exaggerate the decline in prevalence seen in the ANC sample relative to the general population. Recent data suggest that fertility is suppressed before the final stages of HIV infection [47, 243]. Simulations show that this sub-fertility and exclusion from the ANC sample of those infected will occur rapidly (Figure 2.4(A)). The early decline in fertility is in part a product of the initial acute peak in incidence, but without this pattern a more gradual decline in prevalence is produced. Second, the ANC sample might over-represent the women most likely to be infected with HIV, since sexual behaviour that exposes the women to the infection (e.g. unprotected sex) also exposes the women to the risk of pregnancy [46]. Because prevalence estimated biased towards those higher risk women rises quickly and falls steeply, such an ANC sample may represent the most extreme changes in prevalence (Figure 2.4(B)).

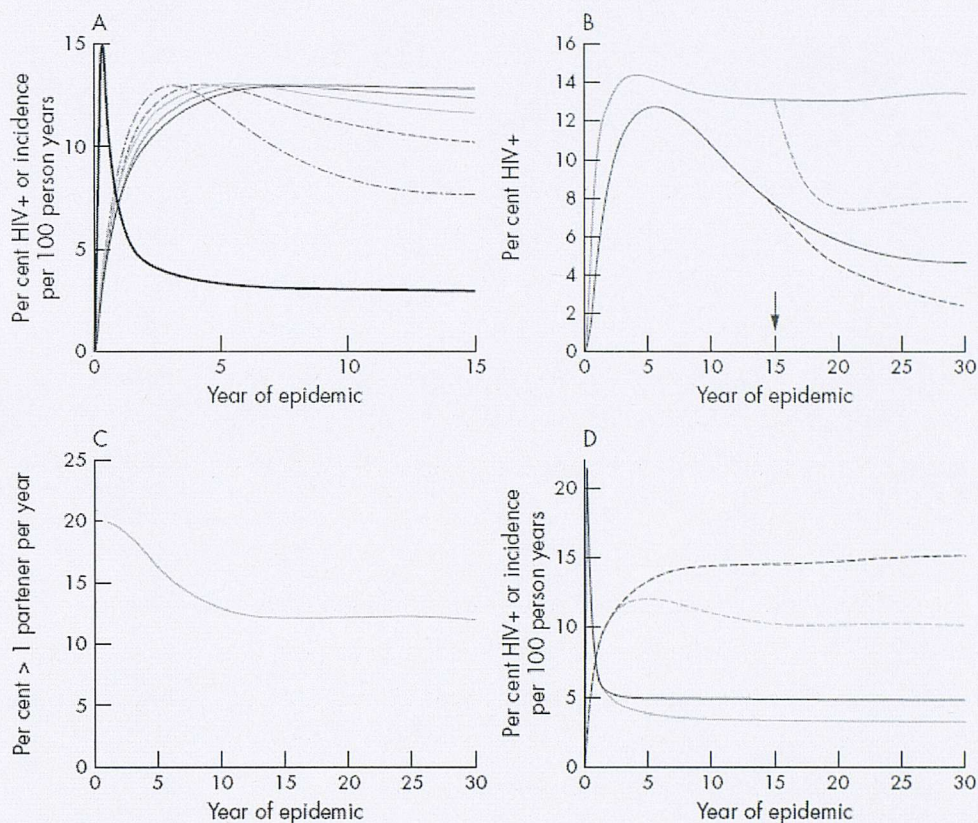


Figure 2.3 Natural dynamics of generalised HIV epidemic. (A) Predicted HIV incidence per 100 person years at risk (thick black line) and HIV prevalence among women for varying periods from infection to death. For 25 year olds mean interval from infection until death is 11 years (thin black line), 9 years (dark grey line), 7 years (light grey line), 5 year (dashed line), and 3 years (dotted/dashed line). (B) HIV prevalence among women aged 20–24 years (grey lines) and 30–35 years (black lines) without behaviour change (solid lines) and with the transmission probability halving at year 15 (dashed lines). (C) The proportion of men and women currently forming more than one sexual partnership per year. (D) Predicted HIV incidence per 100 person years at risk (solid lines) and HIV prevalence among women (dashed lines) with the relative size of sexual activity groups being allowed to change freely (grey lines) and being held constant with recruitment to the high activity groups from lower activity groups (black lines).

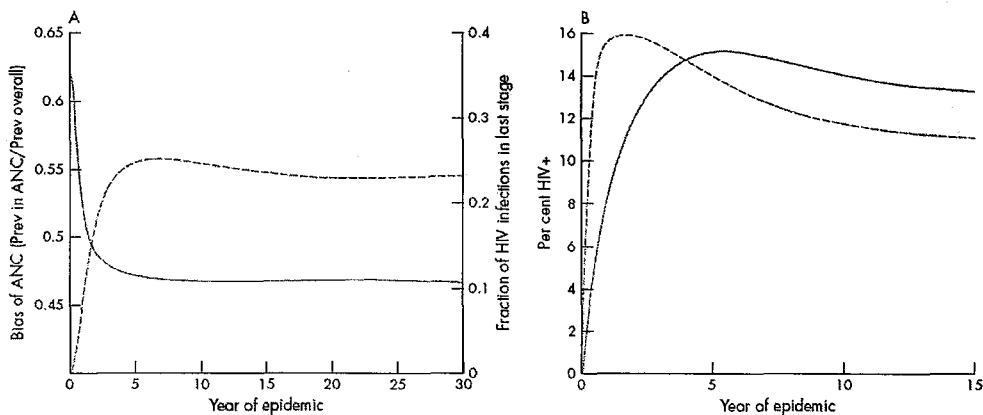


Figure 2.4 Biases in antenatal clinic (ANC) sample. (A) Ratio of percentage of women attending ANCs who are HIV+ and percentage of all HIV+ women, assuming that the probability of women being included in the ANC sample depends on stage of HIV (solid line) and the fraction of HIV cases in late stage of infection (tertiary stage or full-blown AIDS) (dashed line). (B) Percentage of women attending ANC who are HIV+ (dashed line) and percentage of all women HIV+ (solid line), assuming that the probability of being included in the ANC sample depends on sexual activity group.

The exploratory analysis found that the most extreme natural declines in prevalence arise from the greatest contrast between the initial peak and subsequent low incidence level, and from the shortest period from infection to death. Within reasonable limits, the initial heterogeneity in rate of sexual partnership formation and the variation in transmission probability with stage of HIV infection are maximised. The acute peak in incidence reflects a lack of geographic space, stochastic effects and waiting times between sexual partnership formation and HIV transmission. These all distribute the peak in incidence over time and lessen the predicted prevalence decline. Prevalence declines most when there is no compensatory recruitment into the high sexual activity groups in response to differential mortality and appears most extreme when assuming that the ANC over-samples high risk individuals.

2.4.2 Analysis of Country-level Data

In the case of Uganda, urban Kenya, Zimbabwe and urban Haiti, under a range of realistic and extreme assumptions, our model can only replicate observed declines in prevalence by assuming that risk behaviour has also declined.

The decline in Uganda is the earliest and most researched [24, 55]. Sites in the north, centre and west of the country have a similar epidemic curve with prevalence amongst 15-49 year-old and 20-24 year-old women both declining from approximately 30% to 10% (Figure 2.5(A-B)). These declines could be generated in

the model with a reduction in the transmission probability per partnership of 75% in 1992 - a similar reduction to that previously estimated [24, 55]. No subsequent reduction is necessary to generate the observed trends and the assumed change in risk predates observational cohort data from Rakai used to argue that incidence has not fallen [244]. In Eastern sites (Jinja hospital and Mbale hospital) the decline in prevalence in women aged 15-49 from approximately 15% to 5% (Figure 2.5(C)) is only possible with behaviour change, whereas prevalence estimates for women aged 20-24 show more fluctuations and are possible to model without risk behaviour changing (Figure 2.5(D)). Such seemingly contradictory results may arise from the greater error in prevalence estimates from a more restricted age group (sample sizes were not available to estimate confidence intervals), or from shifting behavioural parameters (in particular, age at first sex), which alter the distribution of the infection with respect to age, at the same time as overall prevalence is decreasing [49].

In parts of urban Kenya, HIV prevalence amongst women aged 15 to 49 fell from approximately 12% in 2001 to 9% in 2003 with a concomitant decline in those age 20-24 from 13% to 10%. The downturn in prevalence was particularly pronounced in four urban sites (Busia, Meru, Nakuru and Thika) where median prevalence fell from 28% in 1999 to 9% in 2003 among 15-49 year old women and from 29% in 1998 to 9% in 2002 among 15-24 year olds (Figure 2.5(E-F)). Again, to reproduce these changes requires assuming that risk behaviour has changed. Between behavioural surveys in 1993, 1998 and 2003 there were substantial reductions in the proportions of men and women having more than one sexual partner. Additionally, between 1998 and 2003, median age at first sex for females increased. To represent these changes in the model, reductions in the mean rate of partner change were assumed in 1998 and 2001 and a step change in females' age at first sex was included in 2001. The decrease in prevalence, though, is better matched with a reduction in the transmission probability of 70% in 1997 (dotted lines). Four other urban sites (Garissa, Kisii, Kitui and Nyeri) also experienced a reduction in median prevalence: 14% in 2000 to 7% in 2003 among 15-49 years old and the same behaviour changes were assumed to bring the model into agreement with the data (Figure 2.5(G)). However, the trend in prevalence among 15-24 year olds is less clear and does not seem inconsistent with the null model (Figure 2.5(H)).

In Zimbabwe a decline in prevalence from 29% to 24% is recorded between 2002 and 2004 amongst 15-49 year-old women, and from 25% to 20% among women aged 15-24 year-old (Figure 2.5(I-J)). In both cases, the observed trend cannot be reproduced through the natural evolution of the epidemic alone, but can be generated if the overall probability of infection is reduced by half in 2001.

In urban Haiti, prevalence has decreased since 2000 from approximately 5.5% to 3% among 15-44 year women – a decline that could not be generated in the absence of behaviour change (Figure 2.5(K)). Among 15-24 year olds, prevalence has also declined although the uncertainty associated with these estimates does not rule out the possibility that prevalence has remained constant (Figure 2.5(L)). In behavioural surveys there was a 20% decline in the mean number of sexual partners between 1994 and 2000 and condom use increased two- to threefold between 2000/1 and 2002. These changes were represented in the model by a step-change in partner change rates in 1994 and in condom use in 1999.

Another effect that could lead to changes in prevalence without changes in incidence is the selective migration of infected people. Particularly in Zimbabwe, there has been extensive migration since 1990, which accelerated after 2000 [17]. If infected individuals are more likely to leave the country than others (e.g. in search of treatment) national estimates of HIV prevalence would decrease. To investigate this effect, five different scenarios were simulated where the natural decline in prevalence is augmented by coincident increases in different patterns of migration (Figure 2.6). The scenarios are: (1) natural dynamics and no migration; (2) natural dynamics and a linear increase in migration from 0-5% of the total population per annum, 1997-2000, followed by constant 5% migration per annum – symptomatic individuals (pre-AIDS & AIDS) five-times as likely to migrate as others; (3) as for (2) but with maximum migration rate of 10% per year; (4) as for (3) except that symptomatic individuals are twenty-times more likely to migrate than uninfected individuals; (5) as for (4) except that asymptomatic HIV-positive individuals are also (on average) 20% more likely to migrate than uninfected individuals. All scenarios assume no volitional behaviour change. Only in scenario (5), where asymptomatic individuals disproportionately migrate, can this null model reproduce a decline in prevalence almost as great as those observed.

Adult prevalence (15-49 years) in urban Ethiopia fell from 14% in 2001 to 12% in 2003 (Figure 2.7(A)) and from 15% to 13% over the same time among 20-24 year olds (Figure 2.7(B)). These modest declines could be reproduced by the model without assuming any changes to sexual risk behaviour.

The data analysed from Malawi, urban Cote d'Ivoire and Rwanda show no sign of a decrease in prevalence amongst all adults, or selected age-groups (Figure 2.7(C-E)). There is some evidence that the fraction of men and women having had more than one or two sexual partners in the last twelve months has decreased in Malawi and Cote d'Ivoire [233, 238].

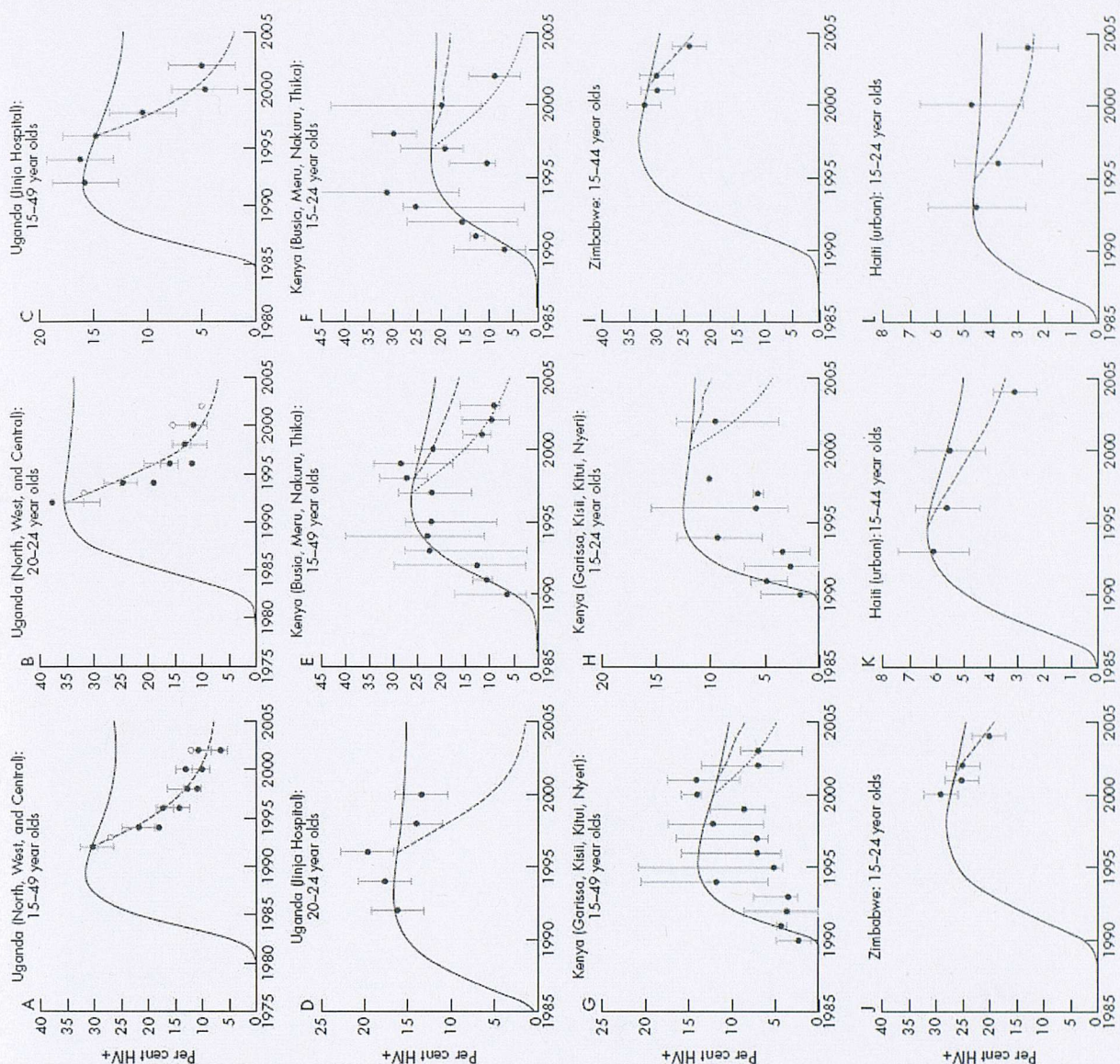


Figure 2.5 ANC prevalence data (dots), model output assuming no behaviour change (full lines) and model output assuming behaviour change (dashed lines). Uganda: St Mary's Hospital, Lacor, Gulu, St Francis Hospital, Nsambya, Kampala, and Mbarara Hospital (A) 15-49 years olds and (B) 20-24 year olds; Jinja Hospital (C) 15-49 year olds and (D) 20-24 year olds (error bars $\pm 3\%$). Urban Kenya: Busia, Meru, Nakuru, and Thika (E) 15-49 year olds and (F) 15-24 year olds (error bars show range); Garissa, Kisii, Kitui and Nyeri (G) 15-49 year olds and (H) 15-24 year olds (error bars show range). Zimbabwe: (I) 15-44 year olds and (J) 15-24 year olds, (error bars $\pm 3\%$). Urban Haiti: (K) 15-44 year olds and (L) 15-24 year olds (error bars are 95% CI).

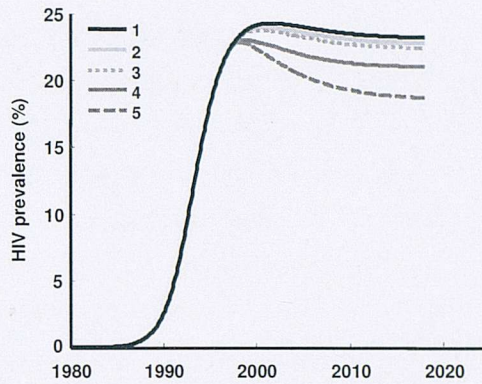


Figure 2.6 Mathematical model projections of the potential impact of international out-migration on recent trends in HIV prevalence in Zimbabwe: (1) no migration; (2) linear increase in migration from 0-5% of the total population per annum, 1997-2000, followed by constant 5% migration per annum; (3) linear increase in migration from 0-10% of the total population per annum, 1997-2000, followed by constant 10% migration per annum; (4) as for (3) except that HIV-positive persons with symptomatic infection (AIDS) are 20-times more likely to migrate than uninfected individuals; (5) as for (4) except that non-symptomatic HIV-positive are 20% more likely to migrate than others.

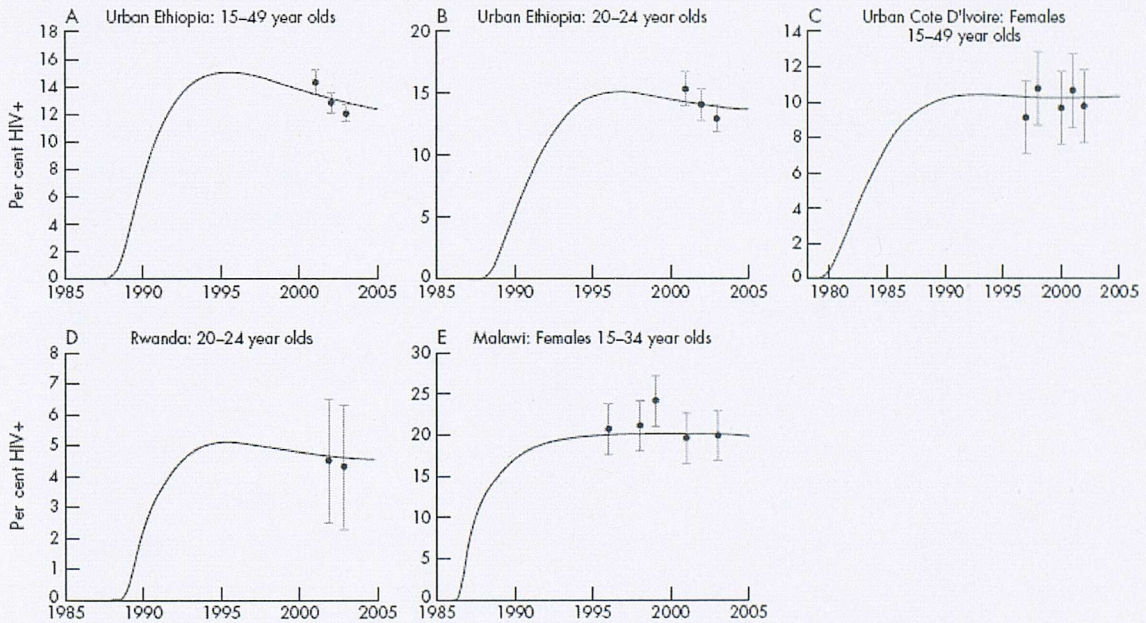


Figure 2.7 ANC prevalence data (dots) and model output assuming no behaviour change (full lines). Urban Ethiopia: (A) 15-49 year olds, and (B) 20-24 year olds (error bars are 95% CI). (C) Urban Cote d'Ivoire 15-49 year olds (error bars are $\pm 3\%$). (D) Rwanda 20-24 year olds (error bars are $\pm 3\%$). (E) Malawi: 15-34 year olds (error bars are $\pm 3\%$).

2.4.3 Further Analysis of Zimbabwe Data

In most consistently sampled ANC sites in Zimbabwe, there have been substantial declines in prevalence since year 2000 (Table 2.8). The speed and magnitude of the decline is consistent with a large reduction in risk before year 2000 (Figure 2.8 and Table 2.10). The estimate of the magnitude of the risk reduction depends on the weighting given to the prevalence estimates from early in the epidemic, which may not be perfectly comparable with later estimates. In general, these early data indicate that HIV prevalence had reached a very high level by the mid-1990s and when these data are taken into account in the model fitting, the reduction in risk required to generate the observed decline in prevalence is less. This is because without this information, the model assumes that small differences in prevalence between 1997, 2000 and 2001 indicate that the epidemic is still growing fast at that time; this means that the risk level fitted before the intervention is higher and so the proportional reduction to get the same decline in prevalence must be greater. With the earlier data, the fitting process interprets changes between 1997 and 2001 as random variation.

The effect of sampling error cannot be taken into account without sample sizes, but we expect this error to be smaller when the sites are aggregated by location (urban, rural and other) and the comparable model estimates of risk reduction may therefore be more reliable. Taking all urban sites together, the decline in prevalence is consistent with risk reducing from 1998 or 1999, depending on whether the earliest data are used or not (Figure 2.9). In rural areas, the decline in risk may have been greater and occurred slightly later. The decline in other (semi-urban) areas may have occurred before the change in urban areas, but this finding cannot be confirmed without data from the earlier in the epidemic.

The average time from HIV infection to death could influence the estimated changes in risk. With shorter survival times, the same reduction in risk leads to faster and larger reductions in prevalence (Figure 2.10(A)) and the same decline in prevalence can be fit with smaller reductions in risk (Figure 2.10(B)). However, the estimate of the timing of behaviour change is not very sensitive to the survival assumptions, within a realistic range (Figure 2.10).

		<i>Fit 1</i>		<i>Fit 2</i>	
		1st Yr of Risk Reduc.	% Risk Reduc.	1st Yr of Risk Reduc.	% Risk Reduc.
Urban Sites	Bindura	2001	71	2001	100
	Nkulamane (Bulawayo)	2000	100	NA	NA
	Chitungwiza (Harare)	2000	78	NA	NA
	Gweru	None	None	2001	100
	Kuwadzana (Harare)	2001	83	2000	100
	Chinotimba	2000	38	2000	100
	<i>Aggregate</i>	<i>1998</i>	<i>27</i>	<i>1999</i>	<i>66</i>
Other Sites	Beitbridge	1997	77	NA	NA
	Chiredzi	2001	100	1997	100
	Gwanda	2001	100	1997	66
	<i>Aggregate</i>	<i>2000</i>	<i>36</i>	<i>1996</i>	<i>68</i>
Rural Sites	Binga	2001	100	2000	100
	Karanda	2001	87	2001	100
	Mutoko	2001	100	2000	100
	Sadza	2000	44	1999	100
	<i>Aggregate</i>	<i>2000</i>	<i>88</i>	<i>2000</i>	<i>95</i>

Table 2.10 Summary of result from model fitting. The fitted year of change and fractional decrease in risk are given for each site. Fit 1 makes use of all data available, although estimates from before 1997 may not be comparable with later estimates; Fit 2 only uses measurements from 1997 onwards. The % risk reduction is the reduction in the value from baseline of *R*, a composite measure of risk.

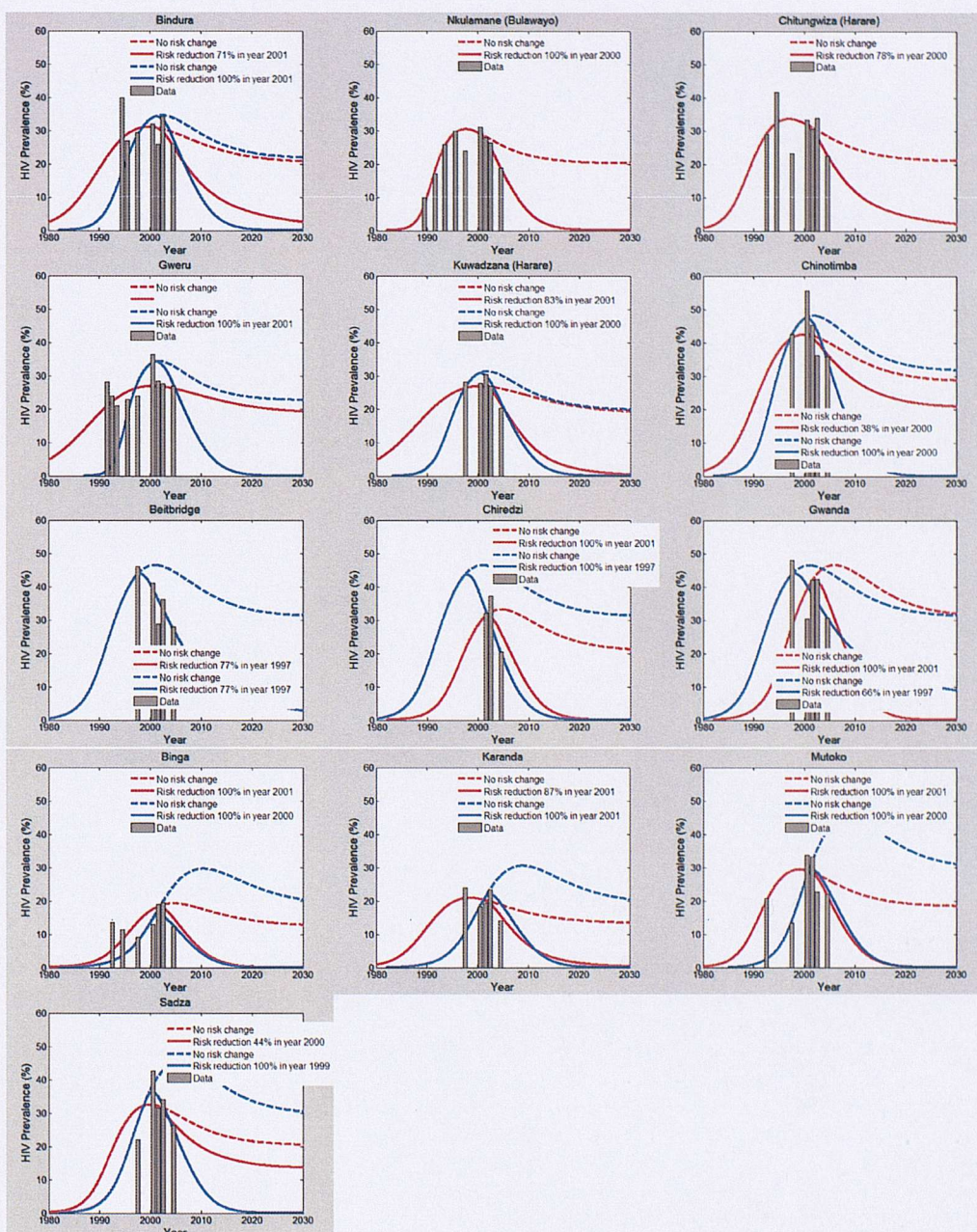


Figure 2.8 Model fits to data for each antenatal clinic site. Bars show data and lines show model fits. Solid lines show epidemic with fitted change in risk; dotted lines show the course of the epidemic in the absence of changes in risk. The red line is “Fit 1” (includes all data available); the blue line is “Fit 2” (includes only data from 1997 onwards). Fitted parameter values are given in the legend in each panel.

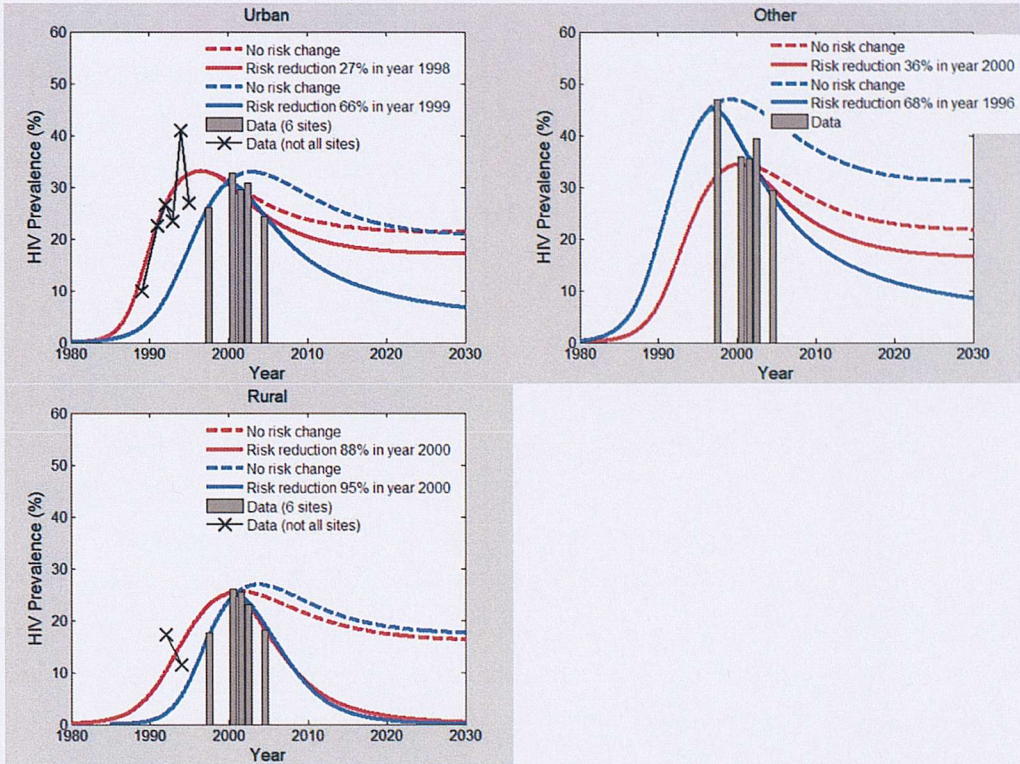


Figure 2.9 Model fits to data for the antenatal clinics sites grouped by location. Bars show median prevalence among ANC sites from 1997; crosses show median prevalence at earlier time, where possible. The red line is “Fit 1” (includes all data available); the blue line is “Fit 2” (includes only data from 1997 onwards). Fitted parameter values are given in the legend in each panel.

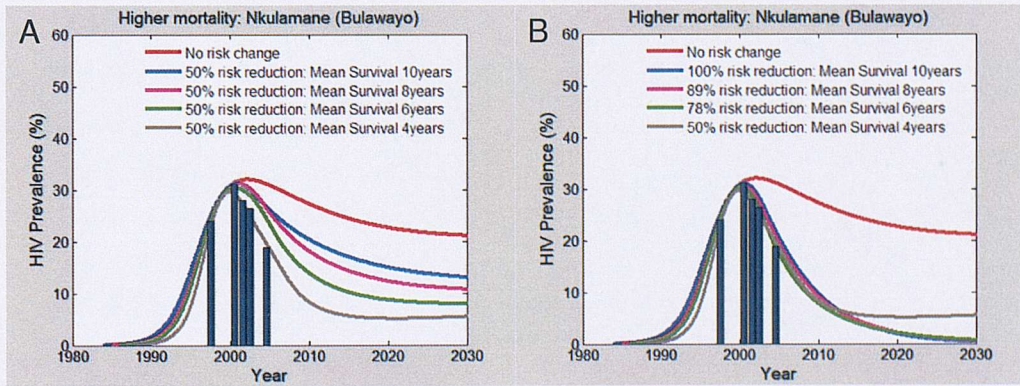


Figure 2.10 The effect of mean survival time after infection on the estimated reduction in risk. (a) With a 50% reduction in risk, a better fit is achieved with shorter survival times. (b) A lower reduction in risk is required to fit to data when a shorter survival time is assumed. Data from Nkulamane (near Bulawayo, Zimbabwe) is used to illustrate (bars).

2.5 Discussion

The model illustrates the potential for HIV prevalence to decline without individuals deliberately adopting safer sexual behaviours. However, the inability of the model to replicate the extent of observed declines allows us to be more confident that changes in prevalence in Uganda, urban Kenya, Zimbabwe and urban Haiti are unlikely to be a product of these natural dynamics. The declines observed can be contrasted with urban Ethiopia where the prevalence patterns could be reproduced with sexual behaviour and HIV transmission remaining unchanged and urban Cote d'Ivoire, Malawi and Rwanda where aggregated prevalence has not recently decreased, although this does not exclude the possibility that behaviour change has had a significant impact on the HIV epidemic. In Zimbabwe, risk may have substantially reduced between 1998 and 2002, which coincides with the timing of behaviour change that has been recorded in independent surveys [17].

The model of HIV transmission is influenced by a large number of interacting variables which, without a dramatic increase in data sources, limits the possibility of statistically fitting the model and estimating the most likely value of particular parameters. A statistical interpretation of the results depends upon the confidence intervals around the prevalence estimates at particular time points and whether the extreme decline in prevalence falls within them. It should be noted that some of the prevalence estimates used here did not have reported sample sizes or statistical confidence intervals. In addition to statistical error, changing biases could lead to the observed and predicted trends separating. One such bias is suggested by recent data indicating that fertility is suppressed before the final stages of HIV infection [47]. Sub-fertility in those with long standing HIV infection could lead to their exclusion from the ANC sample, but the model indicates that the effects of this bias will predate the declines in prevalence recently observed. Nationally, estimates of prevalence often fall as samples are recruited from progressively remoter populations or as HIV tests become more specific. To avoid these problems, only data from consistently sampled clinics were used.

For Zimbabwe, there is the additional concern that the decline in prevalence could have been driven by migration, which has greatly increased over recent years [17]. In the range of scenarios simulated, the decline in prevalence observed could only be replicated without individual behaviour change when it was assumed that asymptomatic individuals are more likely than others to migrate. This scenario is equivalent to approximately 10% of asymptomatic individuals knowing their status and being three-times more likely to migrate than uninfected individuals, which would have been unlikely given that HIV testing was uncommon until recently [148]. A more

plausible scenario would be if both migration and HIV infection were correlated with a third variable such as educational attainment. This could lead to greater migration of HIV positives. However, in an investigation of migration from Manicaland, no such relationship has been found [245]. HIV prevalence among Zimbabwean-born women in the UK (one of the main destination of emigrants) has not substantially increased during the time of prevalence decline [17] and HIV prevalence among Zimbabwean-born women in the UK is much lower than in Zimbabwe, indicating that overall, Zimbabwean migrants are disproportionately *not* infected.

Restricting HIV prevalence data to the younger age-groups often fails to help identify recent reductions in HIV incidence. In young age-groups the confounding effects of mortality and sub-fertility on prevalence trends are minimised and reductions in incidence will be translated rapidly into reduced prevalence. However, the uncertainty associated with the prevalence point-estimates is often too great to detect trends. In contrast, although prevalence estimates from across all adult ages are prone to natural reductions, they may be determined more precisely and so allow trends due to the natural evolution of the epidemic and due to behaviour change to be distinguished.

One of the problems in reconstructing HIV epidemics is that current sexual behaviour already includes reductions in risky sexual behaviour brought about by the HIV epidemic and associated mortality in those who were previously at the greatest risk of infection [54, 231]. To overcome this, it can be assumed that the heterogeneity in sexual partner change rates was originally greater than that observed today. Although it was the aim to reconstruct country specific epidemics, local patterns of risk were often not available, necessitating the adoption of standard patterns for condom use and age-specific partner change rates. Fortunately, despite being important for fitting age and sex-specific prevalence, these patterns have little bearing on the course of the epidemic once its magnitude is established.

It was estimated that the decline in risk behaviour in Zimbabwe occurred between 1998 and 2002 and happened first in urban areas. This seems to be consistent with data on behavioural changes. A recent comprehensive epidemiological review in Zimbabwe [17] found declines in the proportion of men and women that reported a non-regular partner in the last year since the late 1990s (although there was little data from earlier) and sales of socially-marked condoms increased dramatically from 1997. Behaviour change between 1994 and 1999 was also greatest in urban areas, where programmes were usually focussed initially [246].

The estimates of the timing of risk reduction were made using a model that takes a naïve view of risk; that individuals stayed at the same risk level for their entire

lives; that risk had been constant until the behaviour change and then declined linearly for three years; and, that risk reductions occurred to all individuals at the same time regardless of age or sexual behaviour. In reality, risk is more likely to have changed gradually over time, although it may have gathered momentum and changed most over a shorter period. This model does not distinguish between different types of risk behaviour (concurrency of sexual partners, condom use, sexually transmitted infection etc), but instead measures a proportional decrease in the total risk behaviour. More data would be required to determine the relative contributions of particular aspects of risk behaviour.

Without sample sizes, it is not possible to quantify the uncertainty in the estimates of the changes in patterns of risk behaviour. It is also unclear whether all the measurement of prevalence were made in the same way. The data points in 1997 are low compared with those from 2000, which may be due to different methods being used. If it is assumed that they are directly comparable, the model interprets the difference between them as indicating substantial epidemic growth in this period which is difficult to reconcile with independent estimates that incidence peaked in about 1991 [16, 246]. To generate epidemic growth between 1997 and 2000 and peak incidence in 1991, a high risk level is fitted, which could lead to overestimates in the reduction in risk subsequently required to match the observed decline in prevalence. Data collected earlier in the epidemic show that prevalence was high and stable by the mid 1990s, which is broadly consistent with peak incidence in 1991, and allows a more conservative estimate of the initial risk level.

Estimates of the magnitude of the risk reduction will be sensitive to assumptions about survival from infection to death. In this model the distribution of time from infection to death would be gamma distributed, which should lead to more realistic temporal changes in prevalence than are generated in the earlier model. However, there is only one estimate of median survival time for infected individuals in Africa [230]. In that study, participants were afforded good access to medical care [230, 247], which could mean that the estimated survival time was longer than in more typical settings. Smaller reductions in risk are consistent with observed prevalence declines when shorter survival times are assumed, although the estimated timing of behaviour change is not severely affected.

The estimated magnitudes of the reduction in risk behaviour are very large for some sites and for all the rural areas taken together. These estimates are particularly sensitive to the most recent prevalence estimate and will be substantially overestimated if there are small downward biases. For this reason, it is too early to make firm conclusions on the timing and magnitude of behaviour change in Zimbabwe. Ten

years ago, there was a similar problem in analysing prevalence trends in Kampala, Uganda [54, 55]. As more data has become available, initial estimates of very large risk reduction (80%) have been verified [24].

This method of estimating timing of incidence reduction is unable to detect changes in risk behaviour that took place before the time-series starts. For example, prevalence could have been steadily declining since 1995, but this could not be detected if the first estimate of prevalence is in 1997. Furthermore, even if prevalence estimates are available from before prevalence began to decline, it would still be impossible to detect the impact of behaviour change if it occurred before incidence peaked. In this case, prevalence would never reach the level that it would have if risk had not reduced, and recent prevalence estimates will be steady or decline slightly (due to natural dynamics), leading to the erroneous conclusion that risk behaviour has not changed (Figure 2.1 (dashed lines)). This severely compromises our ability to form firm conclusions on the causes of risk reduction. Thus, while we can detect a change in risk after the mid 1990s, we cannot know if there were earlier successful programmes before this.

Why did behaviour change occur at this time and why has it occurred in Zimbabwe and not neighbouring countries with similarly severe epidemics? In 2000 the Zimbabwean government introduced a special tax ("AIDS levy") dedicated to responding to the HIV/AIDS epidemic [93]. At this time, many non-governmental organisations were also working intensively on intervention projects, and uptake of voluntary counselling and testing (VCT) increased substantially [248]. However, none of the trials of interventions proved very successful [17, 94, 249] and there is little evidence that VCT can have a strong effect on behaviour in this setting [17, 140, 250]. One of the most persuasive theories is that the true motivation for behaviour change is to witness first-hand a loss of a close friend or relative to the disease – the "funeral effect", first identified amongst gay men in San Francisco [95]. Models suggest that by the late 1990s mortality was rising fast in lower risk parts of the population, and an increasing fraction of the population had suffered a loss. In other countries, knowledge of the disease may be just as high, but the funeral effect may not yet have bitten so hard; it is notable that the epidemic decline in Zimbabwe took hold at a comparable stage of the epidemic to that in Uganda [24, 55]. The Zimbabwean population is also better educated than neighbouring countries and education may help empower individuals to make the changes that are personally relevant [92].

For a long time Uganda [24, 55] has been the key national level example of success in reducing HIV incidence in a generalised epidemic and the main source of

evidence on HIV prevention. Perhaps it is time for Kenya and Zimbabwe to be added to the list.

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Chapter 3: Estimating Incidence from Prevalence - Methods and Validation

3.1 Introduction

Monitoring the continuing spread of the HIV epidemic is essential for determining public health priorities, assessing the impact of interventions and making estimates of current and future health care needs [2]. Currently, surveillance systems in generalized epidemics primarily rely on HIV prevalence (fraction of population infected) data collected from women attending selected antenatal clinics [44, 56]. Interpretation of these data is complicated by natural epidemiological changes that arise from the long and variable incubation of HIV and AIDS-related mortality [54, 251], by biases in the sample due to sub-fertility associated with bacterial STIs and HIV [46], and the disproportionate selection of sites in urban areas [53]. Recently serological testing has been added to the Demographic and Health Surveys (DHS+) [61, 62], giving estimates of HIV prevalence in the general adult population based on a standard methodology. In addition, a number of countries have conducted other general population-based sero-surveys [252]. Measures that relate to the general population are more useful, but there remain several important limitations in using prevalence data to monitor the epidemic. These include:

- (i) Changes in prevalence do not necessarily indicate a reduction in risk of infection (see Chapter One and ref. [251]);
- (ii) Changes in prevalence lag behind real changes in risk, particularly at older ages;
- (iii) Comparisons of prevalence between countries can be confounded by different survival times following infection (e.g. if survival following infection is shorter in Asia than in Europe or Africa [230, 234, 253], prevalence would be lower even if incidence rates were the same);
- (iv) The weak association between prevalent infection and risk makes it difficult to identify “high risk” groups (e.g. higher average prevalence among women does not necessarily mean they are at overall greater risk than men).

A better measure for monitoring the HIV epidemic is incidence (rate of new infections among those at risk). If incidence is known, temporal changes in the epidemic can be better identified and characterised, the pattern of risk over age can be examined to aid the understanding of transmission patterns and highlight targets for interventions, and future health care needs can be predicted. However, whereas prevalence can be measured with independent, anonymised, cross-sectional sero-surveys, direct measurement of incidence would require individuals to be identified and followed-up from one sero-survey to the next. In all settings, achieving high follow-up rates is a major logistical challenge and is more expensive than selecting a

new panel of participants at each survey round. New types of HIV test that can discriminate recent infections from a single specimen have not so far been able to generate reliable estimates of incidence [64, 66]. The DHS+ surveys will not follow-up individuals but it may still be possible to estimate incidence from prevalence estimates in successive surveys, without resort to complex projection packages. This chapter describes and tests two methods for doing this, with the intention that they can be applied in future to sequential prevalence data collected in DHS+ surveys.

Several methods have already been proposed to estimate incidence from one or two measures of prevalence [68, 69, 254-260]. Some of these only work under stable conditions, with long time-series or involve complicated and computationally intensive model fitting procedures. None of the methods have been validated by comparing derived estimates with actual measurements from general population samples of African communities with mature HIV epidemics.

Both of the methods presented here are simple to use and are based on the idea of demographic accounting [69]. They examine the change in HIV prevalence in a cohort observed at two time periods, allowing for changes due to new infections and mortality among infected and uninfected persons. To gather the mortality data required to do this exactly would also need cohort follow-up, but it is suggested that mortality information collected from external sources, such as long-running cohort studies, can be used in place of direct measurements. *Method 1* uses cohort mortality rates among those infected whilst *Method 2* uses the distribution of survival after infection. The performance of these methods is tested using data generated by a mathematical simulation model and actual measurements of prevalence and incidence from three community-based cohort studies in sub-Saharan Africa.

3.2 Methods

3.2.1 Calculating incidence from cross-sectional prevalence

Consider two cross-sectional measures of prevalence separated by an interval of T years in age-groups of width r years (Figure 3.1). Denote the total number of individuals in age-group i , at time j as $N_{i,j}$ and the number of HIV-infected individuals as $H_{i,j}$. Prevalence is defined as $p_{i,j} = H_{i,j} / N_{i,j}$. If cohort age-groups are constructed centred on ages $a_i \left(a_i - \frac{r}{2}, a_i + \frac{r}{2} \right)$ at the start of each interval, then the age-groups at the end of the interval will be $\left(a_i - \frac{r}{2} + T, a_i + \frac{r}{2} + T \right)$. Denote the

cohort experiences of incidence as $\tilde{\lambda}_i$ and the incidence rate in the cross-sectional age-groups $\left(a_i - \frac{r}{2}, a_i + \frac{r}{2}\right)$ as λ_i (Figure 3.1). In addition, $\tilde{\pi}_i$ is defined as the fraction of infected individuals in the i^{th} age-group at the start of the interval that survive to the second sero-survey.

In a real cohort, an estimate of HIV incidence can be obtained by considering the change in the number of HIV-infected individuals and finding an approximation to the person-years spent at risk of infection in the cohort [67], as follows:

$$\text{Number of sero-conversions} \approx H_{i,T} - \tilde{\pi}_i H_{i,0} \dots (3.1)$$

$$\text{Number of person-years spent at risk} \approx T \left(\frac{(N_{i,0} - H_{i,0}) + (N_{i,T} - H_{i,T})}{2} \right) \dots (3.2)$$

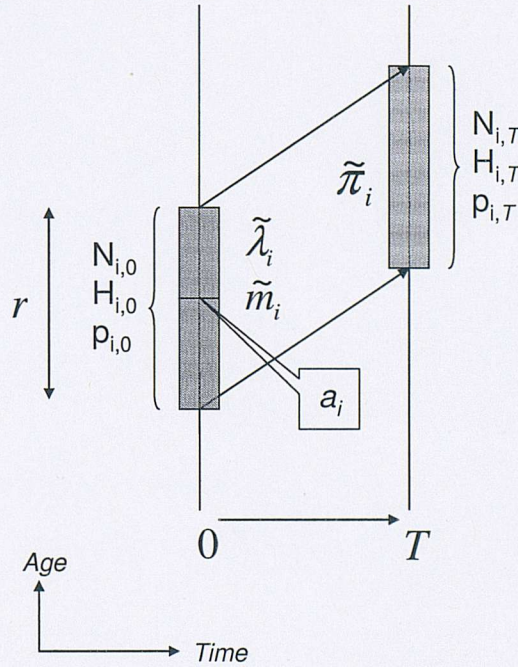


Figure 3.1 Lexis diagram showing values used in the methods. Two sero-surveys T years apart quantify prevalence in age-groups of width r . One age-group (i) is shown. $N_{i,j}$ is the total number in survey; $H_{i,j}$ is the number infected; $p_{i,j}$ is HIV prevalence; $\tilde{\pi}_i$ is the fraction of infected individuals that survive between surveys; $\tilde{m}_i$ is mortality rate of infected individuals in the cohort; $\tilde{\lambda}_i$ is the rate of HIV incidence in the cohort. N and H are not required to use the methods but do appear in the mathematical derivation.

From equations (3.1) and (3.2) on estimates of the number of seroconversions and person-years in the cohort, an estimate of incidence can be derived:

$$\tilde{\lambda}_i = \frac{\text{seroconversions}}{\text{person-years}} \approx \frac{H_{i,T} - \tilde{\pi}_i H_{i,0}}{T \left(\frac{(N_{i,0} - H_{i,0}) + (N_{i,T} - H_{i,T})}{2} \right)} = \frac{2(H_{i,T} - \tilde{\pi}_i H_{i,0})}{T(N_{i,0} - H_{i,0} + N_{i,T} - H_{i,T})} \dots (3.3)$$

Then replacing values of $H_{i,j}$ with $H_{i,j} = p_{i,j} N_{i,j}$ and dividing the numerator and the denominator by $N_{i,0}$:

$$\tilde{\lambda}_i \approx \frac{2 \left(p_{i,T} \frac{N_{i,T}}{N_{i,0}} - \tilde{\pi}_i p_{i,0} \right)}{T \left(1 - p_{i,0} + \frac{N_{i,T}}{N_{i,0}} - p_{i,T} \frac{N_{i,T}}{N_{i,0}} \right)} = \frac{2(Q_i p_{i,T} - \tilde{\pi}_i p_{i,0})}{T(1 - p_{i,0} + Q_i(1 - p_{i,T}))} \dots (3.4)$$

$$Q_i = \frac{N_{i,T}}{N_{i,0}}$$

Here Q_i represents the change in size of the cohort over time. Ignoring the possibility of sero-conversion and death occurring in the same interval, Q_i can be approximated in the following way:

$$N_{i,T} \approx N_{i,0} - (1 - \tilde{\pi}_i) H_{i,0} - (1 - \exp(-\tilde{\mu}_i T))(N_{i,0} - H_{i,0}) \dots (3.5)$$

where $\tilde{\mu}_i$ is the mortality rate for those not infected with HIV. Dividing by $N_{i,0}$:

$$Q = \frac{N_{i,T}}{N_{i,0}} \approx 1 - (1 - \tilde{\pi}_i) p_{i,0} - (1 - \exp(-\tilde{\mu}_i T))(1 - p_{i,0}) \dots (3.6)$$

For the calculations presented here, $\tilde{\mu}_i = 0.01$ is used for all ages, which approximates the observed crude rate for uninfected individuals [261].

To estimate incidence in the cohort that is not included in the data at the start of the time interval (but enters the youngest cross-sectional age-group during the interval), it can be assumed that incidence is zero at all ages younger than the

youngest person in the dataset (i.e. younger than $a_1 - \frac{r}{2}$). If incidence is further assumed to be constant over the interval and that mortality is negligibly small at this age, then prevalence in this unseen cohort can be described as: $p_{0,T} = 1 - \exp(-T\tilde{\lambda}_0/2)$, where $p_{0,T}$ is the prevalence in the second sero-survey in the age range $\left(a_1 - \frac{r}{2}, a_1 - \frac{r}{2} + T\right)$. From this, a corresponding estimate of incidence can be generated:

$$\tilde{\lambda}_0 = \frac{-\ln(1 - p_{0,T})}{T/2} \dots (3.7)$$

3.2.2 Method 1

Method 1 makes use of empirical values of age-specific cohort mortality rates among those infected, which we denote $\tilde{m}_i$ (Figure 3.1). In this way, $\tilde{\pi}_i$ can be approximated by $\tilde{\pi}_i = \exp(-\tilde{m}_i T)$. Values of $\tilde{m}_i$ used in subsequent calculations are shown in Table 3.1.

Age-group	<u>Males</u>			<u>Females</u>		
	Cohort mortality rates			Cohort mortality rates		
	low	average	high	low	average	high
15-19	0.020	0.032	0.046	0.027	0.046	0.066
20-24	0.028	0.046	0.067	0.033	0.055	0.079
25-29	0.039	0.063	0.091	0.038	0.064	0.092
30-34	0.050	0.081	0.118	0.043	0.073	0.104
35-39	0.062	0.102	0.147	0.048	0.081	0.116
40-44	0.076	0.124	0.179	0.053	0.090	0.128
45-49	0.090	0.147	0.214	0.058	0.098	0.139
50-54	0.106	0.173	0.250	0.062	0.105	0.151
55-59	0.122	0.199	0.289	0.067	0.113	0.162
60-64	0.139	0.228	0.330	0.072	0.121	0.173

Table 3.1 Cohort mortality rates for HIV-infected persons ($\tilde{m}_i$), tabulated by age of cohort at start of 5-year interval [261]. ‘Average’ values were used in calculations but ‘low’ and ‘high’ values are also included so that a credible interval of incidence estimates may be calculated.

3.2.3 Method 2

Alternatively, if cohort mortality rates are not available, $\tilde{\pi}_i$ can be estimated using survival after infection information [69] and an approximation of the current age-specific pattern of HIV incidence. If $s(a, z)$ is defined as the probability of survival to age z given infection at age a , and assuming that the age-pattern of incidence has

remained constant for as long as the oldest person in the data has been at risk of infection, then provided $T \approx r$:

$$\begin{aligned}\tilde{\pi}_1 &\approx \frac{s(a_1 - \frac{r}{2}, a_1 + T)}{s(a_1 - \frac{r}{2}, a_i)} \\ \tilde{\pi}_i &\approx \frac{s(a_1 - \frac{r}{2}, a_1 + T)\tilde{\lambda}_0 + \sum_{k=1}^{i-1} \left\{ s(a_k + \frac{r}{2}, a_i + T)\tilde{\lambda}_k \exp\left(-\sum_{z=1}^{k-1} \tilde{\lambda}_z\right) \right\}}{s(a_1 - \frac{r}{2}, a_i)\tilde{\lambda}_0 + \sum_{k=1}^{i-1} \left\{ s(a_k + \frac{r}{2}, a_i)\tilde{\lambda}_k \exp\left(-\sum_{z=1}^{k-1} \tilde{\lambda}_z\right) \right\}} \dots (3.8)\end{aligned}$$

This expression works out the chance that infected individuals die during the follow-up period by assuming that the composition of the infected populations at each age-group reflects the pattern of incidence at younger ages. Assuming that the pattern of incidence over time has remained constant and $T \approx r$, the cohort incidence estimates from younger ages reflect the experiences of the older cohorts (Figure 3.2(a)). The overall chance of survival is calculated as the weighted average of survival from the mid-point of the younger ages (dotted lines) to the end of the inter-survey period.

When $T < r$ the estimates of incidence calculated from younger cohorts do not directly reflect the experience of incidence in older cohorts because they pertain to different age ranges at different times. However, experimentation using equation (3.8) when $T \neq r$ suggests that small departures (<2 years) from this do not introduce large errors. A more satisfactory solution is found by calculating the experience of incidence for the current cohorts by approximating incidence in the younger cross-sectional age groups (Figure 3.2(b)). Incidence in the period of time that the average member of an age-group has spent at risk since they entered the age-group (for which a cross-sectional measure cannot be found), can be estimated by the cohort measure of incidence for the overlapping period. Hence, strictly this approximation will hold when $r/2 \leq T < r$.

$$\tilde{\pi}_1 \approx s(a_1, a_1 + T)$$

$$\tilde{\pi}_2 \approx \frac{s(a_1, a_2 + T)\lambda_1 + s(a_2 - r/4, a_2 + T)\tilde{\lambda}_{i-1} \exp(-\lambda_1)}{s(a_1, a_2)\lambda_1 + s(a_2 - r/4, a_2)\tilde{\lambda}_{i-1} \exp(-\lambda_1)}$$

$$\tilde{\pi}_i \approx \frac{\sum_{k=1}^{i-1} \left\{ s(a_k, a_i + T)\lambda_k \exp\left(-\sum_{z=1}^{k-1} \lambda_z\right) \right\} + s(a_i - r/4, a_i + T)\tilde{\lambda}_{i-1} \exp\left(-\sum_{k=1}^{i-1} \lambda_k\right)}{\sum_{k=1}^{i-1} \left\{ s(a_k, a_i)\lambda_k \exp\left(-\sum_{z=1}^{k-1} \lambda_z\right) \right\} + s(a_i - r/4, a_i)\tilde{\lambda}_{i-1} \exp\left(-\sum_{k=1}^{i-1} \lambda_k\right)} \quad \text{for } i > 2$$

....(3.9)

Since values of $\tilde{\pi}_i$ are calculated using estimates of incidence from younger age-groups, which themselves depend on $\tilde{\pi}_i$, the order of calculation matters, and should be; $\tilde{\lambda}_0$, $\tilde{\pi}_1$, $\tilde{\lambda}_1$, $\tilde{\pi}_2$, $\tilde{\lambda}_2$, and so on. Using standard spreadsheet software, these expressions can be evaluated in full automatically by using arbitrary initial conditions.

Survival after infection is modelled as a Weibull distribution ($S(x) = \exp(-\{(x/\beta)^k\})$) where k and β are the shape and scale parameters, respectively. Parameter values are given in Table 3.2.

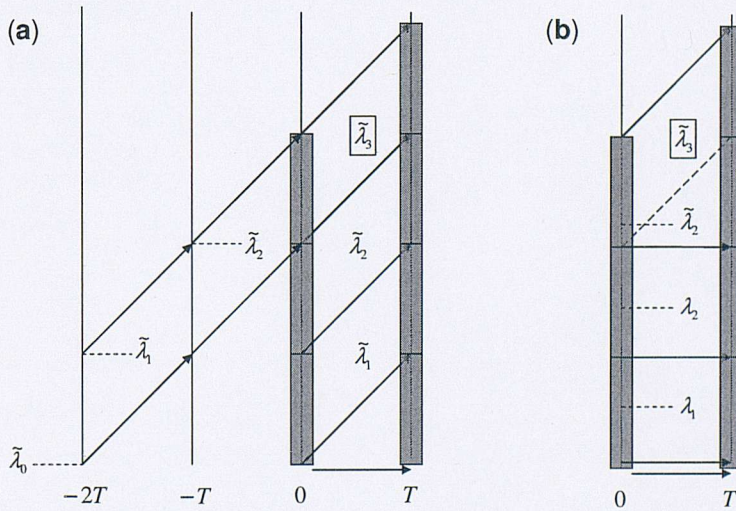


Figure 3.2 Lexis diagram showing the basis for estimating cohort mortality rates using only data on survival after infection. (a) When the inter-survey period is the same as the width of the age-groups, and if the pattern of incidence is constant, then the experience of incidence in one cohort (here $i = 3$), can be estimated from the estimates of incidence in younger cohorts. (b) When the inter-survey period is shorter, the experience of incidence in a cohort can be approximated using estimates of incidence in younger cross-sectional age-groups.

Age-group	Weibull survival distribution parameters		
	shape	scale	median
15-19	2.0	16.0	13.3
20-24	2.0	15.4	12.8
25-29	2.0	14.1	11.7
30-34	2.0	12.1	10.0
35-39	2.0	11.0	9.1
40-44	2.0	10.1	8.4
45-49	2.0	7.9	6.6

Table 3.2 Parametric model estimates of survival after infection in southern Africa. These values are model fits to previously published data [230, 262-264] [261].

3.2.4 Methods 1 and 2: derivation of cross-sectional measures

The final step for Methods 1 and 2 is to convert the cohort incidence rates into incidence rates that relate to conventional cross-sectional age-groups (Figure 3.3). By assuming that the seroconversions in the cohorts are distributed uniformly over the follow-up period, an average incidence rate can be calculated from these two cohort incidence rates, weighted according to the time spent by the cohorts in the fixed age-group. The time spent by each cohort is proportional to the shaded areas in Figure 3.3.

Total person-years spent in fixed age-group: $T.r$

Fraction of person-years spent by cohort $i-1$: $0.5T^2/T.r = T/2r$

Fraction of person-years spent by cohort i : $1 - T/2r$

$$\lambda_i = \left(1 - \frac{T}{2r}\right) \tilde{\lambda}_i + \left(\frac{T}{2r}\right) \tilde{\lambda}_{i-1} \dots (3.10)$$

The estimate pertains to the interval between two sero-surveys and relies on the inter-survey interval being no greater than the width of the age-groups ($T \leq r$), both of which are usually five years. If $T > r$ then the same logic holds but, because more cohorts pass through the cross-sectional age-groups in the period T , a new expression 3.10 for the relative weightings of the cohorts should be found.

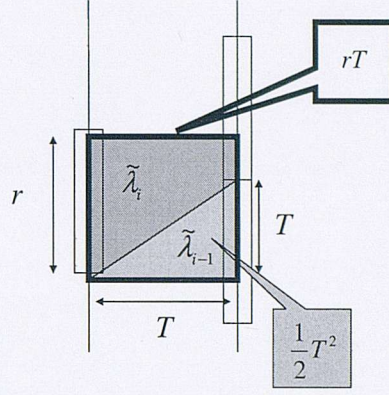


Figure 3.3 Incidence in the cross-sectional age-group can be approximated by measures of cohort incidence ($\tilde{\lambda}_i$ and $\tilde{\lambda}_{i-1}$) from two different cohorts. The relative contribution of each cohort to incidence in the cross-sectional age-group can be found by considering the person-years that each spends in the age-group, which is proportional to area in a Lexis diagram. For details see text.

3.2.5 Details of simulation model

A simulation model was used to validate the methods. The simulation model generates prevalence and mortality measurement as a function of time for a given pattern of incidence. Here a is the time since started sex, $S(a)$ is the number of susceptible and $I(a)$ is the number infected with that many years of sexual activity. The rate of change of $S(a)$ and $I(a)$ is described by the following partial differential equations.

$$\begin{aligned} \frac{d}{dt}S(a,t) + \frac{d}{da}S(a,t) &= -S(a,t)(\lambda(a,t) + \mu(a)) \\ \frac{d}{dt}I(a,t,w) + \frac{d}{da}I(a,t,w) + \frac{d}{dw}I(a,t,w) &= \lambda(a,t)S(a,t) - I(a,t,z)(h(a-w,w) + \mu(a)) \\ h(x,z) &= \left(\frac{k}{\beta_x}\right)\left(\frac{z}{\beta_x}\right)^{k-1} \end{aligned}$$

...(3.11)

$\lambda(a,t)$ is the instantaneous incidence rate; $\mu(a)$ is the rate of mortality from causes other than AIDS; $h(x,z)$ is the hazard of AIDS-death for those infected at age x that have survived z years. In these simulations, survival after infection is parameterised using the values given Table 3.2 and the background mortality rates are based on World Bank estimates for Africa in the pre-AIDS era [207].

The boundary conditions are:

$$\begin{aligned}
I(0,0,0) &= 0 \\
S(a,0) &= \phi(a)N_0 \dots (3.12) \\
S(1,t) &= \phi(1)N_0
\end{aligned}$$

where $\phi(a)$ is the fraction of the population that age, in the absence of AIDS-mortality.

Three scenarios for the pattern incidence over age are considered – constant over age, incidence highest at older ages (reflecting patterns expected early in epidemics) and incidence highest at younger age (reflecting patterns observed in mature epidemics) (see later for exact pattern). To generate changes over time, age-specific rates are multiplied by a variable, which is set to unity and then increases or decreases (or remain the same) after ten years.

3.2.6 Validating the methods in community-based cohort studies in Africa

To test how well these methods perform, incidence estimates derived using these two methods were compared with actual measurements made in cohort studies. Data were available from three community cohort studies in sub-Saharan Africa; the Manicaland HIV/STD Prevention Project in Zimbabwe [91], the MRC/UVRI Uganda Research Unit on AIDS, which runs a cohort in Masaka district [265] and the NIMR TAZAMA cohort study in Kisesa ward, Tanzania [266]. The Manicaland study furnishes suitable data for only one time interval (two sero-surveys three years apart); the Kisesa study covers three intervals (four surveys, each separated by about three years). The Masaka study has conducted seventeen annual sero-surveys, but one-year intervals do not generate enough incident cases for robust age-specific incidence estimates. To overcome this, longitudinal knowledge of HIV status was used to establish HIV prevalence measures at four points in time giving three intervals in which to measure prevalence, separated by roughly four years.

For validation purposes, the data used are from “closed cohorts”; that is, individuals who entered the cohort during a particular interval or were not seen at follow-up and were not known to have died, were not included. Sero-conversion dates were assigned between the last negative and first positive test results in accordance with analysis procedures developed at each site [90, 267-269]. Poisson-based confidence intervals were calculated for each incidence measurement, which do not take account of any clustering effects in the samples.

Objective measures of goodness-of-fit (between estimates and observation) were chosen *a priori* to assess the relative performance of the two methods. These were:

1. Root-mean-square-error divided by average measured incidence.

2. Fraction of estimates (over all ages and both genders from one period) that fall within the 95% confidence interval of the cohort measurement.
3. Estimated cumulative risk of infection [69] (here called lifetime risk of infection (LTR) for convenience) divided by measured LTR. Here we calculate LTR as:

$$LTR = \exp\left(-\sum_{\text{all } i} r\lambda_i\right)$$

4. Maximum absolute error divided by measured incidence rate.
5. Difference in location of estimate and observation, with the location

summarised by: $\frac{\sum_{\text{all } i} a_i \lambda_i}{\sum_{\text{all } i} a_i}.$

3.2.7 Application to DHS Data

The methods have been designed to make use of two successive rounds of cross-sectional prevalence measures, as will soon be available for a number of countries [61]. However, as an interim measure, preliminary estimates can be made using a single sero-survey if we assume that prevalence has been stable for r years preceding the survey: $p_{i,2} = p_{i+1,1}$. This restriction means that incidence estimates can not be made for the oldest age-group for which there is prevalence data so estimates of incidence are restricted in the range 15-44 years.

3.3 Contributions

In addition my supervisors, I am indebted to Basia Zaba (London School of Hygiene and Tropical Medicine, and National Institute for Medical Research, Tanzania) and Ties Boerma (World Health Organization) for the constructive collaboration that helped develop the paper that forms the basis of this chapter. In particular, BZ and TB were responsible for initially proposing a method using directly observed cohort mortality rates. For access to the data and assistance in its analysis, I am grateful to Ben Lopman (Department of Infectious Disease Epidemiology), Jim Todd (MRC/UVRI Uganda Research Unit on AIDS, Uganda), Mwita Wambura (National Institute for Medical Research, Tanzania) and Ties Boerma (World Health Organization).

3.4 Results

3.4.1 Testing the methods on simulated data

Simulating data and comparing the known incidence rates with estimates using these methods confirms that incidence can be accurately estimated from serial measures of cross-sectional prevalence. Both methods slightly under-estimate incidence when the rate is high and in younger age-groups, because infections occur rapidly and the person-years spent at risk are over-estimated estimated by the linear assumptions that underlie the approximations. Although the methods assume that incidence is constant in the period between sero-surveys, accurate estimates of average incidence can be obtained for this period if incidence is increasing or decreasing (Figure 3.4(a-b)). When incidence falls suddenly, estimates of incidence are immediately reduced and continue to estimate incidence accurately (Figure 3.4(c)). In these circumstances, measures of prevalence are slower to respond; after a dramatic fall in incidence of 50% over five years, prevalence has declined by only 14% whereas estimates of incidence indicate a 22% reduction (the true average reduction in the five-year interval is 25%). Immediately after a sudden change in incidence, the estimates are slightly too low because mortality in the older age-groups is transiently higher than at equilibrium with the new pattern of incidence. This bias is smaller when the reduction in incidence is more gradual or when incidence is lower in older age-groups.

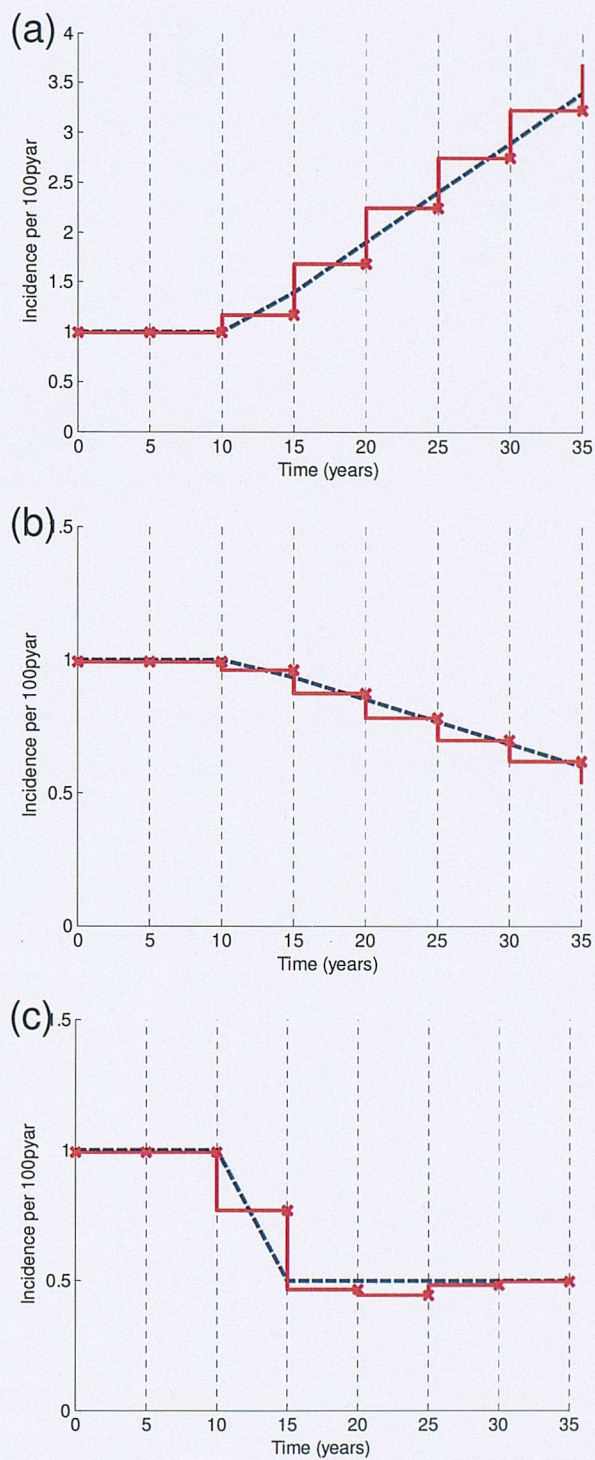


Figure 3.4 Comparison of 'true' simulated incidence rate (blue dashed lines) and estimates using Method 2 (Method 1 gives same results) (red solid line) when true incidence (a) increases steadily; (b) decreases steadily; (c) decreases suddenly. (Incidence assumed to be constant over age). The vertical lines indicate when five-yearly sero-surveys are done. The estimates of incidence are made at the time of the sero-survey (red crosses) but relate to the preceding five-year period.

The methods for estimating incidence depend on using mortality information from an external source. A potential difficulty is that the pattern of mortality actually depends on the pattern of incidence, which is determined by many behavioural factors and could vary between populations and over time. Simulating two alternative scenarios, where incidence is highest at young ages (typical in mature epidemics for women) or highest at middle ages (typical in nascent epidemics and in mature epidemics for men), we can compare the attendant patterns of mortality (Figure 3.5(a)). For both scenarios, mortality is low at young ages but much higher at older ages if incidence peaks at young ages. Estimating incidence using *Method 1* requires age-specific mortality rates for infected individuals and if the rates used accurately reflect the pattern of mortality in the population, the estimates will be good (Figure 3.5(b) – solid lines). However, if the mortality rates are taken from a population with a different distribution of incidence and mortality, the derived incidence estimates will be biased, particularly at older ages (Figure 3.5(b) – dashed lines). This bias is small if incidence is concentrated at young ages. *Method 2*, which does not rely on using age-specific mortality rates, is able to accurately predict incidence in either scenario using the same data on survival after infection and assuming that incidence age patterns in the years preceding the survey have remained constant.

3.4.2 Testing the methods on data from cohort studies

Measurements of incidence in adult and young people, together with the estimates from both methods are given in Table 3.3. The goodness-of-fit indicators are shown in Table 3.4. All estimates from both methods fall within the 95% confidence interval of the corresponding measurement. The difference between the measurement and estimate is less than 10% in half of the comparisons for each method. The mean difference between measurements of incidence and estimates is 14% for both methods. Neither method tends to systematically over or under-estimate incidence.

Measured and estimated incidence rates are compared by age-group in Figure 3.6. The overall performance of both methods is very good; the pattern and approximate level of incidence is captured successfully in all cases. The estimates from both Methods are inside the 95% confidence interval in about 90% of comparisons. The average error across all estimates is 20-40%, with estimates at older age-ages the most likely to deviate substantially. Aggregate measures of risk are estimated very accurately; the error in the estimate of LTR is usually less than 10% (5% excluding Masaka) and the measure of location is rarely more than one year out. Both methods give very similar estimates in most cases and none of the

goodness-of-fit statistics indicate a clear advantage to either Method. The estimates of incidence for the first period in Masaka are the least accurate.

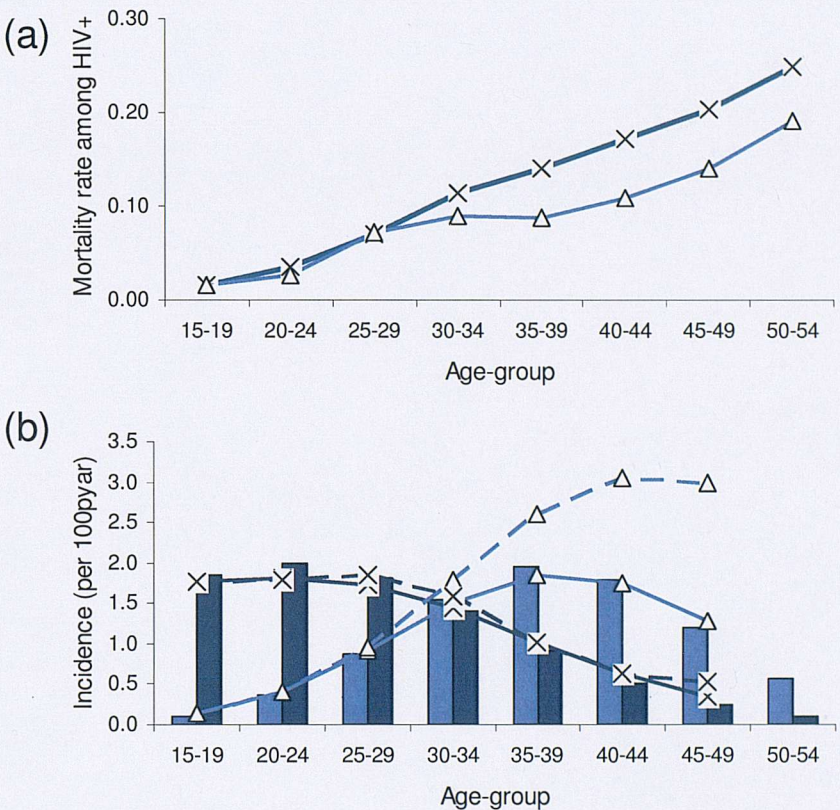


Figure 3.5 (a) The age-specific mortality rates for HIV-infected individuals when incidence is highest at young ages (dark line with crosses) or middle ages (light line with triangles). (b) Estimates of incidence using Method 2 (solid lines), and Method 1 when the “wrong” pattern age-specific mortality rates (i.e. from the alternative scenario – see part (a)) are used (dashed lines). Bars show actual simulated incidence rates.

Population and period	Gender	Age-group	Measurement			Estimate (age-standardised)			
			Obs	95% CI		Method 1		Method 2	
Adults									
Manicaland - 1	Males	15-54	1.76	1.43	2.16	1.83	***	1.74	***
Manicaland - 1	Females	15-54	1.48	1.23	1.79	1.60	***	1.78	*
Masaka - 1	Males	15-44	0.44	0.29	0.67	0.24		0.28	
Masaka - 1	Females	15-44	0.61	0.43	0.86	0.40		0.38	
Masaka - 2	Males	15-44	0.63	0.43	0.91	0.54	**	0.52	**
Masaka - 2	Females	15-44	0.37	0.23	0.61	0.35	***	0.40	***
Masaka - 3	Males	15-44	0.40	0.28	0.57	0.41	***	0.42	***
Masaka - 3	Females	15-44	0.57	0.43	0.75	0.49	**	0.53	***
Kisesa - 1	Males	15-44	0.74	0.51	1.09	0.77	***	0.74	***
Kisesa - 1	Females	15-44	0.87	0.63	1.21	0.84	***	0.81	***
Kisesa - 2	Males	15-44	1.42	1.09	1.84	1.20	**	1.17	**
Kisesa - 2	Females	15-44	1.32	1.03	1.67	1.07	**	1.08	**
Kisesa - 3	Males	15-54	1.21	0.93	1.58	1.04	**	1.05	**
Kisesa - 3	Females	15-54	1.19	0.94	1.49	1.04	**	1.11	***
Young people									
Manicaland - 1	Males	17-25	1.24	0.59	2.61	1.56	*	1.56	*
Manicaland - 1	Females	15-25	2.00	1.33	3.01	2.18	***	2.18	***
Masaka - 1	Males	15-24	0.31	0.16	0.62	0.35	**	0.34	***
Masaka - 1	Females	15-24	0.98	0.64	1.50	0.89	***	0.80	**
Masaka - 2	Males	15-24	0.29	0.14	0.61	0.40		0.39	
Masaka - 2	Females	15-24	0.52	0.28	0.97	0.60	**	0.52	***
Masaka - 3	Males	15-24	0.27	0.15	0.50	0.42		0.41	
Masaka - 3	Females	15-24	0.73	0.50	1.07	0.86	**	0.80	***
Kisesa - 1	Males	15-24	0.39	0.10	1.56	0.45	**	0.44	**
Kisesa - 1	Females	15-24	1.09	0.45	2.61	1.10	***	1.02	***
Kisesa - 2	Males	15-24	1.42	0.68	2.98	1.48	***	1.47	***
Kisesa - 2	Females	15-24	1.93	1.17	3.21	1.54	*	1.48	*
Kisesa - 3	Males	15-24	1.15	0.37	3.57	1.15	***	1.13	***
Kisesa - 3	Females	15-24	1.25	0.56	2.79	1.01	**	0.93	*

Table 3.3 Results of cohort studies analysis. Measurements and estimates of incidence in adults. All incidence values given per 100 person-years at risk. Estimated values are standardised to the same age-distribution as the measurement. Stars indicate level of agreement between estimate and measurement: *** absolute error <10%; ** <20%; * <30%.

Objective Measure:	1: RMSD / average incidence			2: Fraction Ests within 95% CI Obs		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Manicaland Males	0.38	0.29	0.28	0.88	1.00	0.88
Manicaland Females	0.34	0.52	0.26	1.00	0.75	1.00
Masaka (P1) Males	0.70	0.71	0.89	0.67	0.67	0.67
Masaka (P1) Females	0.42	0.49	0.64	0.33	0.67	0.33
Masaka (P2) Males	0.20	0.44	0.44	1.00	0.67	0.67
Masaka (P2) Females	0.29	0.24	0.39	1.00	1.00	1.00
Masaka (P3) Males	0.39	0.27	0.35	1.00	1.00	1.00
Masaka (P3) Femalea	0.35	0.34	0.56	0.67	1.00	0.33
Kisesa (P1) Males	0.29	0.30	0.51	1.00	1.00	0.83
Kisesa (P1) Females	0.21	0.24	0.23	1.00	1.00	1.00
Kisesa (P1) Males	0.30	0.35	0.48	0.83	0.83	0.67
Kisesa (P2) Females	0.37	0.39	0.29	0.83	0.83	0.83
Kisesa (P3) Males	0.29	0.31	0.35	1.00	1.00	1.00
Kisesa (P3) Females	0.26	0.29	0.47	1.00	0.88	0.75
Average	0.34	0.37	0.44	0.87	0.88	0.78

	3: LTR, Est / Obs			4: Max Relative Error			5: Location, Obs - Est		
	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3	Method 1	Method 2	Method 3
Manicaland Males	1.15	0.95	1.00	2.18	1.04	0.71	1.01	-0.39	-1.23
Manicaland Females	0.97	0.99	0.88	0.95	1.47	1.08	2.20	4.25	1.88
Masaka (P1) Males	0.65	0.57	0.46	0.81	0.82	1.00	0.01	-0.74	-3.78
Masaka (P1) Females	0.64	0.59	0.43	1.00	0.78	1.00	-3.49	-1.89	-4.88
Masaka (P2) Males	0.93	0.72	0.80	0.38	0.73	0.79	-1.50	-2.90	-3.52
Masaka (P2) Females	1.00	1.06	0.73	0.55	0.89	0.52	-1.97	0.34	-1.32
Masaka (P3) Males	1.26	0.94	1.04	0.52	0.46	0.64	-0.02	-1.69	-0.95
Masaka (P3) Femalea	0.90	0.89	0.73	0.62	0.34	1.00	-2.04	-0.51	-3.48
Kisesa (P1) Males	1.07	1.02	1.10	0.39	0.44	1.00	0.55	0.72	0.54
Kisesa (P1) Females	1.00	0.97	0.99	0.73	0.87	0.60	-0.17	0.36	-0.65
Kisesa (P1) Males	0.86	0.81	0.82	0.47	0.54	0.93	-0.95	-1.39	-2.79
Kisesa (P2) Females	0.85	0.83	0.83	0.44	0.46	0.58	1.11	1.49	0.10
Kisesa (P3) Males	0.99	0.86	0.94	0.95	0.92	1.85	0.37	-1.04	-1.22
Kisesa (P3) Females	0.98	0.97	0.97	0.39	0.47	0.65	1.42	1.99	2.10
Average Error	0.12	0.14	0.18	0.74	0.73	0.88	1.20	1.41	2.03

Table 3.4 Results of cohort studies analysis. The value of each of the five objective measures of fit are given for the two methods for each site and period. See text for details of the indicators.

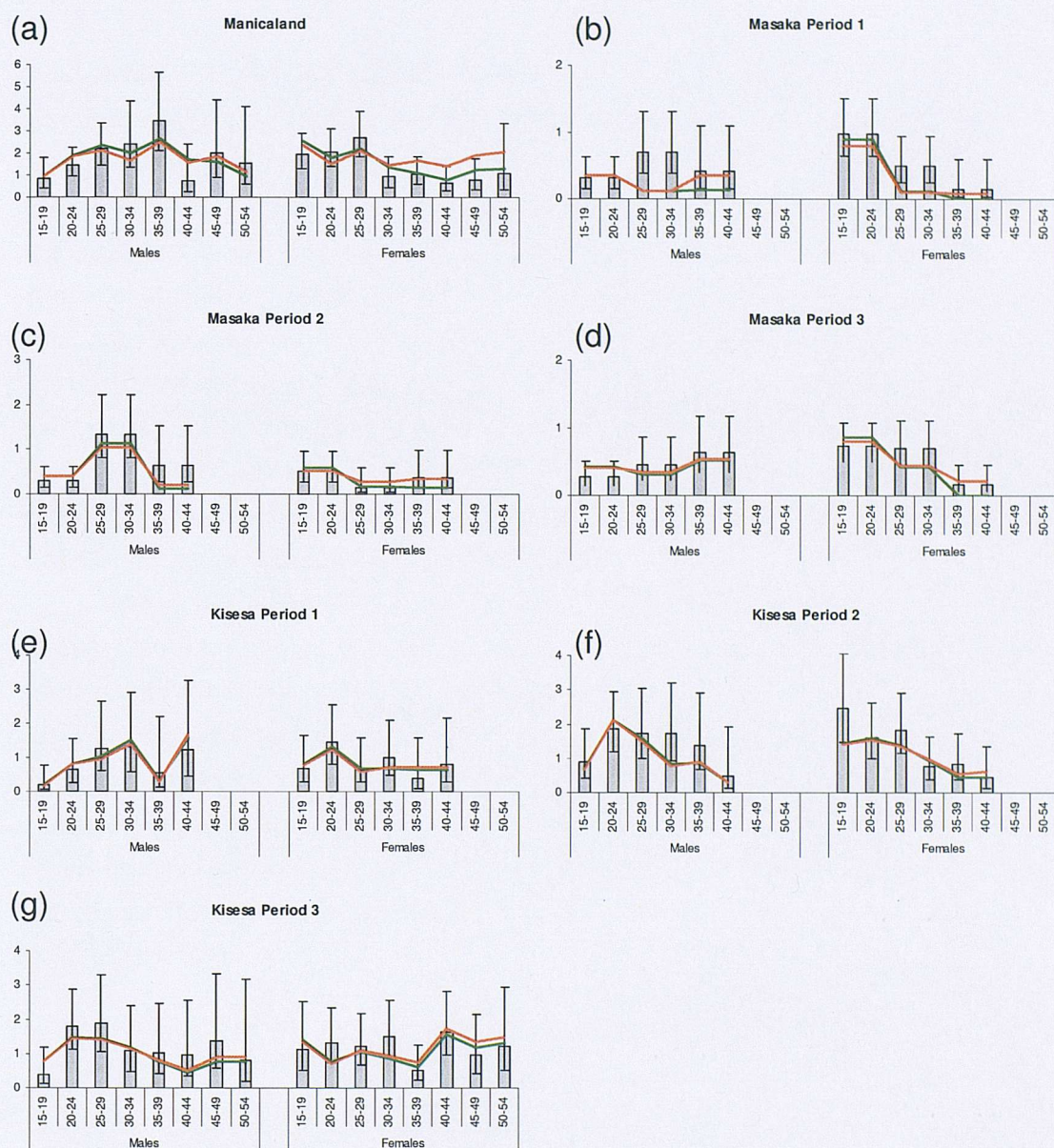


Figure 3.6 Result from the cohort studies analysis. For each panel, the bars show incidence measured in the closed cohort with 95% confidence intervals and the lines show derived incidence estimates using Method 1 (dark grey lines) and Method 2 (light grey line).

3.4.3 Application of the methods to DHS data

The methods are applied to the first DHS+ sero-surveys, with the additional assumption that prevalence has remained constant in the last five years. The mean prevalence (15-49 years) in these countries ranges from 1% (Senegal) to 27% (Lesotho) and is generally higher in Southern and Eastern African countries. The pattern of prevalence over age varies substantially between countries, particularly at older ages in women and in men (Figure 3.7). The incidence estimates are shown for a selection of countries in Figure 8. Methods 1 and 2 give similar estimates for younger ages but disparities arise at older ages with Method 2 giving higher estimates than Method 1. The contribution to changes in prevalence is driven by deaths more than new infections at older ages and the mortality rates predicted here by Method 2 are greater than those used in Method 1.

Although the pattern of incidence varies substantially between countries, a familiar theme is apparent in nearly all; at young ages, incidence is higher among women than men but at older ages incidence is higher for men. In many countries there are two peaks in incidence; one in young people (15-24 years) and a second among older people (40-54 years). There is a 10-fold difference between LTR in the lowest (Senegal) and highest (Lesotho) risk countries (Figure 3.9). In two countries (Zimbabwe and Lesotho), it is estimated that the chance that a 15 year old is infected before their 45th birthday exceeds 50%.

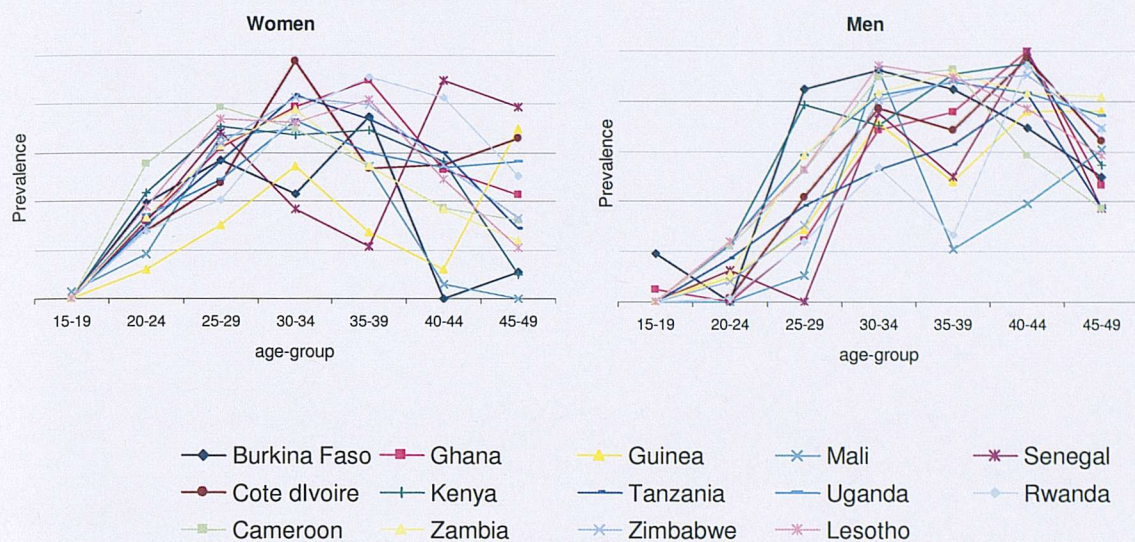


Figure 3.7 Prevalence in countries in southern, eastern and western Africa measured in the first DHS+ sero-surveys. Values are normalized to the same vertical scale for comparison.

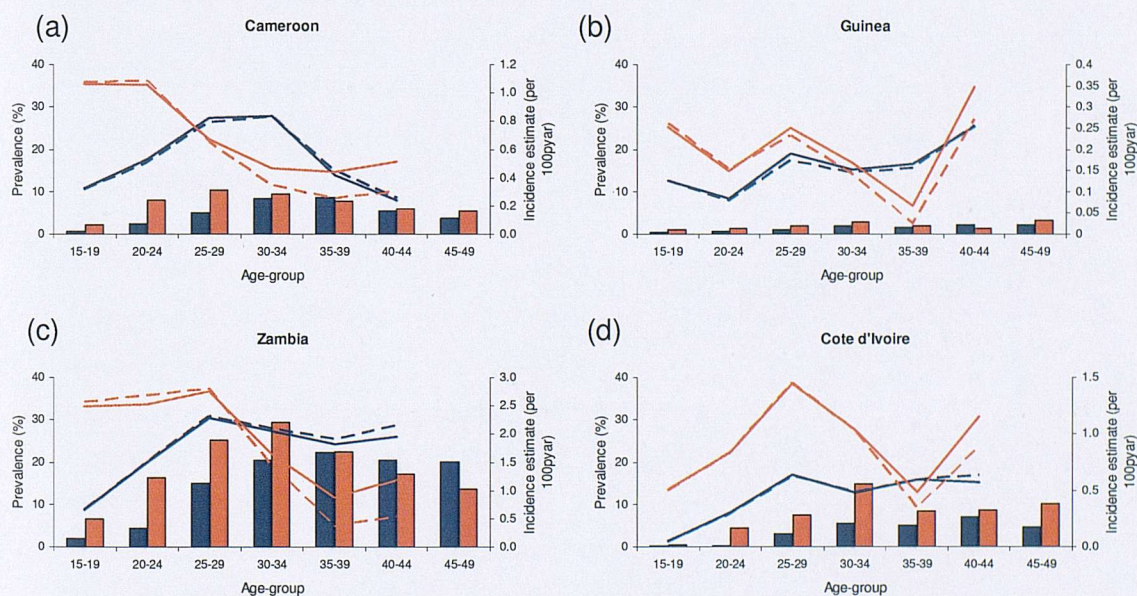


Figure 3.8 Results of DHS analysis. Prevalence (bars on left axis) and derived incidence estimates (lines on right axis; dashed line for *Method 1*; solid line for *Method 2*) for in (a) Cameroon; (b) Guinea; (c) Zambia; (d) Cote d'Ivoire. In each case, lines and bars are blue for men and orange for women.

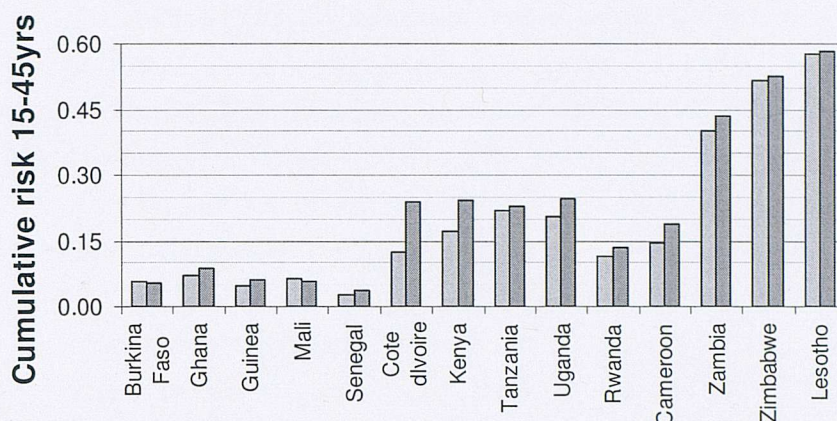


Figure 3.9 Cumulative risk of infection ('lifetime risk') between 15-45 years of age for men (lighter bars) and women (darker bars) estimated for the first round of DHS+ sero-surveys using Method 2 (Method 1 gives very similar results).

3.5 Discussion

Two methods were developed for estimating incidence in the general population using successive rounds of cross-sectional prevalence data, and they were tested using simulated data and real data from three African cohort studies. Both methods were able to accurately estimate incidence in adults and young people and to capture the pattern of incidence with respect to age. These methods could, therefore, be of substantial use in the analysis of serial measures of cross-sectional prevalence as will be shortly available from DHS+ surveys.

In the comparison with actual measurements of incidence, estimates of incidence in adult and young people were in very close agreement, whereas greater errors sometimes occurred at older ages. This is because the estimates at older ages are most sensitive to the assumptions about mortality and because the incidence measurement itself is more uncertain due to relatively small numbers of seroconversions. Both methods markedly underestimate incidence in the first period from Masaka among 25-34 year old men and women. This error is unlikely to result from the application of inappropriate mortality data because at this time (1991-5) the epidemic was still growing in this region [269] and mortality among infected individuals would be lower than later on, which should lead to the derived estimates being greater than the measurement. The cause of this discrepancy is therefore unclear, but the role of random errors in the prevalence measurements or miss-representative samples followed-up cannot be ruled out.

For both methods, the mean error in these estimates of incidence in adults is 14%, or 10% if the early data from Masaka are excluded. The uncertainty in estimates made in other settings is hard to quantify and will extend beyond random statistical errors because the extent to which assumptions and approximations made in the methods hold will not be known. A further insight into the uncertainty of the estimates could be derived by using a range of scenarios for the mortality data (Table 3.1).

The choice of which method to use will depend on which assumptions seem more likely to be true for the population in question and on the availability of locally-collected data. The investigations using simulated data highlight the danger of using the wrong age-specific mortality rates in *Method 1*, which can vary according to the phase of the epidemic and the prevailing pattern of incidence. It is reassuring that, at least in these three settings, the age-specific mortality rates are remarkably similar but this does not necessarily mean that they will be so elsewhere (e.g. urban communities or sites in Southern, Central or Western Africa). *Method 2*, on the other hand, may be applied to settings with different incidence patterns using the same data on survival after infection because it effectively calculates its own mortality rates by assuming that incidence patterns have remained constant in the recent past. The agreement between the results from the two methods indicates how successfully the procedure for estimating mortality rates in *Method 2* works. Therefore the recommendation is that *Method 1* should be used where recent age-specific cohort mortality data that pertain to the population in question is available; when they are not, *Method 2* can be used instead with a regional estimate on survival after infection.

In the tests against actual measurement of incidence, the mortality data used were taken from the same cohort studies. This may overstate how well *Method 1* will perform at a national level because there would not necessarily be such agreement between the actual mortality in the population in question and in the external mortality rates that are used. Also, whilst in these tests it was possible to use closed cohorts to measure incidence, in the application to the DHS+ sero-surveys, prevalence measures for birth cohorts will be used. However, as long as participation rates remain constant with respect to sero-status over age, no additional biases will be introduced.

The methods do not correct for differential migration between infected and uninfected individuals and, by using closed populations in the tests, the effect of migration has been removed from the test data, which may improve their performance. However, at the national level, the difference in net migration between infected and uninfected individuals should be small enough to ignore. If effective

treatment with anti-retroviral therapy (ART) becomes more common, the mortality rate of infected people will change and the values used here would lead to substantial over-estimates of incidence, particularly at older ages where the effect of ART will be greatest. As ART access increases, new mortality measurements from cohort studies will be needed, and their utility will depend on criteria for treatment access and uptake levels being broadly similar in the cohort studies and national populations. It is also expected that estimates of incidence among young people derived in this way using existing data will remain reliable even when ART is common.

An important application of these methods could be to the DHS+ sero-survey data and a preliminary analysis was done on just one round of data, making the additional assumption that prevalence in the next survey will be roughly the same. The derived estimates highlight the greater risk that young women experience compared with their male peers and the much higher incidence rate among older men compared to older women. They also reveal that there are two periods of elevated risk for women - at young and older ages. In fact, this has been observed in the cohort studies too (see Figure 3.6 and [260, 270]) and it may be linked to increases in risk behaviour as older women 'reconnect' to the sexual network after their spouses die or divorce [270].

A reliable comparison of risk between populations is cumulative risk of infection (LTR) [69] and the methods quantify a ten-fold difference in the LTR between the lowest and highest prevalence countries in this analysis, that are all classified as experiencing "generalised epidemics" [2]. In nearly all countries, LTR in the range 15-44 is higher in women than men, although over a wider age-range it would probably be higher for men because incidence in older men is greater than among older women.

In conclusion, it is possible to estimate incidence from cross-sectional prevalence with sufficient accuracy to monitor the epidemic. The choice of method (1 or 2) will depend on the local availability of mortality data. In comparison to other methods suggested [68, 69, 254-260], these methods are simple to understand and implement, they do not require opaque and computationally-intensive fitting procedures, and they have been validated with observed incidence estimates for the general population in several African countries experiencing mature generalised epidemics.

Chapter 4: The impact of reducing cross-generational sex and delaying age at sexual debut in a mature generalised epidemic

4.1 Introduction

In the generalised epidemics of sub-Saharan Africa, the majority of infection risk is associated with heterosexual sex [124, 271-273] and behaviour change is essential to reduce the number of new infections. Funding has been made available for interventions to promote behaviour change [83, 163] but care must be taken to target resources at changing those aspects of sexual behaviour that are most important to the spread of HIV.

Observational studies show that HIV prevalence among young women usually far exceeds that among young men [121] and this has prompted some to stress the importance of protecting young women from infection in particular [121-125]. Statistical analyses of individual behaviour data show that the risk of HIV infection is lower amongst women that avoid older sexual partners [40, 126] and begin sexual activity later [40, 127, 128]. For this reason, it has been suggested that behaviour interventions should focus on reducing cross-generational sex and delaying sexual debut [121, 130, 131]. The importance of these changes at the population-level has been presumed but not scientifically investigated and quantified [41, 121, 125, 126, 130, 131, 133, 134].

Mathematical models allow an assessment of the potential effects of proposed interventions aimed at changing behaviour and can provide a guide to the factors most critical to their success [86]. Increasingly, the insights gained from mathematical models are well understood and applied [201, 274, 275], and consulting mathematical models before implementing epidemiological interventions has become standard practice for emerging epidemiological problems [276-278]. It can be argued that the same approach should be used to assess the effects of proposed behavioural change interventions on generalized HIV epidemics.

Two questions about proposed behavioural change interventions are considered:

- (i) What population-level effect could reducing cross-generational sex and delayed age at first sex have on the HIV epidemic?
- (ii) What properties of the sexual network determine the size of this impact?

To address these questions, a deterministic mathematical model of the heterosexual transmission of HIV was developed with a detailed yearly age-structure so that changes in age at sexual debut, ages of sexual partners and rates of partner change in those recently entering the sexually active population could be investigated. These interventions are compared with increases in condom use by older men, which is currently very low, possibly related to the power imbalance in partnerships between

older men and young women [40, 41]. The model was parameterised using data collected in a cross-sectional survey in rural Zimbabwe [40] in order to provide a detailed and well informed example to illustrate the qualitative results rather than provide an exhaustive description of the various generalised HIV epidemics in Africa.

4.2 Methods

A deterministic mathematical model of the heterosexual transmission of HIV in a sex, age and activity-stratified population was used. To permit study of the effect of varying age at first sex and the pattern of partnership formation with respect to age, a detailed yearly age-structure was incorporated. The model is based on the one used in Chapter 2, but with some modifications. Sexual behaviour data from Manicaland, Zimbabwe [40] were used to parameterise the mean number of sexual partnerships formed by age and gender, the pattern of age mixing and the usage of condoms.

4.2.1 Changes to the Mathematical Simulation Model

As described in Chapter 2, for consistency, the derived pattern of partnership-formation for one gender must match that of the other and the extent to which males' demand for sexual partnerships is accommodated by the female population (or vice versa) has to be specified. In analyses relating to the impact of changing the pattern of mixing it is necessary to assume that one sex controls the mixing pattern. If this was not the case, the parameterised pattern of mixing could be distorted by the age-specific partner change rates of males and females, because male and female reports of sexual behaviour do not necessarily 'agree' in the way they have to in a mathematical model. Furthermore, the pattern of age mixing could be modified over time as the age-structure of the population changes in response to AIDS deaths. By choosing one gender to control the mixing pattern, the distribution of their contacts across the ages of the other gender will remain fixed in the simulation so that alternative patterns can be compared properly. It was decided that the pattern of mixing by age should be parameterised from females' reports and therefore that the pattern of partnership formation should be mostly controlled by females. This was to make the model structure simpler because preliminary investigations indicated that whilst the distribution of age differences between sexual partners was similar for females of all ages it was not for males. Following others [48, 279], equation 2.9 in the original specification was replaced with equation 4.2 with $\theta = 0.1$:

$$\begin{aligned}
D_{i,m,i',m'} &= \frac{N_{1,i,m} c_{1,i,m,i',m'}}{N_{2,i',m'} c_{2,i',m',i,m}} \\
c_{1,i,m,i',m'} &\rightarrow c_{1,i,m,i',m'} D_{i,m,i',m'}^{-(1-\theta)} \dots (4.2) \\
c_{2,i',m',i,m} &\rightarrow c_{2,i',m',i,m} D_{i,m,i',m'}^{\theta}
\end{aligned}$$

where $c_{k,i,m,i',m'}$ is the number of partnerships formed by individuals of gender k (1 for males, 2 for females), age i and activity group m , with individuals of the opposite gender aged i' and in activity group m' , and $N_{k,i,m}$ is the number of sexually-active individuals of that gender, age and activity group. $D_{i,m,i',m'}$ quantifies the disparity between the number of partnerships formed between each group and θ determines the extent to which the males control the resulting overall pattern of partnership formation. In other analyses, the influence of the parameter θ is investigated.

Another model modification was that the parameterisation of the fraction of partnerships in which there is consistent condom use was adapted so that it could vary according to the sexual activity groups of the partners. In the updated model, the chance that condoms are used throughout a sexual partnership is $\psi_{i,i',\max(m,m')}$, so that condom use is determined by the ages of the partners and the sexual activity group of the partner in the highest sexual activity group.

A measure of the risk of infection is the “lifetime risk” (R_k), which is the expected probability at birth that an individual of that sex will be infected with HIV by their 55th birthday [69]. The measure is taken ten years after the intervention is implemented at time T .

$$\begin{aligned}
R_k &= 1 - \prod_{i=0}^{i=55} (1 - \Gamma_{k,i}(T+10)) \\
\Gamma_{k,i}(t) &= \sum_m \left(\frac{N_{k,i,m}(t)}{\sum_m N_{k,i,m}(t)} F_{k,i,m}(t) \right) \dots (4.3)
\end{aligned}$$

where $F_{k,i,m}(t)$ is the force of infection for individuals of that gender, age and activity group, at time t .

The impact of an intervention can be summarised with the relative lifetime risk, which is denoted RR_k . This compares the lifetime risk of HIV infection when the intervention operates (R_k^1) with that to when there is no intervention (R_k^0).

$$RR_k = R_k^1 / R_k^0 \dots (4.4)$$

The fractional reduction in lifetime risk is then equal to $1 - RR$.

The importance of the timing of marriage when first sex is delayed is investigated with a different analytical model that divides a woman's sexual lifetime into years spent before marriage and years spent married. Here, the lifetime risk of infection, p , can be approximated by:

$$p(y, Y) = 1 - (1 - r_u)^{Y-y} (1 - r_m)^{S-y} \dots (4.5)$$

where S is total years spent sexually active (before or after marriage); y is age at sexual debut and Y is the age at first marriage; r_u is the yearly chance of infection when sexually active before marriage; and, r_m is the yearly chance of infection when sexually active after marriage.

4.2.2 Model Parameterisation

The model was parameterised using data from the Manicaland HIV/STD Prevention project [40]. This source has already been described in Chapter 1, but a brief note is also included here. The data is from a stratified population-based survey that was carried out in the Manicaland province of eastern Zimbabwe between July 1998 and January 2000 [40] and a follow-up survey completed after 3 years [91]. A structured face-to-face questionnaire was conducted with almost ten thousand men and women in twelve distinct communities; two forestry plantations, two tea and coffee estates, two small towns, two roadside trading centres and four subsistence farming areas. In three-quarters of interviews with literate respondents, answers to sensitive questions about sexual behaviour were recorded using a confidential voting method, the use of which has been associated with reporting of greater sexual activity [228].

Participants were asked how many different sexual partners each had in the last year (Table 4.1). The number of partnerships formed by men declines over age, but is greater than the number reported by women at all ages. In the model, it was assumed that these values represent yearly rates of sexual partnership formation ($M_{k,i}$ in equation 2.8).

	Mean number of sexual partnerships formed in the last year	
Age-range	Male	Female
<25	2.1	1.0
25-34	1.9	1.1
35-44	1.7	0.92
45+	1.6	—*

Table 4.1 Reported mean number of sexual partners in the last year, in the baseline Manicaland survey. *No data was collected for females aged 45 years or older, but in the model it was assumed that the rate was the same as for women aged 35-44 years.

Women were asked the age of their last sexual partner and from this the distribution of age-difference between sexual partners (d = male's age minus female's age) was calculated (Figure 4.1(a)). The distribution takes a similar form for women of all ages (Figure 4.1(a)); the mean age-difference is seven years and in approximately 25% of partnerships the age-difference is ten years or more. The distribution can be modelled by a log-logistic function (Equation 4.1) with the following fitted parameter values: $r = 0.11$, $\kappa = 3.04$, $\rho = 2.85$ (Figure 4.1(b)).

$$p(d) = \frac{\kappa \rho^\kappa (d + r)^{\kappa-1}}{(1 + (\rho(d + r))^\kappa)^2} \quad \text{for } d \geq 0 \dots (4.1)$$

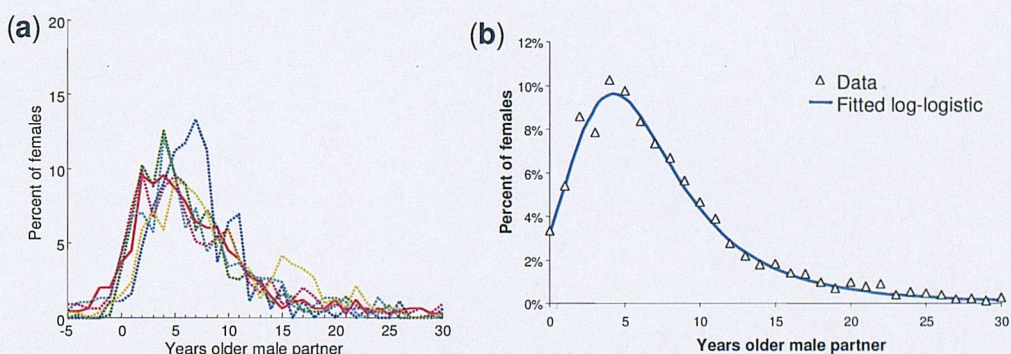


Figure 4.1 Observed distribution of age-difference in last reported sexual partnership. (a) The percentage of females' partnerships formed with males a given number of years older by females aged 15-19 (blue), 20-24 (dark green), 25-29 (red), 30-34 (light green), 35-39 (purple) and 40-44 (yellow) years. (b) Age-difference (male age minus female age) for all sexual partnerships reported by females (triangles) with fitted log-logistic distribution for all non-negative age-differences (line).

Condoms were reported to be used in all reported sex acts in the last sexual partnership by 17% of males and 8% of females that had a sexual partnership in the last month. Sex acts were self-defined in the questionnaire, but here we assume that all sex acts are insertive penile-vaginal. Reported condom use is particularly low for

older men (25 years or older) but is higher if either partner has had many sexual partners (here defined as having more than six lifetime partners) (Figure 4.2).

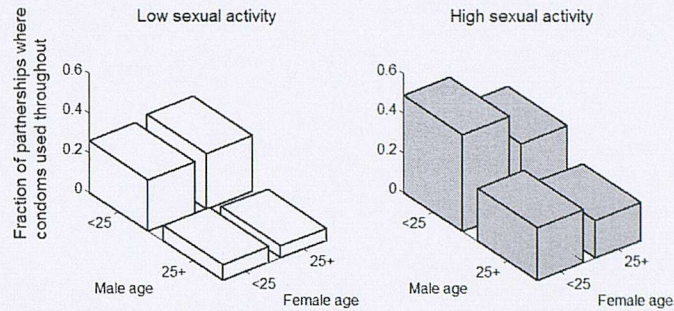


Figure 4.2 The proportion of reported partnerships in which condoms were used in all sex acts, by the age of each partner and whether the reporting partner had six or more previous sexual partners (“high sexual activity”). Values are the averages of reports from males and females.

For the analytical model that investigates the risk of infection before marriage and when married, S is set to 55 years and the yearly risk of HIV infection has been estimated in the Manicaland observation cohort [267] as $r_u = 0.02$ for sexually active unmarried women and $r_m = 0.01$ sexually active married women.

4.2.3. Simulated Intervention

4.2.3.1 Changes in cross-generational mixing

Two types of intervention to reduce cross-generational mixing are simulated;

- (i) A change in the distributional form of the allocation of young women’s partnerships among older men, preserving the total number of partnerships formed (Figure 4.3);
- (ii) Removal of a fraction of partnerships with a ten year or more age-difference, so that there are less partnerships in total.

Both of these interventions can generate the same reduction in the fraction of young women’s sexual partnerships that are ‘cross-generational’ but the former replaces those cross-generational partnerships with partnerships among peers, whereas the latter does not.

To simulate ‘peer-to-peer mixing’, individuals enter the population in yearly cohorts and form partnerships exclusively within their own cohort. In an alternative scenario, 0.5% of partnerships are directed to individuals one year older and 0.5% of partnerships are directed to individuals one year younger.

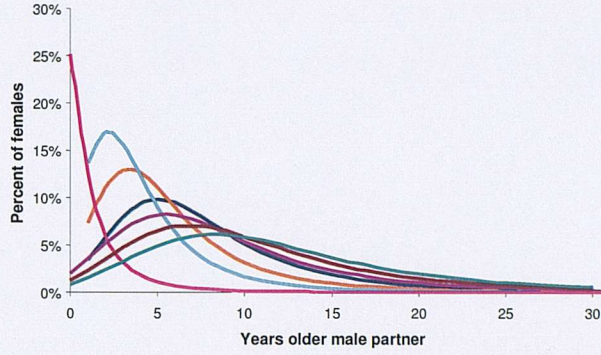


Figure 4.3 Alternative model scenarios with different degrees of cross-generational sex; 1% (pink), 5%, (light blue) 10% (orange), 20% (dark blue), 30% (purple), 40% (dark red), 50% (green). These are the distributions used to create Figure 4.4(a).

4.2.3.2 Changes in age at first sex

The parameter A_k specifies the age at which individuals of that gender begin sexual activity. When age at first sex is delayed by J_k years, the distribution of sexual partnerships formed as a function of age changes as:

$$\begin{aligned} c_{1,[A_1, A_1+J_1], m, i', m'} &\rightarrow 0 \\ c_{2,[A_2, A_2+J_2], m, i', m'} &\rightarrow 0 \end{aligned} \dots (4.3)$$

If males seek to maintain their current number of sexual partnerships formed per year then the following change is also made:

$$c_{1,i,m,[A_2+J_2, A_2+J_2+H], m'} \rightarrow c_{1,i,m,[A_2+J_2, A_2+J_2+H], m'} + \frac{\sum_{i'=A_2}^{A_2+J_2} c_{1,i,m,i', m'}}{H} \dots (4.4)$$

This allows males to seek to recoup the sexual partnerships they lost when their young would-be partners became abstinent from the sexual partnerships offered by young women in the first H years of sexually activity. The extent to which this new preference is reflected in the pattern of partnerships formed is determined by the parameter θ .

In some analyses it assumed that the biological susceptibility of women decreases as they age between 15 and 22 years [280, 281]. To represent this, the probability of male-to-female transmission is multiplied by a coefficient that takes the value 1.5 for females aged younger than 15 years, decreases linearly to 1.0 between ages 15 and 22 and remains at 1.0 for all older ages.

The influence of the timing of marriage and delaying first sex on the lifetime risk of infection for women was investigated using the simple analytical model by examining the surface $R(y, Y)$, varying y (the age at sexual debut) and Y (the age at first marriage) simultaneously.

▪ 4.2.3.3 Changes in condom use

The probability that condoms are used consistently in sexual partnerships ($\psi_{i,i',\max(m,m')}$) is altered in two different ways

- (i) The fraction of partnerships in which condoms are used consistently is doubled, irrespective of the partners involved

$$\psi_{1,i,i',\max(m,m')} \rightarrow 2\psi_{1,i,i',\max(m,m')} \dots (4.6)$$

- (ii) The fraction of partnerships with men aged 25 years or older in which condoms are used consistently is increased to match the reported fraction of partnerships with men younger than 25 years in which condoms are used consistently.

$$\begin{aligned} \psi_{1,[25,B_1],i',\max(m,m')} &\rightarrow \psi_{1,24,i',\max(m,m')} \\ \psi_{2,i,[25,B_1],\max(m,m')} &\rightarrow \psi_{2,i,24,\max(m,m')} \end{aligned} \dots (4.7)$$

where B_1 is the age at which males are assumed to stop sex.

4.3 Contributions

The analysis of age-difference between sexual partners was informed by previous work by Nick Grassley and James JC Lewis, and the incidence of HIV infected for married and unmarried women was investigated in collaboration with Ben Lopman.

4.4 Results

Running the model with the different mixing patterns shows that, with more cross-generational mixing, endemic prevalence (among those aged 15-49 years) is slightly higher (Figure 4.4(a) bars). Female-to-male prevalence ratios for 15-24 year-olds at least equal to those observed can be created in the model without assuming any difference in susceptibility to HIV infection between men or women or over age (Figure 4.4(a) line).

If all sexual partnerships are formed between peers the epidemic cannot become established (Figure 4.4(b)). If 1% of sexual partnerships are formed with partners one year older or younger, HIV can become endemic.

Simulating an intervention that reduces cross-generational mixing but preserves the total number of sexual partnerships formed, shows that such a behavioural change could substantially reduce HIV prevalence among young women but prevalence among young men might rise (Figure 4.4(c) – solid lines). With this intervention, the lifetime risk of infection (the expected chance at birth that an individual will have been infected with HIV by their 55th birthday) is only slightly reduced; by 10% for females and 5% for males. In contrast, if the same reduction in cross-generational mixing is simulated but without any compensatory increase in the number of partnerships among peers (dashed lines), prevalence among males can decrease and prevalence among females can decrease further. With this intervention, the lifetime risk of infection is reduced much more; by 25% for females and 22% for males.

The observed pattern of sexual mixing (young women forming partnerships with older men) means that the impact of young women delaying sexual debut is sensitive to the behavioural response of older men – i.e. if males' prospective young sexual partners become abstinent, they may seek to replace those lost partnerships with the youngest sexually active females that are still "available". Females' risk of infection in the first years of sexual activity is therefore linked to whether or not males seek to replace lost partnerships and the extent to which males control the structure of the sexual network (Figure 4.5(a)). If males do seek to replace the lost partnerships, incidence is increased among women for the first years of sexual activity and this effect is greater if males are able to control the structure of the sexual network. The reduction in lifetime risk of infection for women is greater if males do not seek to replace lost partnerships (Figure 4.5(b)). The benefit of delaying sexual debut is even greater if women become less susceptible to infection as they get older. However, under all scenarios the reduction in lifetime risk of infection associated with delaying sexual debut is modest.

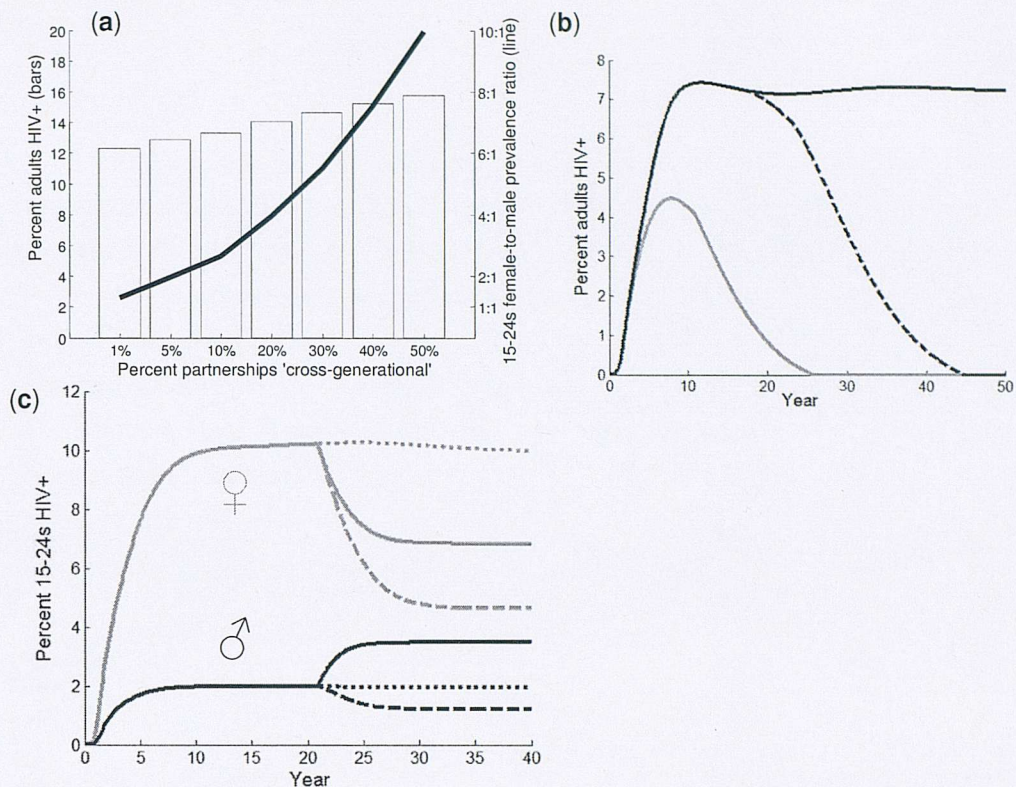


Figure 4.4 The impact of reducing cross-generational sex on the heterosexual spread of HIV. (a) HIV prevalence among 15-49 year-olds (bars) and ratio of female-to-male prevalence among 15-24 year-olds (line) with different levels of cross-generational mixing (percent of females' partnerships formed with males 10 or more years older), 20 years after infection introduced. (b) HIV prevalence over time if all partnerships are formed between individuals the same age (grey line) or if 1% of partnerships are formed between individuals one year older or younger (black line), or if an intervention eliminates any non-peer-to-peer partnerships at year 20 (dashed line). (c) HIV prevalence over time for 15-24 year-old males (black) and females (grey) if the proportion of cross-generational partnerships is reduced from 20% to 5% at year 20 and if there is replacement with peer-to-peer partnerships (solid lines) or if there is no replacement (dashed lines); dotted lines show 'no change' scenario.

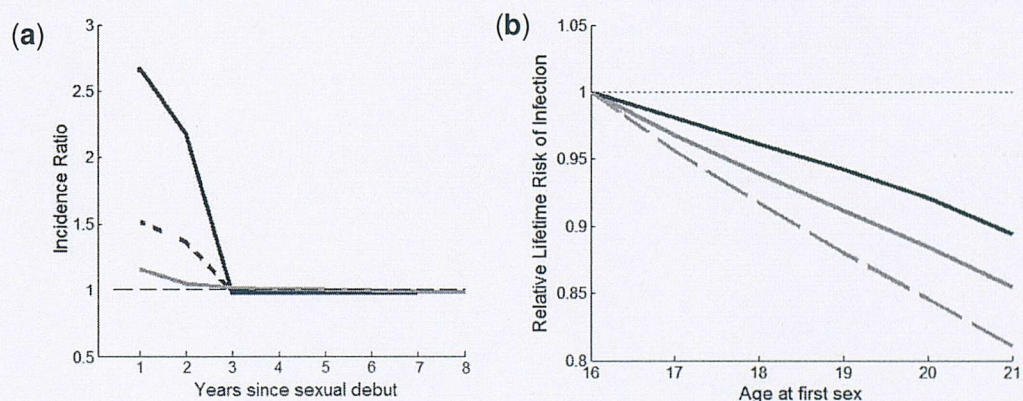


Figure 4.5 The impact of delaying age at first sex on the heterosexual spread of HIV. (a) HIV incidence ratio (relative to the no intervention scenario) for women when age at first sex is delayed by two years for both sexes if males seek to maintain their current level of sexual activity and if mixing is determined by males (black line), females (grey line) or is an equal compromise (dashed line). (b) Relative lifetime risk of infection when age at first sex is increased from 16 years if males seek to maintain their number of sexual partnerships (black line) or if partnerships are not replaced (grey line) or if partnerships are not replaced and susceptibility to infection decreases with age (dashed line).

A further issue is the relative timing of sexual debut and marriage [282]. The association between lifetime risk of infection for women when the age at first sex and the age at first marriage vary (with all other factors remaining constant) is shown in Figure 4.6. In recent years in Manicaland, the risk of infection when sexually active but not married is greater than when married. This means that the benefit of delaying first sex depends on the time spent unmarried. For example, increasing the age at first sex from 18 to 21 could lead to lifetime risk of infection being reduced by 9% (if women are unmarried for 12 months less), reduced by 6% (no change in relative timing of marriage) or remain almost unchanged (if women are unmarried for an extra 3 years).

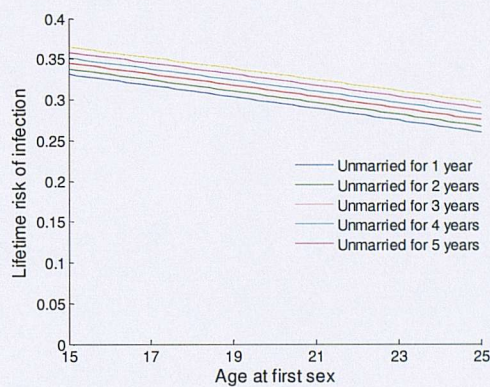


Figure 4.6 Estimated lifetime risk of infection for women, by age at first sex and age at first marriage.

In rural Zimbabwe, the probability of reporting having used a condom consistently with their most recent sexual partner is particularly low for older men (25 years or older) but is higher if either the man or his partner has had many sexual partners (Figure 4.2). If condom use by older men is increased to the level currently reported by younger men, the lifetime risk of infection could be reduced by ~20% for both males and females. This exceeds the impact of doubling condom use in the whole population or males and females delaying sexual debut by 2 years under the most optimistic assumptions (Figure 4.7).

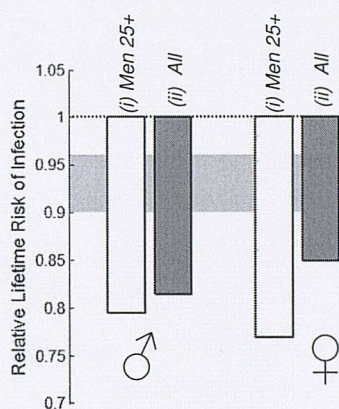


Figure 4.7 The impact of increasing condom use on the heterosexual spread of HIV. Relative lifetime risk of infection for males and females if (i) condom use among males older than 25 increases to the level reported by males under 25 (open bars), (ii) condom use overall is doubled (grey bars). The horizontal grey shading gives the comparable range of effects that could be expected if age at first sex for males and females is increased by 2 years.

4.5 Discussion

Sexual behaviour change is crucial to prevent HIV infections in sub-Saharan Africa [124]. Cross-sectional surveys of individuals' self-reported sexual behaviour show that young women that have had sex with an older man or begun sexual activity when young are more likely to have been infected with HIV [40, 126-128]. On this basis, interventions aiming to change behaviour have been proposed that focus on discouraging cross-generational sex and delaying sexual debut [121, 130, 131]. Although it is clear that these changes will somewhat reduce the risk of infection to the individual it was not known what impact they could have on the spread of HIV through the population. Despite this uncertainty the importance of cross-generational sex in supporting high HIV prevalence has been presumed [131] and an increase in abstinence among young people has been partially credited with the decline in HIV prevalence rates in Uganda [24, 80]. In this chapter, a mathematical model was used to quantify the reduction in the average lifetime risk of HIV infection that reducing cross-generational sex and delaying first sex could bring. The model was carefully parameterised using detailed data from a rural district in eastern Zimbabwe [40] but it can be expected that the qualitative insights will be transferable to other African settings with generalised epidemics.

The model simulations suggest that HIV prevalence is only slightly higher with much more cross-generational mixing. Furthermore, even if 99% of sexual partnerships are formed between peers, HIV can still reach a high endemic level. This is contrary to the suggestion that without cross-generational mixing HIV could not persist endemically [131]. Cross-generational sex helps increase prevalence because few of the partnerships of infected older males are with already-infected older females and are more likely to be with uninfected younger females. However, the link is not strong because the infection will reach all age-groups eventually under almost any mixing scenario, and then young women will be exposed instead to the high rates of sexual activity of their male peers. Sex with older men is more risky than sex with younger men partly because the former are more likely to be infected with HIV, having been exposed to the risk of infection for longer. However, the observed gradient in HIV prevalence among males by age is partly a *result* of the cross-generational mixing; prevalence among young men is suppressed by cross-generational mixing because they have only limited access to their peers and instead have sex with even younger uninfected women. A switch to peer-to-peer mixing will increase prevalence among young men making, from a female perspective, formerly 'low-risk' contacts increasingly 'high-risk'. In this way, the benefit of peer-to-peer over cross-generational mixing to the young women is negatively frequency-dependent;

one young woman will put herself at less risk by choosing partners her own age over older men but as more women come to do the same the benefit of this behaviour change is reduced as HIV prevalence among young men increases.

The real impact of cross-generational sex on the population level spread of HIV is the power imbalance in those partnerships and the implications this has for the chance that condoms will be used [40, 41]. The results show that behaviour change interventions should aim to minimise unprotected sexual contact by young women with anyone and not target the age difference between sexual partners *per se*. Nonetheless, this pattern of partnership formation between older men and younger women does seem to underlie the high female-to-male HIV prevalence ratio among young people; the model generates ratios at least as extreme as those observed without assuming any difference in susceptibility to infection by gender or age. Cross-generational mixing must be considered when examining other types of behavioural intervention; the demand for their sexual partnerships could undermine the benefit young women get from remaining abstinent for longer and the importance of transmission from older men makes the frequency with which they use condoms especially important.

Abstinence (through delaying the onset of sexual activity) removes the risk of infection for only a few years – a small fraction of one's lifetime exposure. This period may be important because the first years of a woman's sexual activity may carry the greatest risk of transmission for a number of biological [280, 281, 283] and behavioural [40, 133] reasons. However, even assuming that susceptibility declines strongly with age, the lifetime benefit of delaying sex for two years is expected to be, at most, only 8%. The benefit is smaller (3%) if the "demand" for their sexual partnerships is not reduced. Although abstinence undeniably reduces the risk of infection, its impact on the spread of HIV and the average chance of infection over a lifetime is small. Corroborating this conclusion, detailed statistical analyses indicate that most of the excess risk of prevalent infection that is associated with earlier sexual debut is actually mediated by risk behaviour later in life [127, 129].

Given the limited population-level effect of delaying age at first sex, it is unlikely that the dramatic prevalence decline in Uganda [24] was primarily driven by the two year delay in first sex [80]. Nonetheless, in the American HIV/AIDS PEPFAR initiative [163], abstinence gets equal billing with increased condom use and decreasing casual sex, which have been shown to have a much greater impact on lifetime risk of infection [23, 75, 77].

In the coming years, on-going and proposed behaviour interventions will be assessed and their potential effect estimated. This modelling work has highlighted

the sensitivity of the effectiveness of some behaviour changes to unknown properties of the sexual network (e.g. the response of males to female behaviour change) and projections should incorporate this uncertainty. From an individual-level perspective it is possible to identify those elements of sexual behaviour that are associated with the highest risk of infection. However, without a dynamic description of HIV transmission it is not clear how these changes will limit the spread of HIV at the population-level.

Publication

This work has been published:

Hallett, T.B., et al., *Behaviour change in generalised HIV epidemics: The impact of reducing cross-generational sex and delaying age at sexual debut*. Sex Transm Infect, 2007.

Chapter 5: The Role of Testing and Counselling
For HIV Prevention and Care in the Era of
Scaling-Up Antiretroviral Therapy

5.1 Introduction

Testing and counselling (TC) services, whereby individuals are tested for HIV and receive behaviour change advice, are being scaled-up in many African countries [143, 147, 248]. In addition, recent years have seen unprecedented financial and logistical commitments to providing antiretroviral treatment (ART) to those in need [284, 285]. Testing centres therefore have a dual-role; providing arguably the best opportunity to motivate behavioural changes to curb the spread of HIV, and as a point of entry to the health care system and ART programmes.

The laudable clinical goal of saving individuals from AIDS will be sustainable only if new infections can simultaneously be prevented [10]. ART may contribute to prevention efforts by reducing transmission directly through decreased infectiousness [286] and indirectly through reduced stigma [287]. However, programme policy that focuses on achieving clinical care targets without an explicit focus on prevention through behaviour change may lead to a testing strategy dominated by identifying HIV-positive individuals requiring ART rather than also providing HIV-negative individuals with behaviour change services to prevent future HIV infections and reduce the need for ART [288, 289].

High quality HIV prevention counselling is focused on promoting sexual behaviours that minimise the risk of acquiring and transmitting infection and includes the following elements: personalized risk assessment; support for positive changes already made; clarification of critical misconceptions; negotiated achievable behaviour change steps; flexibility in the HIV prevention approach; an opportunity to build skills; and, use of clear language to explain test results [290]. Periodic assessments of counselling services can help maintain these standards [290]. In one trial in America (Project REPSECT), HIV testing and high quality infection-prevention counselling was shown to reduce the incidence of sexually transmitted infections among HIV-negative men and women [136]. Other TC services, which may not include all the elements outlined above, have also been shown to lead to protective behavioural changes in low-income settings, particularly among those already infected [137]. However, observational studies, where TC was not delivered as part of a trial, indicate less promising results, and a tendency for only infected individuals to make protective behaviour changes [139]. Furthermore, in two recent studies in Zimbabwe, there are indications that some uninfected individuals increase their risk behaviour following TC [140, 250].

Given the complicated transmission dynamics in mature generalised HIV epidemics, the multifaceted nature of TC and the range of observed behavioural outcomes in studies and trials, the impact of TC at the population level is not clear

[291]. Mathematical models have generated important insights about the spread of the virus through networks of sexual partnerships and the impact of HIV interventions [275]. Optimistic predictions of the impact of multiple interventions, including TC, on the incidence of HIV globally were influential in setting the target of preventing seven million infections that was adopted by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) programmes [6]. However, the contribution of TC to the predicted prevention goals has not been analysed, nor has the influence of particular aspects of behaviour change associated with TC or patterns of roll out of TC been explored. In order to provide information to policymakers, the impact of TC programmes on the spread of HIV was investigated through mathematical modelling.

5.2 Methods

5.2.1 Introduction to the Model

The model used in this chapter is similar to those described in earlier chapters in the way that it simulates the transmission of HIV in a gender, age, and sexual-activity structured population. However, significant developments have been made to incorporate the following aspects of TC:

- Change over time in number of individuals that receive TC;
- Individuals changing behaviour following TC dependant on HIV status;
- Individuals needing ART at advanced stages of infection;
- Choice of sexual partners and condom use depending upon HIV status;
- Incorrect 'knowledge' of HIV status (where individuals are infected after receiving a negative test result).

The structure of TC delivery in the model and its effect on sexual behaviour is shown diagrammatically in Figure 5.1. It is assumed that only a fraction of the population has access to TC services – this is called the “TC catchment”. The size of the TC catchment can increase over time to reflect TC reaching more disconnected members of the community as well as its widening geographic availability (labelled (i)). The rate at which individuals in the catchment receive TC is an independent parameter, called “TC uptake”. This can also change over time to reflect increasing demand for TC. Uptake can vary between population sub-groups to simulate

differences in the demand for TC (e.g. higher for older individuals or for those with symptoms of immune-suppression).

The hatched area in Figure 5.1 shows the fraction of the population that have received TC and have changed their sexual behaviour. It assumed that all individuals that receive TC change their sexual behaviour: the way in which they do so is parameterised to reflect the findings of studies of the effect of TC in African populations (see later for details). This behavioural change can be permanent, or individuals may revert to their previous patterns of behaviour over time (labelled (iii)).

Among those individuals that have received TC and have changed their behaviour, some will not be infected and have received a negative test result, others will be infected and have received a positive test result, but a few will be infected and have received a negative test result (because they were infected after receiving TC). In the model, individual behaviour can be set by the perceived HIV-status (i.e. result at last test) and, for brevity, the technical specification refers to the behaviour of individuals that “think” they are infected or uninfected, and individuals that have not received TC are said to “not know” their HIV-status.

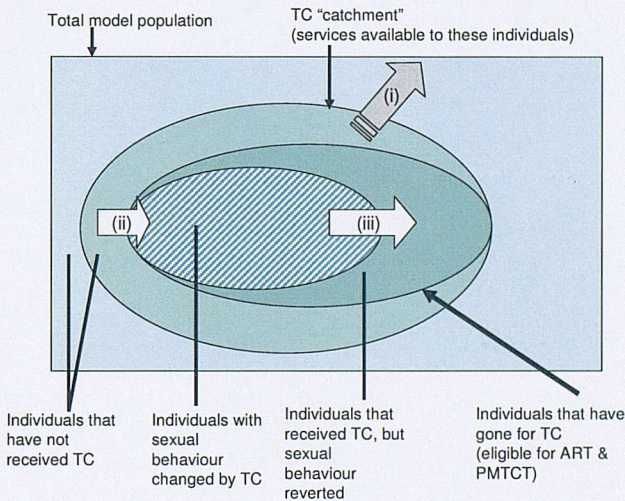


Figure 5.1 Structure of the TC model, showing (i) expanding catchment of TC, (ii) uptake of TC, and (iii) individuals that have received TC reverting to previous patterns of sexual behaviour. The hatched area shows the fraction of the population that have received TC and whose sexual behaviour is changed.

The full technical specification of the model is detailed in four sections:

- i. Simulating Heterosexual Transmission of HIV;

- ii. Simulating The Effects of TC;
- iii. Fitting to Epidemiological Conditions in Zimbabwe;
- iv. Parameters for behaviour change scenarios.

5.2.2 Simulating Heterosexual Transmission of HIV

The model is defined by a set of ordinary differential equations which are solved numerically using Euler's method with a time-step of 1/12 years. The state variables are given by $X_{k,l,a}^{s,v}$: k refers to gender ($k=0$ men and $k=1$ women); l refers to sexual activity group ($l=1$ sex work group (i.e. female sex workers and their male clients), $l=2$ casual sex group (i.e. men and women that have casual partners) and $l=3$ spousal sex group (i.e. men and women in stable relationships)); a refers to age (five-year group: $a=0$:15-19 years, $a=1$: 20-24 years, ..., $a=14$: 80-84 years); s refers to HIV-status ($s=0$ susceptible, $s=1$ primary HIV infection, $s=2$ latent HIV infection, $s=3$ pre-AIDS, $s=4$ full-blown AIDS, $s=5$ HIV infection and on ART and $s=6$ HIV infection and ART failed); v refers to TC-status and serostatus that the individual "thinks" they are ($v=0$ "thinks HIV negative", $v=1$ "thinks HIV positive", $v=2$ "doesn't know but is in the TC catchment", $v=3$ "doesn't know and is not in the TC catchment", $v=4$ "has received TC but reverted to previous sexual behaviour").

The equations describing the susceptible individuals are:

$$\begin{aligned}
\frac{dX_{k,l,a}^{0,4}}{dt} &= g(X_{k,l,a}^{0,0} + X_{k,l,a}^{0,1}) - (\mu_{k,a} + \lambda_{k,l,a}^4)X_{k,l,a}^{0,4} \\
\frac{dX_{k,l,a}^{0,3}}{dt} &= -(\mu_{k,a} + \lambda_{k,l,a}^3)X_{k,l,a}^{0,3} \\
\frac{dX_{k,l,a}^{0,2}}{dt} &= -(\mu_{k,a} + \lambda_{k,l,a}^2 + v_{k,l,a}^s(t))X_{k,l,a}^{0,2} \quad \dots(5.1) \\
\frac{dX_{k,l,a}^{0,1}}{dt} &= v_{k,l,a}^s(t)\pi_0 X_{k,l,a}^{0,2} + r\pi_0 X_{k,l,a}^{0,0} - (\mu_{k,a} + \lambda_{k,l,a}^1 + g)X_{k,l,a}^{0,1} \\
\frac{dX_{k,l,a}^{0,0}}{dt} &= v_{k,l,a}^s(t)(1 - \pi_0)X_{k,l,a}^{0,2} - (\mu_{k,a} + \lambda_{k,l,a}^0 + r\pi_0 + g)X_{k,l,a}^{0,0}
\end{aligned}$$

In the equations: $\lambda_{k,l,a}^v$ is the rate at which individuals of that gender, age, sexual activity group and perception of HIV-status are infected with HIV; $v_{k,l,a}^s(t)$ is the rate at

which individuals of that gender, age, sexual activity group and HIV-status receive TC; r is the rate at which those who think they are HIV negative are retested; $\mu_{k,a}$ is the per capita death rate; π_s is the probability of the test returning a positive result for an individual of HIV-status s (so that π_0 is the probability of a positive result for an HIV negative individual and is equal to one minus the test specificity). The rate at which those who have received TC revert to the behaviour of those that do not know their HIV-status is g ; these individuals will not receive TC again but are eligible for ART when they develop symptoms of immune-suppression (ie. start pre-AIDS) or treatment to prevent mother-to-child transmission (PMTCT) when pregnant.

The number of individuals entering the youngest sexually-active age group of each gender and sexual activity group each year is $B_{k,l}^{s,v}(t)$:

$$B_{k,l}^{0,2}(t) = \theta(t) \kappa_k \phi_{k,l} q \sum_{s=0}^3 \sum_{l=1}^2 \sum_{a=1}^8 \tau_a \left((1 - \zeta_s) [X_{2,l,a}^{s,1}(t-A) + X_{2,l,a}^{s,3}(t-A) + X_{2,l,a}^{s,4}(t-A)] + \right. \\ \left. (Q(1 - \zeta_s P) + (1-Q)(1 - \zeta_s)) [X_{2,l,a}^{s,5}(t-A) + X_{2,l,a}^{s,2}(t-A)] \right) \\ B_{k,l}^{0,3}(t) = (1 - \theta(t)) \kappa_k \phi_{k,l} q \sum_{s=0}^3 \sum_{l=1}^2 \sum_{a=1}^8 \tau_a \left((1 - \zeta_s) [X_{2,l,a}^{s,1}(t-A) + X_{2,l,a}^{s,3}(t-A) + X_{2,l,a}^{s,4}(t-A)] + \right. \\ \left. (Q(1 - \zeta_s P) + (1-Q)(1 - \zeta_s)) [X_{2,l,a}^{s,2}(t-A) + X_{2,l,a}^{s,5}(t-A)] \right) \\ \dots(5.2)$$

where A is the age at which individuals begin sexual activity; κ_k is the fraction of those that begin sexual activity of that gender; $\phi_{k,l}$ is the fraction of those that begin sexual activity of that gender that enter that sexual activity group; $\theta(t)$ is the fraction of the population to which TC is available at time t (i.e. "catchment"); q is the fraction of live births that survive to age A ; τ_a is the fertility rate (live births per person-year) of females of that age group; ζ_s is the probability that a woman of that HIV-status transmits the infection to her baby; Q is the fraction of pregnant women that know they are infected that receive PMTCT; P is the efficacy of PMTCT (fractional change in probability of transmission of infection from mother-to-child). This assumes that no child born with HIV lives older than A to enter the sexually-active population and that women with AIDS and those on ART are infertile.

The number of infants born each year that will die of maternally-transmitted HIV infection is:

$$\sum_{s=1}^3 \sum_{l=1}^2 \sum_{a=1}^8 \tau_a \left((1-Q)\zeta PX_{2,l,a}^{s,2}(t-A) + (1-Q)\zeta PX_{2,l,a}^{s,5}(t-A) \right. \\ \left. + \zeta PX_{2,l,a}^{s,1}(t-A) + \zeta PX_{2,l,a}^{s,3}(t-A) + \zeta PX_{2,l,a}^{s,4}(t-A) \right) \dots (5.3)$$

These deaths can be included in calculations of all AIDS-related deaths, distributed exponentially (with mean 5 years) after birth.

The number of new heterosexually-acquired and vertically-acquired infections at time t are:

$$\text{heterosexual} : \sum_{s=1}^3 \sum_{l=1}^2 \sum_{v=0}^4 \sum_{a=1}^8 (\lambda_{k,l,a}^v X_{k,l,a}^{0,v}) \\ \text{vertical} : \kappa_k \phi_{k,l} q \sum_{s=1}^3 \sum_{l=1}^2 \sum_{a=1}^8 \tau_{s,l,a} \zeta_s \left(X_{2,l,a}^{s,0}(t) + X_{2,l,a}^{s,2}(t) + X_{2,l,a}^{s,3}(t) + X_{2,l,a}^{s,4}(t) \right. \\ \left. + (1-Q)[X_{2,l,a}^{s,5}(t) + X_{2,l,a}^{s,2}(t)] + (QP)[X_{2,l,a}^{s,5}(t) + X_{2,l,a}^{s,2}(t)] \right) \\ \dots (5.4)$$

The equations describing those with primary HIV infection are:

$$\frac{dX_{k,l,a}^{1,4}}{dt} = \lambda_{k,l,a}^4 X_{k,l,a}^{0,4} + g(X_{k,l,a}^{1,0} + X_{k,l,a}^{1,1}) - (\mu_{k,a} + \sigma_1) X_{k,l,a}^{1,4} \\ \frac{dX_{k,l,a}^{1,3}}{dt} = \lambda_{k,l,a}^3 X_{k,l,a}^{0,3} - (\mu_{k,a} + \sigma_1) X_{k,l,a}^{1,3} \\ \frac{dX_{k,l,a}^{1,2}}{dt} = \lambda_{k,l,a}^2 X_{k,l,a}^{0,2} - (\mu_{k,a} + \sigma_1 + v_{k,l,a}^s(t)) X_{k,l,a}^{1,2} \dots (5.5) \\ \frac{dX_{k,l,a}^{1,1}}{dt} = \lambda_{k,l,a}^1 X_{k,l,a}^{0,1} + v_{k,l,a}^s(t) \pi_1 X_{k,l,a}^{1,2} + r \pi_1 X_{k,l,a}^{1,0} - (\mu_{k,a} + \sigma_1 + g) X_{k,l,a}^{1,1} \\ \frac{dX_{k,l,a}^{1,0}}{dt} = \lambda_{k,l,a}^0 X_{k,l,a}^{0,0} + v_{k,l,a}^s(t) (1 - \pi_1) X_{k,l,a}^{1,2} - (\mu_{k,a} + \sigma_1 + r \pi_1 + g) X_{k,l,a}^{1,0}$$

The equations describing those in the later stages of HIV infection that do not know they are infected, or who have reverted to their patterns of sexual behaviour before receiving TC, are:

$$\left. \begin{aligned}
\frac{dX_{k,l,a}^{s,4}}{dt} &= \sigma_{s-1} X_{k,l,a}^{s-1,4} - (\mu_{k,a} + \sigma_s) X_{k,l,a}^{s,4} + g(X_{k,l,a}^{s,0} + X_{k,l,a}^{s,1}) \\
\frac{dX_{k,l,a}^{s,3}}{dt} &= \sigma_{s-1} X_{k,l,a}^{s-1,3} - (\mu_{k,a} + \sigma_s) X_{k,l,a}^{s,3} \\
\frac{dX_{k,l,a}^{s,2}}{dt} &= \sigma_{s-1} X_{k,l,a}^{s-1,2} - (\mu_{k,a} + \sigma_s + v_{k,l,a}^s(t)) X_{k,l,a}^{s,2} \\
\frac{dX_{k,l,a}^{s,0}}{dt} &= \sigma_{s-1} X_{k,l,a}^{s-1,0} + v_{k,l,a}^s(t)(1 - \pi_s) X_{k,l,a}^{s,2} - (\mu_{k,a} + \sigma_s + r\pi_s + g) X_{k,l,a}^{s,0}
\end{aligned} \right\} \text{for } s = 2, 3, 4$$

...(5.6)

Here σ_s is the rate of progress from stage of HIV infection s to the next stage, $s+1$. The parameter σ_4 is the AIDS-associated death rate.

The equations describing those in the later stages of HIV infection that know they are infected are:

$$\begin{aligned}
\frac{dX_{k,l,a}^{2,1}}{dt} &= \sigma_1 X_{k,l,a}^{1,1} + v_{k,l,a}^2(t) \pi_2 X_{k,l,a}^{2,2} + r\pi_2 X_{k,l,a}^{2,0} - (\mu_{k,a} + \sigma_s + g) X_{k,l,a}^{2,1} \\
\frac{dX_{k,l,a}^{3,1}}{dt} &= \sigma_2 X_{k,l,a}^{2,1} + v_{k,l,a}^3(t) \pi_3 X_{k,l,a}^{3,2} + r\pi_3 X_{k,l,a}^{3,0} - (\mu_{k,a} + \sigma_4 + g) X_{k,l,a}^{3,1} \\
\frac{dX_{k,l,a}^{4,1}}{dt} &= (1-f) \sigma_3 X_{k,l,a}^{3,1} + (1-f) v_{k,l,a}^4(t) \pi_4 X_{k,l,a}^{4,2} + r\pi_4 X_{k,l,a}^{4,0} - (\mu_{k,a} + \sigma_4 + g) X_{k,l,a}^{4,1} \\
\frac{dX_{k,l,a}^{5,1}}{dt} &= \sigma_4 X_{k,l,a}^{3,1} + (1-f) v_{k,l,a}^5(t) \pi_5 X_{k,l,a}^{4,2} + r\pi_5 X_{k,l,a}^{5,0} - (\mu_{k,a} + \sigma_5 + g) X_{k,l,a}^{5,1} \\
\frac{dX_{k,l,a}^{6,1}}{dt} &= f(\sigma_3 X_{k,l,a}^{3,1} + v_{k,l,a}^4(t) \pi_4 X_{k,l,a}^{4,2} + v_{k,l,a}^5(t) \pi_5 X_{k,l,a}^{5,2}) - (\mu_{k,a} + \sigma_6 + g) X_{k,l,a}^{6,1} \\
\frac{dX_{k,l,a}^{7,1}}{dt} &= \sigma_6 (X_{k,l,a}^{6,1} + X_{k,l,a}^{6,5}) - (\mu_{k,a} + \sigma_7) X_{k,l,a}^{7,1} \\
\frac{dX_{k,l,a}^{6,5}}{dt} &= g X_{k,l,a}^{6,1} - (\mu_{k,a} + \sigma_6) X_{k,l,a}^{6,5}
\end{aligned}$$

...(5.7)

where the fraction of those that have received TC and found to be infected that receive ART is f ; the rate of failure for those on treatment is σ_6 ; the rate of mortality

for those who treatment has failed is σ_7 . It follows that the rate of adult AIDS-related death (including those whose treated has failed) at time t is:

$$\sum_{a=0}^{14} \sum_{l=1}^3 \sum_{k=0}^1 \left(\sigma_7 X_{k,l,a}^{7,1} + \sum_{v=1}^4 \sigma_4 X_{k,l,a}^{4,0} \right) \quad \dots(5.8)$$

The per capita force of infection is defined with respect to gender, HIV-status, TC-status, and sexual activity group in the following way. For ease of notation, the state variables ($X_{k,l,a}^{s,v}$) are re-classified as $W_{k,l,a}^b$, where b is the *behaviour-mode* variable (corresponding to perception of own HIV-status). The parameter S_s determines the relative partner change rate (i.e. sexual activity) with respect to HIV-status; those who have full-blown AIDS or failed ART are assumed not to be sexually active; those with pre-AIDS are assumed to partnerships at half the rate they had previously.

$$\begin{aligned} W_{k,l,a}^2 &= \sum_{s=0}^6 S_s (X_{k,l,a}^{s,2} + X_{k,l,a}^{s,3} + X_{k,l,a}^{s,4}) \quad (b=2; \text{doesn't know HIV status}) \\ W_{k,l,a}^1 &= \sum_{s=0}^6 S_s X_{k,l,a}^{s,1} \quad (b=1; \text{thinks HIV positive}) \quad \dots(5.9) \\ W_{k,l,a}^0 &= \sum_{s=0}^6 S_s X_{k,l,a}^{s,0} \quad (b=0; \text{thinks HIV negative}) \end{aligned}$$

In this way 'sero-sorting' can be simulated by a tendency for assortative mixing with respect to b : that is, males that think they are HIV negative ($b=0$) preferentially forming partnerships with females that also think they are HIV negative; males that think they are HIV positive ($b=1$) preferentially forming partnerships with females that also think they are HIV positive; and, males that do not know their serostatus preferentially forming partnerships with females that do not know their HIV status either. The tendency of individuals to form sexual partnerships assortatively with respect to behavioural-mode is ε_B .

There is also a tendency for males to preferentially form sexual partnerships with females in the same sexual activity group, which is specified by ε_L .

The number of partnerships formed per year is $c_{k,l,a}^b$ for individuals of that gender, sexual activity group, age group and behaviour mode, if they are sexually

active (i.e. not full-blown AIDS or failed ART). For males this is parameterised with a mean rate of partnership formation for each age group ($\bar{c}_a(t)$) and two ratios of partnership formation rate for the two higher sexual activity groups relative to those in the lowest sexual activity group (ω_1 and ω_2). The rate of partner change for each male sexual activity group is then calculated as:

$$\begin{aligned} c_{1,1,a}^b &= c_{1,3,a}^b \omega_1 \\ c_{1,2,a}^b &= c_{1,3,a}^b \omega_2 \\ c_{1,3,a}^b &= \frac{\bar{c}_a(t)}{(\phi_{1,1} \omega_{1,a} + \phi_{1,2} \omega_{2,a} + \phi_{1,3})} \end{aligned} \quad \dots(5.10)$$

The females' rates of partner change are determined by the distribution of partnership formation by the males:

$$c_{2,l',a'}^b = c_{1,l,a}^b \frac{W_{1,l,a}^\bullet}{W_{2,l',a'}^\bullet} \quad \dots(5.11)$$

$\rho_{1,e,f,g,h,m,n}$ is defined as the proportion of sexual partnerships that a male of sexual activity group e , age group f and behavioural-mode g forms with females in activity group h , age group m and behavioural-mode n ;

$$\rho_{1,e,f,g,h,m,n} = \left(\begin{aligned} &\varepsilon_B \delta_{g,n} \left[\varepsilon_L \delta_{e,h} + (1 - \varepsilon_L) \frac{c_{2,1,m} W_{2,1,m}^n}{c_{2,1,m} W_{2,1,m}^n + c_{2,2,m} W_{2,2,m}^n + c_{2,3,m} W_{2,3,m}^n} \right] \\ &+ (1 - \varepsilon_B) \left[\varepsilon_L \delta_{e,h} \frac{c_{2,h,m} W_{2,h,m}^n}{c_{2,h,m} W_{2,h,m}^\bullet} \right. \\ &\quad \left. + (1 - \varepsilon_L) \frac{c_{2,1,m} W_{2,1,m}^n}{c_{2,1,m} W_{2,1,m}^\bullet + c_{2,2,m} W_{2,2,m}^\bullet + c_{2,3,m} W_{2,3,m}^\bullet} \right] \end{aligned} \right) \Delta_{f,m} \quad \dots(5.12)$$

Here $\Delta_{f,m}$ is the proportion of sexual partnerships of males in age group f that are formed with females in age group m ($\sum_{m=1}^8 \Delta_{f,m} = 1$). As in other models in this thesis, $\Delta_{f,m}$ is parameterised so that most partnerships are formed between men and

women who are 5-10 years younger (mean = 7.4 years). $\delta_{i,j}$ is the identity matrix; $\delta_{i,j} = 1$ if $i=j$; $\delta_{i,j} = 0$ otherwise.

From this, the distribution of each female's partnerships is calculated; $\rho_{2,h,m,n,e,f,g}$ is the proportion of sexual partnerships that a female of sexual activity group h , age group m and behavioural-mode n forms with males in sexual activity group e , age group f and behavioural-mode g :

$$\rho_{2,h,m,n,e,f,g} = \rho_{1,e,f,g,h,m,n} \left(\frac{c_{1,e,f} W_{1,e,f}^g}{c_{2,h,m} W_{2,h,m}^n} \right) \quad \dots(5.13)$$

The number of sexual acts that comprise a sexual partnership depends on the sexual activity group and behavioural modes of both partners $n_{l,b,l',b'}$. The proportion of sexual acts in which a condom is used throughout depends on the sexual activity group, age group and behavioural-mode of both partners $\gamma_{l,a,b,l',a',b'}(t)$. Since these values are the same when calculating the force of infection for males or females, it is easier to distinguish the characteristic of the individual (k, s, a, l, b) from those of their sexual partners with a prime (k', s', a', l', b') . It is assumed that condom use eliminates the chance of HIV transmission.

The overall risk of transmission per partnership is thus given by $\beta_{k,l,a,b,l',a',b'}$:

$$\beta_{k,l,a,b,l',a',b'} = 1 - (1 - \ell_{k',l',a',b'})^{T_{l,a,b,l',a',b'}(t)} \quad \dots(5.14)$$

$$\ell_{k',l',a',b'} = \frac{\sum_{s'=0}^6 (a_{k'}^{s'} S_{s'} (X_{k',l',a'}^{s',2} + X_{k',l',a'}^{s',3} + X_{k',l',a'}^{s',4}))}{\sum_{s'=0}^6 S_{s'} (X_{k',l',a'}^{s',2} + X_{k',l',a'}^{s',3})} \quad \text{for } b'=2$$

$$\ell_{k',l',a',b'} = \frac{\sum_{s' \in V}^7 a_{k'}^{s'} S_{s'} X_{k',l',a'}^{s',b'}}{\sum_{s'=0}^6 S_{s'} X_{k',l',a'}^{s',b'}} \quad \text{for } b'=0 \text{ or } 1$$

...(5.15)

$$T_{l,a,b,l',a',b'}(t) = n_{l,b,l',b'} (1 - \gamma_{l,a,b,l',a',b'}(t)) \quad \dots(16)$$

where $\ell_{k',l',a',b'}$ is the average infectiousness of sexual partners of that gender, sexual activity group, age and behavioural mode; $T_{l,a,b,l',a',b'}(t)$ is the number of unprotected sex acts; $n_{l,b,l',b'}$ is the number of sex acts in a partnership between individuals of those sexual activity groups and behavioural modes, and $\gamma_{l,a,b,l',a',b'}(t)$ is the fraction of sex acts in which condoms are used correctly and consistently in partnerships involving individuals of those sexual activity groups, age groups and behavioural modes. $a_k^{s'}$ is the probability of acquiring HIV in one sex act with a partner of that gender and HIV-status. It is assumed that transmission from males-to-females is twice as efficacious as from females-to-males [292, 293], that transmission during acute infection and full-blown AIDS is ten times as efficacious as during latent infection [286], that transmission is five times as efficacious during pre-AIDS as during latent infection, and that infectiousness of individuals on ART is reduced by a fraction E relative to those with pre-AIDS:

$$\begin{aligned} a_k^0 &= 0 \\ a_k^1 &= a_k^4 = a_k^6 = 10a_k^2 \\ a_k^3 &= 5a_k^2 \\ a_k^5 &= (1-E)a_k^3 \\ a_2^s &= 2a_1^s \end{aligned} \quad \dots(5.17)$$

The overall force of infection to individuals of each gender, sexual activity group and behavioural mode is thus the product of the number of partnerships made and the risk of infection associated with each such partnership:

$$\begin{aligned} \lambda_{k,l,a}^4 &= \lambda_{k,l}^3 = \lambda_{k,l}^2 = \sum_{l'=1}^3 \sum_{a'=1}^8 \sum_{b'=0}^2 (c_{k,l,a}^2 \rho_{l,2,l',a',b'} \beta_{k',l,2,l',a',b'}) \\ \lambda_{k,l,a}^1 &= \sum_{l'=1}^3 \sum_{a'=1}^8 \sum_{b'=0}^2 (c_{k,l,a}^1 \rho_{l,1,l',a',b'} \beta_{k',l,1,l',a',b'}) \\ \lambda_{k,l,a}^0 &= \sum_{l'=1}^3 \sum_{a'=1}^8 \sum_{b'=0}^2 (c_{k,l,a}^0 \rho_{l,0,l',a',b'} \beta_{k',l,0,l',a',b'}) \end{aligned} \quad \dots(5.18)$$

Individuals have a “preference” for the fraction of sexual acts in which condoms are used consistently based on their age and sexual activity group (ha_a and

$hb_{i,}$, respectively). However, condom use in a particular type of partnership is a compromise of the preferences of both partners, with the preferences of the older partner and the partner with in the lowest sexual activity group taking precedence:

$$\gamma_{l,a,3,l',a',3}(t) = \frac{1}{2}(ha_{\max(a,a')} + hb_{\max(l,l')}) \quad \dots(5.19)$$

Default parameters (used in all simulations unless otherwise stated) for the HIV transmission component of the model are listed in tables 5.1 and 5.2

	Symbol	Interpretation	Default Value
Age at first sex	A	Age at which individuals become sexually active	15 years
Survival 0 to A years	q	Fraction of live-births that survive to age A.	0.84
Fraction females in sexual activity group 1	$\phi_{2,1}$	Fraction of females in highest sexual activity group.	0.1
Fraction females in sexual activity group 2	$\phi_{2,2}$	Fraction of females in next-highest sexual activity group.	0.3
Fraction males in sexual activity group 1	$\phi_{1,1}$	Fraction of males in highest sexual activity group.	0.1
Fraction males in sexual activity group 2	$\phi_{1,2}$	Fraction of males in next-highest sexual activity group.	0.3
Ratio of sexual partnership acquisition rate (group 1 relative to group 3)	ω_1	Ratio of rate of partnership formation between highest and lowest sexual activity groups.	100
Ratio of sexual partnership acquisition rate (group 2 relative to group 3)	ω_2	Ratio of rate of partnership formation between next-highest and lowest sexual activity group.	20
Mixing coefficient	ε_L	Fraction of males' partnerships allocated to females in the same sexual activity group as themselves.	0.5
Years primary infection	$1/\sigma_1$	Mean years with primary HIV infection for those that do not know they are HIV+.	1 year
Years latent infection	$1/\sigma_2$	Mean years with latent HIV infection for those that do not know they are HIV+: varies with age	8 years
Years pre-AIDS	$1/\sigma_3$	Mean years with pre-AIDS for those that do not know they are HIV+.	0.5 years
Years AIDS	$1/\sigma_4$	Mean years with AIDS (before dying) for those that do not know they are HIV+.	0.5 years
Basic HIV transmission rate per sex act	α_1^2	Probability of a male acquiring HIV infection during one sexual act with an female with latent infection.	0.0012
Vertical transmission from infected woman	$\xi_1 = \xi_2 = \xi_3 = \xi_4$	Probability that a woman of that HIV-status transmits the infection to her baby.	0.35

Condom use (sexual activity group 1)	hb_1	Fraction of sexual acts in which condoms are used correctly and consistently throughout, in partnerships by individuals in highest sexual activity group.	0.5
Condom use (sexual activity group 2)	hb_2	Fraction of sexual acts in which condoms are used correctly and consistently throughout, in partnerships by individuals in next-highest sexual activity group.	0.25
Condom use (sexual activity group 3)	hb_3	Fraction of sexual acts in which condom is used correctly and consistently throughout, in partnerships by individuals in lowest sexual activity group	0.10
Number of sex acts per partnership (sexual activity group 1)	$n_{1,3,l',3}$ for $l' < 3$	Number of sexual acts per partnership in partnerships formed by individuals in highest sexual activity group	4
Number of sex acts per partnership (sexual activity group 2)	$n_{2,3,l',3}$	Number of sexual acts per partnership in partnerships formed by individuals in next-highest sexual activity group	40
Number of sex acts per partnership (sexual activity group 3)	$n_{3,3,l',3}$	Number of sexual acts per partnership in partnerships formed by individuals in the lowest sexual activity group	100
PMTCT efficacy	P	Fractional reductions in the probability of mother-to-child transmission for those who receive treatment relative to those that do not.	0.5
Time on ART	$1/\sigma_6$	Mean years spent on ART before treatment failure and progression to full-blown AIDS	5
Reduction in transmission on ART	E	Fractional reduction in probability of transmission for those receiving ART relative to those in pre-AIDS	0.99
Relative partner change rate with respect to HIV-status	S_0	Individuals with pre-AIDS are assumed to form half the number of partnerships of those with acute or latent infections or those susceptible. Individuals with full-blown AIDS or failed ART are assumed not to form any sexual partnerships.	1,
	S_1		1,
	S_2		1,
	S_3		0.5,
	S_4		0,
	S_5		1
	S_6		0

Table 5.1 Default parameters (used in all simulations unless otherwise stated).

Age	Fraction of sexual acts in which condom is used, by age (ha_a)	Mean number of new sexual partnerships formed per year ($\bar{c}_a$)
15-19	0.30	2.2
20-24	0.25	2.3
25-29	0.20	2.4
30-34	0.15	2.6
35-39	0.10	2.1
40-44	0.05	1.5
45-49	0.02	1.0
50-54	0.01	0.2
55-84	NA*	0.0*

Table 5.2 Condom use and mean partners per year assumed in the model. Based on sexual behaviour data from rural eastern Zimbabwe [40]. NA: Not applicable ; *These ages are assumed to be not sexually active.

5.2.3 Fitting to Epidemiological Conditions in Zimbabwe

To ground the analysis in a particular setting, the model was parameterised with sexual behaviour and demographic data from Zimbabwe [17, 91], where the two most recent TC studies were based [140, 250], in consultation with public health professionals and national decision-makers (participants at a workshop in Harare, July 2005: see end of this chapter). To represent the demographic conditions in Zimbabwe, on which the simulations presented here are based, the initial background mortality and fertility rates are based on World Bank estimates from the pre-AIDS era [207]. These generate population growth of approximately 4% per year and a life expectancy at birth of 52.1 for males and 54.7 for females. Successive demographic health surveys [294-296] in Zimbabwe suggest that fertility has decreased since 1998, which can be attributed to social factors as well as AIDS-related sub-fertility [297]. We assume that age-specific fertility rates have declined linearly from 1980 (total fertility rate=7) to 1999 (total fertility rate=4) and remain constant thereafter (Table 5.3).

To reflect the changes in sexual behaviour that have been reported in Zimbabwe in recent years [17, 91], between 1997 and 2003 the overall number of partnerships formed decreases by 20% and the probability of condom use doubles, for all types of individuals in all partnerships. The timing and magnitude of these changes is informed by a recent review of the epidemiological literature in Zimbabwe [17], and through fitting simplified transmission models to prevalence time-series at individual ante-natal clinic surveillance sites (Chapter 2).

The overall agreement between the model and available HIV-surveillance data is shown in Figure 5.2. Adjustments in the value of the following parameters were used to improve the fit of the model to the data; the basic HIV transmission rate (a_1^2), the sizes of the sexual activity groups ($\phi_{k,l}$) and the unprotected number of sex acts per partnership ($n_{l,b,l',b'}$ and hb_l). The value used for the transmission rate (0.0012) is similar to an empirical estimate from Uganda [286] (0.0011: 95% confidence interval 0.008-0.0015). These sexual behaviour parameter were chosen for fitting because they could not be reliably estimated from sexual behaviour reports in general population surveys [228]. This is because they require individuals to be classified in “sexual activity groups” but those with the riskiest behaviour are likely to be under-represented in surveys and reporting biases could distort the true distribution of risk in the population and substantially alter the epidemic projections [228, 231, 298].

National HIV prevalence estimates in Zimbabwe mainly come from women attending selected antenatal clinics (ANC). When analysing trends in such data, only consistently sampled sites that used the same testing methodology should be included [53]. The national aggregated data used here are based on 12 sites (4 rural, 6 urban and 3 peri-urban), weighted according to the urban-rural composition of the national population. These data are used to determine the timing of epidemic growth, plateau and maturation in the model but not the absolute level of HIV prevalence. This is because prevalence estimates among pregnant women are not representative of the general population [48, 52] and the HIV testing protocol that was used throughout this period (Genscreen) tends to over-estimate prevalence [16, 17]. Instead, the level of the epidemic is set by the (provisional) estimate from the 2005/6 Demographic and Health Survey (DHS) [299]. This is the only nationally-representative estimate of HIV prevalence in the general population.

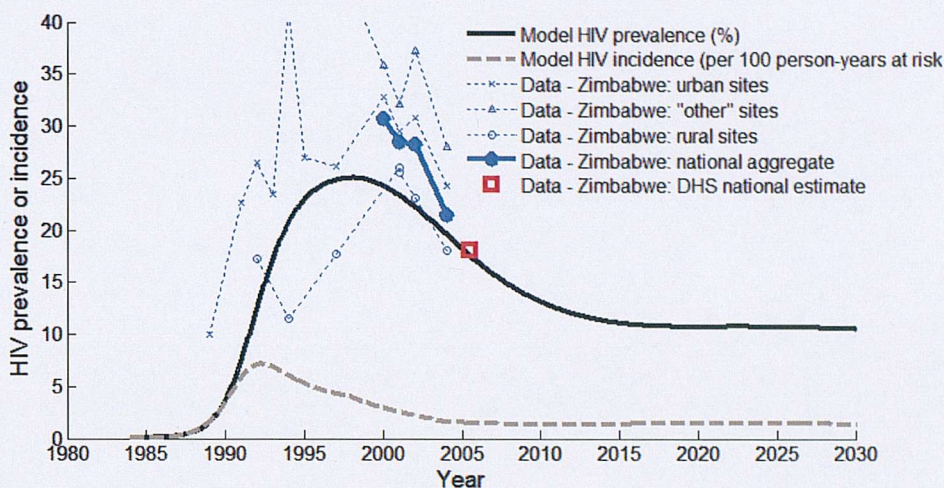


Figure 5.2 Model HIV incidence and prevalence, estimates of HIV prevalence among women attending selected ANC (2000, 2001, 2002 and 2004) and the (provisional) DHS estimate of HIV prevalence in the general population (2005/6). The model projection after 2005 assumes no further behavioural changes.

Source	Population in 1980 (thousands)*		Deaths per person-year (μ_{ka})		Births per female person-year (τ_a)			
	Male	Female	Male	Female	1980**	1988**	1994**	1999**
	World Bank 1991‡		World Bank 1991[300]		World Bank 1991[300]	Z-DHS (1988)[294]	Z-DHS (1994)[295]	Z-DHS (1999)[296]
Age-range	Males	Females	Males	Females	1990	1998	1994	1999
15-19	373	365	0.004	0.004	0.175	0.103	0.099	0.112
20-24	304	299	0.006	0.005	0.313	0.247	0.21	0.199
25-29	247	244	0.007	0.006	0.324	0.247	0.194	0.18
30-34	200	198	0.007	0.006	0.271	0.219	0.172	0.135
35-39	161	161	0.008	0.007	0.201	0.16	0.117	0.108
40-44	129	129	0.010	0.008	0.125	0.086	0.052	0.046
45-49	102	103	0.012	0.009	0.053	0.036	0.014	0.015
50-54	79	81	0.016	0.012	0	0	0	0
55-59	61	63	0.021	0.016	0	0	0	0
60-64	46	49	0.030	0.024	0	0	0	0
65-69	33	36	0.044	0.038	0	0	0	0
70-74	21	23	0.068	0.060	0	0	0	0
75-79	11	13	0.105	0.094	0	0	0	0
80+	4	5	0.189	0.174	0	0	0	0

Table 5.3 Demographic assumptions used in the model. *Total size of population in 1980 chosen to generate population size in 1997 equivalent to population DHS estimate (6.65 million aged 15 or older). **Female fertility is assumed to decrease linearly from 1980 to 1999 (trend fitted through these data) and remain constant after 1999.

5.2.4 Simulating the Effects of TC

The average rate at which individuals receive TC (“uptake”) is $v'(t)$ and the fraction of the population for which TC is available (“catchment”) is $\theta(t)$. Both of these parameters can vary over time, increasing linearly from zero to a constant level at a specified time and rate:

$$\begin{aligned} v'(t) &= 0 & \text{for } t < t_s \\ v'(t) &= \left[\frac{t - t_s}{t_e - t_s} \right] r_{\max} & \text{for } t_s \leq t \leq t_e \\ v'(t) &= v_{\max} & \text{for } t > t_e \end{aligned} \quad \dots(5.20)$$

$$\begin{aligned} \theta(t) &= 0 & \text{for } t < t_s \\ \theta(t) &= \left[\frac{t - t_s}{t_e - t_s} \right] \theta_{\max} & \text{for } t_s \leq t \leq t_e \\ \theta(t) &= \theta_{\max} & \text{for } t > t_e \end{aligned} \quad \dots(5.21)$$

where t_s and t_e respectively refer to the start of implementing the intervention and the time at which the maximum level is reached.

For the same number of individuals receiving TC, the relative probability that individuals from different parts of the population receive TC can be altered according to gender (ηk_k), HIV-status (ηs_s), sexual activity group (ηl_l) and age (ηa_a). The per-capita rate at which individuals of a particular gender, age, HIV-status and sexual activity group receive TC is $v_{k,l,a}^s(t)$;

$$v_{k,l,a}^s(t) = \eta k_k \eta s_s \eta l_l \eta a_a \frac{v'(t)}{\left(\frac{\sum_{k=1}^2 \sum_{s=0}^5 \sum_{l=1}^3 \sum_{a=1}^8 \eta k_k \eta s_s \eta l_l \eta a_a X_{k,l,a}^{s,3}}{X_{\bullet,\bullet,\bullet}^{s,3}} \right)} \quad \dots(5.22)$$

For the parameters (ηk_k , ηs_s , ηl_l and ηa_a) a value greater than one implies that individuals in that sub-group are more likely to receive TC than others; a value of one implies that the chance of receiving TC is the same as the average for the

population. For simplicity, the evaluation of these parameters is set by 'short-hand' summary parameters which are referred to in the main text (Table 5.4).

Short-hand for parameter (used in main text)	Model Parameter
"Focus on females" (i.e. females more likely to receive TC than males)	$\eta k_2=10; \eta k_2=1$
"Focus on males" (i.e. males more likely to receive TC than females)	$\eta k_2=0.1; \eta k_2=1$
"Focus on high-risk" (i.e. those with casual partners more likely to receive TC than those without)	$\eta l_1=10; \eta l_2=10; \eta l_3=1$
"Focus on low-risk" (i.e. those without casual partners more likely to receive TC than those with)	$\eta l_1=0.1; \eta l_2=0.1; \eta l_3=1$
"Focus on sick" (i.e. those with symptoms of immune-suppression versus those without)	$\eta s_3=10; \eta s_4=10;$ $\eta s_1=1; \eta s_2=1$
"Focus on healthy" (i.e. those without symptoms of immune-suppression versus those with)	$\eta s_3=0.1; \eta s_4=0.1;$ $\eta s_1=1; \eta s_2=1$
"Focus on young" (i.e. Linear trend in rate of receiving TC, such that 15-19 year-olds are (ten times) more likely to receive TC than those aged 30-34 years.)	$F=10 *$
"Focus on old" (i.e. Linear trend in rate of receiving TC, such that 30-34 year-olds are (ten times) more likely to receive TC than those 15-19 years.)	$F=0.1 *$

Table 5.4 Parameters that specify TC targeting. All parameters set to unity to represent "random" distribution of those receiving TC. *where $\eta a_a = F^{(4-a)/3}$.

The expansion of the catchment area is simulated by, at each time-step, moving individuals into the catchment as follows.

$$\begin{aligned}
 X_{k,l,a}^{s,3} &\rightarrow X_{k,l,a}^{s,3} + Z_{k,l,a}^s \\
 X_{k,l,a}^{s,4} &\rightarrow X_{k,l,a}^{s,4} - Z_{k,l,a}^s \\
 Z_{k,l,a}^s &= X_{k,l,a}^{s,4} \left(1 - \frac{1 - \theta(t)}{1 - \Pi} \right) \quad \dots(5.23) \\
 \Pi &= \frac{\sum_{v=1,2,3,5} X_{\cdot,\cdot,\cdot}^{s,v}}{X_{\cdot,\cdot,\cdot}^{s,\cdot}}
 \end{aligned}$$

The model allows individuals that have gone for TC to make the following behavioural/biomedical changes:

- Change the proportion of sex acts in which condoms are used

The basic pattern of condom use with respect to the sexual activity group and age group of both partners when neither know their HIV-status is $\gamma_{l,a,3,l',a',3}$. The proportionate change in condom use when individuals know their HIV-status, by sexual activity group is, $N_{l,b}$:

$$\begin{aligned} \gamma_{l,a,0,l',a',0} &= \gamma_{l,a,b,l',a',0} = N_{l,1} \gamma_{l,a,3,l',a',3} && \text{for } b \text{ or } b' = 0,2 \text{ (at least one known uninfected partner)} \\ \gamma_{l,a,1,l',a',1} &= \gamma_{l,a,b,l',a',1} = N_{l,2} \gamma_{l,a,3,l',a',3} && \text{for } b \text{ or } b' = 1,2 \text{ (at least one known HIV infected partner)} \\ \gamma_{l,a,1,l',a',0} &= \gamma_{l,a,0,l',a',1} = N_{l,3} \gamma_{l,a,3,l',a',3} && \text{(known sero - discordant partnership)} \\ \dots(5.24) \end{aligned}$$

- Change the number of sexual acts per partnership

Relative to those that do not know their HIV-status, the change in number of sexual acts per partnership for individuals in each sexual activity group that think they are not infected or are infected is $M_{l,1}$ or $M_{l,2}$, respectively, such that:

$$\begin{aligned} n_{l,1,l',b'} &= n_{l,b,l',1} = M_{l,1} n_{l,3,l',3} \\ n_{l,2,l',b'} &= n_{l,b,l',2} = M_{l,2} n_{l,3,l',3} \\ n_{l,1,l',2} &= n_{l,2,l',1} = \min(M_{l,2}, M_{l,1}) n_{l,3,l',3} \end{aligned} \dots(5.25)$$

- Change the rate of partnership formation

Relative to those that do not know their HIV-status, the change in the rate of sexual partnerships formed by individuals that think they are not infected or infected is H_1 or H_2 , respectively, such that:

$$\begin{aligned} c_{k,l,a}^0 &= H_2 c_{k,l,a}^2 \text{ (partner change rate by those that think they are infected) } \dots(5.26) \\ c_{k,l,a}^1 &= H_1 c_{k,l,a}^2 \text{ (partner change rate by those that think they are not infected).} \end{aligned}$$

- 'Sero-sorting'

As detailed above, the extent to which males that think they are not infected, males that think they are infected and males that do not know their HIV-status bias the

selection of their sexual partners to females that think they are not infected, infected or do not know their HIV-status, respectively, is ε_L .

- Treatment with ART

As detailed above, a fraction, f (which is constant over time), of those that know they are infected are provided with ART when they develop symptoms of immune-suppression. The infectiousness of those on ART is reduced by E relative to those with pre-AIDS:

$$a_k^5 = (1 - E)a_k^3 \quad \dots(5.27)$$

Individuals on ART progress to AIDS (following treatment failure) after, on average, $1/\sigma_6$ years.

- PMTCT

As detailed above, the chance that a baby born to a woman of HIV-status s is ζ_s and the reduction in this probability brought about through PMTCT to mothers that know they are infected is P . The fraction of pregnant women that know they are infected that receive PMTCT treatment is Q .

(iv) Parameters for behaviour change scenarios.

To estimate the behavioural changes that might be expected among those that receive TC, a literature review and meta-analysis was conducted that included studies that have investigated the effects of TC in Africa. (*This was performed by S Dube, in consultation with the author of this thesis.*)

A search was made using MEDLINE (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) for studies published between January 1985 and August 2005 using the MeSH terms: "Voluntary Counselling and Testing" AND "HIV", OR "VCT" AND "HIV" AND "AFRICA". Due to the lack of quality randomised controlled trials in Africa, observational studies were included as well as trials. In total, six studies were identified (cited in legend to Figure 5.3). No particular measure of sexual behaviour change was quoted in all studies, but various definitions of change in condom use were the most comparable.

There is significant heterogeneity in the effects reported in these studies, but the estimated combined effect of TC is a two-fold increase in the odds of 'condom use' (Figure 5.3).

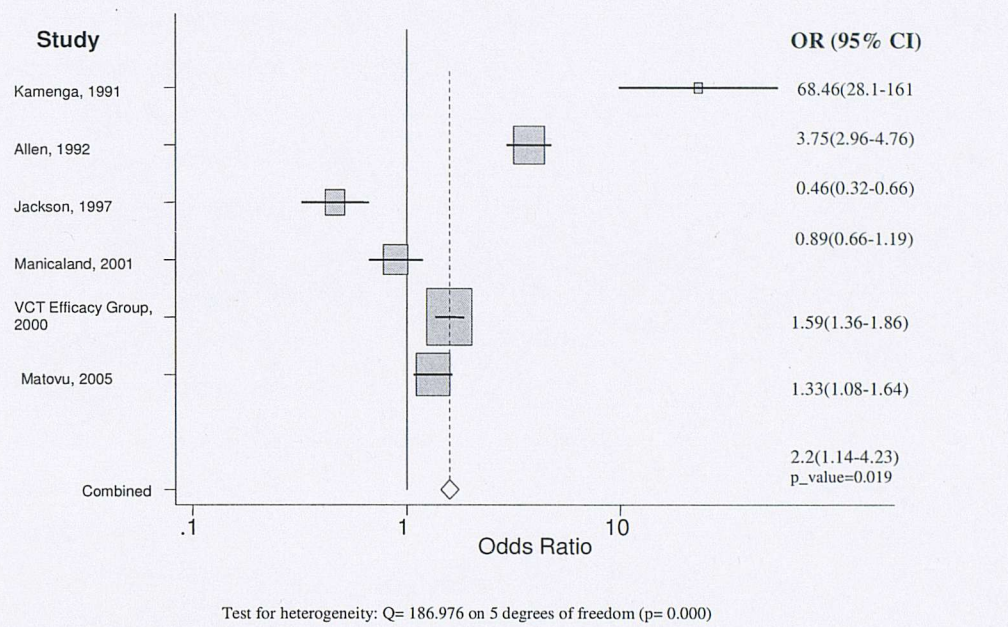


Figure 5.3 Results from meta-analysis – the effect of TC on changes in condom use in African settings. Various measures of ‘condom use’ were given in the studies: Kamaga, 1991 [301], “chance of always using condom with regular partner” among discordant married couples followed over 12 months”; Allen, 1992 [302, 303], “chance of often condom use with regular or irregular partner” by women followed up for 12 months”; Jackson, 1997 [304], “chance of using condom in the past 3 months in any extra-marital sex”: followed up for 4-6 months”; Manicaland, 2001, “chance of using condom with any partner in the past 2 months” (this is an adapted analysis based on the findings later published by Sherr *et al.* [250]); VCT Efficacy Group, 2000 [137], “chance of using condom in the past 2 months with all partners”, followed-up over 12 months”; Motovu, 2005 [305], “chance of using condom with any partner in the past 6 months”.

In Zimbabwe, TC services are set to be greatly expanded in the coming years. In the projections for Zimbabwe (Figure 3 in the main text), it was assumed that the fraction of the population that can access TC will increase steadily to 80% over 10 years (2005-2015), and with uptake in the population such that the average time between services becoming available and attending TC is 2.5 years (Table 5.5). In these projections, no targeting of TC is simulated. This ‘optimistic’ expansion will be realistic if TC policies include routine ‘opt-out’ testing [146, 306], home-based services [307] or services integrated with antenatal care [308].

A number of scenarios for the behaviour changes associated with TC are simulated. The results of the large efficacy trial in low-income settings [137] are in good agreement with those from the other observational studies (Figure 5.3) and due

to the comparative wealth of data and the strength of evidence of such a randomised trial, we parameterised one behaviour change scenario using data only from this one study (Table 5.6). Reports of condom use with the primary partner were taken to relate to partnerships involving the lower two risk groups ($I=2,3$), whereas reports of condom use with non-primary partner were taken to relate to partnerships involving the riskiest sexual activity groups ($I=1$).

An alternative scenario is derived from TC delivered in eastern Zimbabwe (Manicaland HIV/STD Prevention Project) [250] (Analysis undertaken jointly with I Cremin and B Lopman). Behaviour change is estimated from the change in reported sexual behaviour in two surveys conducted three years apart, among those that attended TC within one year of the first survey. HIV-status of individuals at each round was ascertained using standard laboratory procedures [250] and it was assumed that HIV-status recorded at the first survey was the same as the test result received at TC. In line with secular changes in sexual behaviour that have been recorded across Zimbabwe [17], reported numbers of sexual partners in the last year tended to decrease over time for all individuals, irrespective of whether they attended TC. Although multivariate multinomial analyses suggest that uninfected individuals are more likely to increase the number of partnerships formed than either those receiving TC who were infected or those that did not receive TC [250], the overall trend in the mean number of partnership formed was for fewer partnerships for both infected and uninfected individuals receiving TC. The mean individual change, adjusting for secular changes among those not receiving TC, was a 40% reduction in partnerships formed in the last year for those infected receiving TC, and a 20% reduction for those uninfected receiving TC (Table 5.6). There were no substantial changes in reporting consistent condom use in the last two weeks (with any partner), either for those uninfected (no change) or those infected (down 2%).

Results from other studies in Africa (Figure 5.3) suggest that behaviour change following TC can be greater than is reflected in either of these two scenarios. In a large multi-centre study in America (Project RESPECT), changes in behaviour among uninfected individuals were even greater, with reported 100% condom use almost tripling following TC [136]. To reflect the potential for greater degrees of behaviour change following high quality TC, a scenario was devised whereby the probability of consistent condom use doubles following TC, irrespective of HIV-status. This is approximately the same as the average change in condom use over several studies in the meta-analysis (Figure 5.3). In addition, it assumed that the changes in the rate of sexual partnership formation observed among infected men and women in Manicaland are repeated for all individuals receiving TC (Table 5.6). Although this

scenario is clearly somewhat hypothetical, such behaviour changes are arguably realistic and achievable.

It is not clear how long behavioural changes are sustained after going for TC (the length of the studies is not longer than approximately three years), so two versions of each scenario are simulated, where the mean duration of the behaviour change is 2 years or 8 years.

	Symbol	Interpretation	Default Value*
Max catchment	$\theta_{\max}$	Fraction of population (catchment) that can receive TC when scale up of services is complete.	0.8
Maximum TC uptake	$r_{\max}$	Rate at which individuals in the TC catchment receive TC.	0.4
Year TC program starts	t_s	Calendar year in which TC programme scale-up begins	2005
Year reaches maximum	t_e	Calendar year in which TC programme scale-up reaches maximum level	2015
Time until re-test	$1/r$	Mean number of years between first TC visit and re-test, and between all further re-tests	0
TC focus by gender	η_k	The relative probability of individuals going for TC according to their gender	1 for all k
TC focus by HIV-status	η_s	The relative probability of individuals going for TC according to their HIV-status.	1 for all s
TC focus by sexual activity group	η_l	The relative probability of individuals going for TC according to their sexual activity group.	1 for all l
TC focus by age group	η_a	The relative probability of individuals going for TC according to their age group.	1 for all a

Table 5.5 Intervention scale-up assumptions used in the model. *Used in simulation unless otherwise stated.

Parameter*	Interpretation	Scenario 1	Scenario 2	Scenario 3 (High quality counselling and testing)
	<i>Data source / justification:</i>	Low-income VCT trial[137]	Manicaland cohort study[250]	Meta-analysis & Manicaland cohort study[250]
Change in condom use (HIV-)	$N_{l,1}$ Ratio of condom use if one partner is thought to be uninfected relative to partnerships where HIV-status is not known for either partner.	1.19 1.17 1.17	1 1 1	2.00 2.00 2.00
Change in condom use (HIV+)	$N_{l,2}$ Ratio of condom use if one partner is thought to be infected relative to partnerships where HIV-status is not known for either partner.	1.23 1.24 1.24	1 1 1	2.00 2.00 2.00
Change in number of sexual acts (HIV-)	$M_{l,1}$ Ratio of number of sexual acts if one partner is thought to be uninfected relative to partnerships where HIV-status is not known for either partner.	0.80 0.93 0.93	1 1 1	1 1 1
Change in number of sexual acts (HIV+)	$M_{l,2}$ Ratio of number of sexual acts if one partner is thought to be infected relative to partnerships where HIV-status is not known for either partner.	0.97 0.81 0.81	1 1 1	1 1 1
Change in partner acquisition rate (HIV-)	H_1 Ratio of partner acquisition rate if thought to be uninfected relative to partnerships where HIV-status is not known for either partner.	1, 1, 1	0.8 0.8 0.8	0.6 0.6 0.6
Change in partner acquisition rate (HIV+)	H_2 Ratio of partner acquisition rate if thought to be infected relative to partnerships where HIV-status is not known for either partner	1 1 1	0.6 0.6 0.6	0.6 0.6 0.6
Duration of behaviour change	l/g Mean number of years before behaviour of TC attendees reverts to the behaviour of those that do not know their HIV-status	2 or 8	2 or 8	2 or 8

Table 5.6 TC behaviour change intervention scenarios. *Values are given for each sexual activity group in ascending order: $l=1,2,3$. (NB. $l=1$ has the highest rate of partner acquisition).

5.3 Contributions

Sabada Dube (Imperial College London) conducted the meta-analysis. Íde Cremin and Ben Lopman (both Imperial College London) analysed data from the Manicaland cohort study that was used to parameterise some aspects of the model. My supervisors (Geoff Garnett and Simon Gregson) and our collaborator at the Centers for Disease Control and Prevention in Zimbabwe, Stacie Greby, have all made contributions to writing a manuscript, which helped develop this chapter.

This work originates from a report written about a workshop held in Harare in July 2005. The participants (listed in the appendix to this chapter) made some suggestions of questions to explore in model analyses.

5.4 Results

TC programming policy is mainly concerned with two issues: (i) content (what the TC process includes), and (ii) coverage (who gets tested). The influence of content was investigated by varying the model parameters to reflect different types and degrees of behaviour change following TC. The effect of widening service coverage was investigated by increasing the fraction of the population that can receive TC (the 'catchment population'), and adjusting the rate at which individuals receive TC according to their gender, age, sexual activity or presence of symptoms of immune-suppression.

In studies of TC, behaviour change has been greatest among infected individuals [137, 139]. In the model, behaviour change among those infected has a greater effect in reducing HIV incidence than the same changes among those not infected, because they are more likely to be part of ongoing HIV transmission (Figure 5.4(a)). However, for a given number of individuals counselled, the population level impact of TC is greater when uninfected individuals change their behaviour instead (Figure 5.4(b)). This is simply because the majority of clients will be uninfected.

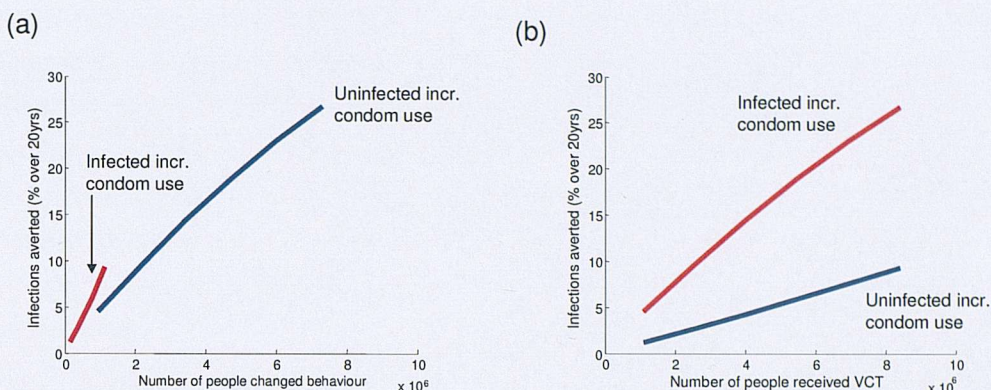


Figure 5.4 The impact of behaviour change, by sero-status of individual. Infections averted over 20 years if only uninfected (blue lines) or only infected (red lines) individuals double condom use, shown in (a) as per person changing their behaviour and in (b) as per person receiving TC.

Maintaining behaviour change is crucial to the impact of the intervention. For example, in the model, a 20-30% increase in condom use that is maintained permanently is equivalent in terms of infections averted over twenty years to a three-fold increase in condom use that lasts for only one year (Figure 5.5(a)). The maintenance of behaviour change is especially important for young clients who are at greatest risk of infection and play a crucial role in onward transmission [40] (Figure 5.5(b)).

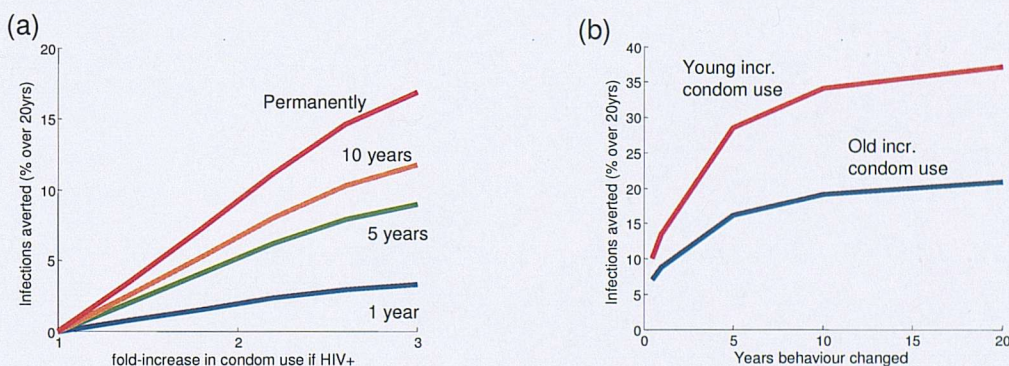


Figure 5.5 The impact of duration of behaviour change. (a) Infections averted over 20 years if increased condom use by infected individuals is maintained for 1 year (blue line), 5 years (green line), 10 years (orange line) or permanently (red line). (b) Infections averted over 20 years if condom use is increased by young (red line) or old (blue line) TC attendees (15-19 year-olds are 10 and 0.1 times as likely than 30-34 year-old to attend TC, respectively) as a function of mean time for which behaviour change is maintained.

Repeat testing is defined here as testing people with a negative result after several months or years (rather than re-testing within a few weeks to confirm a

negative result). Repeat testing can identify individuals with highly infectious incident infections and prevent false complacency in individuals who test negative but continue high risk behaviour, and will be most productive in groups with high incidence. However, the benefits of using limited resources to repeat test people are outweighed by the lost opportunity to test more people once. For the same number of tests and counselling sessions, more infections and AIDS-deaths are averted if priority is given to testing more people once rather than fewer people many times (Figure 5.6).

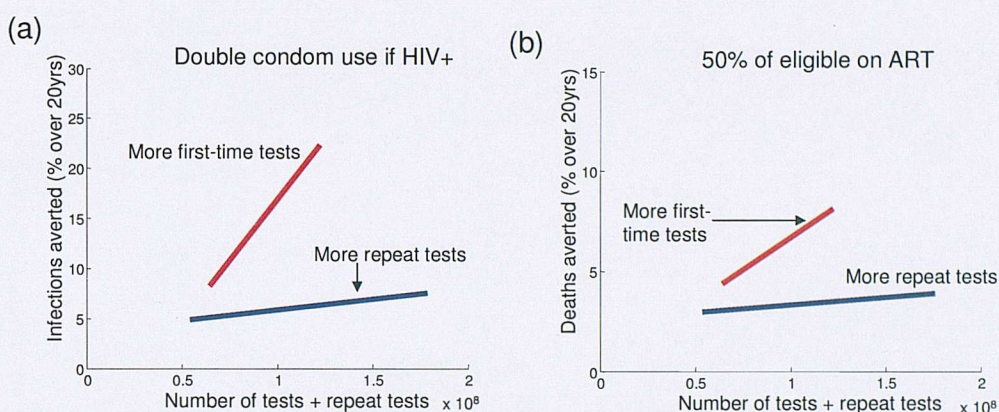


Figure 5.6 The impact of repeat testing. (a) Infections averted over 20 years if infected individuals double condom use and if individuals are retested every 20 years or every 2 years with TC available to 30% of the population (“more repeat tests”; blue line) or individuals are tested only once with TC available to 50 to 95% of the population (“more first time tests”; red line). Horizontal axis shows total number of tests (first time tests plus every repeat test). Values of coverage and repeat testing are chosen to given similar total numbers of tests. (b) As for (a) but with AIDS-deaths averted, assuming no behaviour change and that ART is supplied to 50% of those eligible (diagnosed infection and immune-suppressed).

Provided individuals are willing to disclose their HIV-status, increased testing creates the opportunity for couples to alter behaviour according to the status of both partners, or for partner choice to depend, in part, on HIV-status. High levels of condom use have been observed in discordant couples aware of their status [301, 309] and the model suggests that when knowledge and disclosure of HIV-status is high, consistent condom use in such partnerships could generate a greater reduction in HIV incidence than smaller increases in condom use by infected individuals in all partnerships or casual partnerships (Figure 5.7).

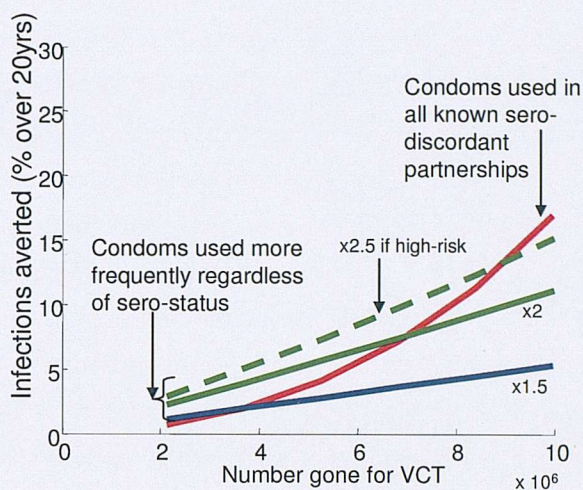


Figure 5.7 The impact of alternative patterns of increased condom use following testing. Infections averted over 20 years if individuals use condoms in all sex acts in partnerships known to be sero-discordant (red line), or if infected individuals that have gone for TC use condoms more frequently regardless of partners' HIV-status; 1.5 times as frequently in all partnerships (blue line), 2 times as frequently in all partnerships (solid green line) or 2.5 times as frequently in 'casual' partnerships (between members of the high-risk groups) (dashed green line).

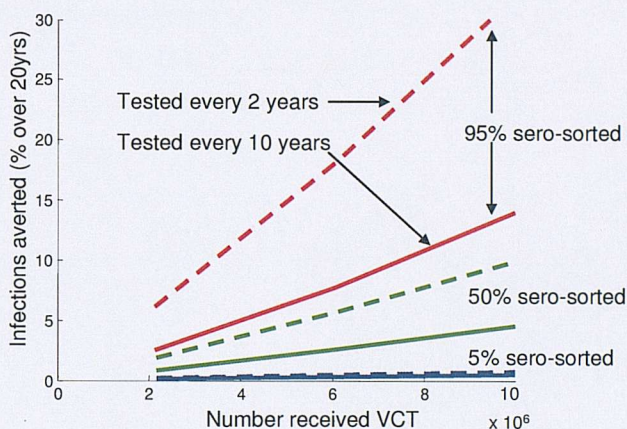


Figure 5.8 The impact of sero-sorting. Infections averted over 20 years if 5% (blue lines), 50% (green lines) or 95% (red lines) of sexual partnerships are 'sero-sorted' and if individuals are tested every two years (dashed lines) or every ten years (solid lines).

The impact of sero-sorting, where individuals tend to form sexual partnerships preferentially with individuals of the same HIV-status as themselves, is weak unless unrealistically large proportions of partnerships are sero-sorted and individuals frequently return for testing (Figure 5.8). Without frequent testing, individuals can incorrectly think they are uninfected (having been infected since their last test) and will preferentially form sero-discordant partnerships. However, up to the extreme level of 95% of sero-sorting, repeat testing fails to outweigh the benefit of testing more people once.

Resource constraints will be the major determinant of TC implementation, but the ideal distribution of clients can be explored to help guide policy. In the model it is possible to keep the number of people receiving TC constant whilst adjusting the relative probability that an individual receives TC according to their gender, age, sexual behaviour and disease symptoms. The optimal target population depends

greatly on the primary role of TC. To maximise the identification of those that will require ART, TC should be focussed on those groups in the population with the highest HIV prevalence, i.e. individuals at most risk of infection, older individuals and those with symptoms of immune-suppression (Figure 5.9). In addition, targeting women could increase uptake of measures to prevent mother-to-child transmission, and therefore avert more child deaths. To promote behaviour change using high quality HIV prevention counselling, more infections are averted if those at highest risk and younger individuals are targeted (Figure 5.9) because these groups contribute disproportionately to the spread of infection [40]. Targeting those with symptoms is not an effective way to avert more infections because they will form few new sexual partnerships in the following years. Therefore, to increase the number of people in care and prevent AIDS deaths immediately, targeted testing of older people, those experiencing symptoms of immune-suppression and women is the recommended strategy. However, to optimise prevention through behaviour change and substantially decrease AIDS deaths in the future, providing TC to the young should be the priority.

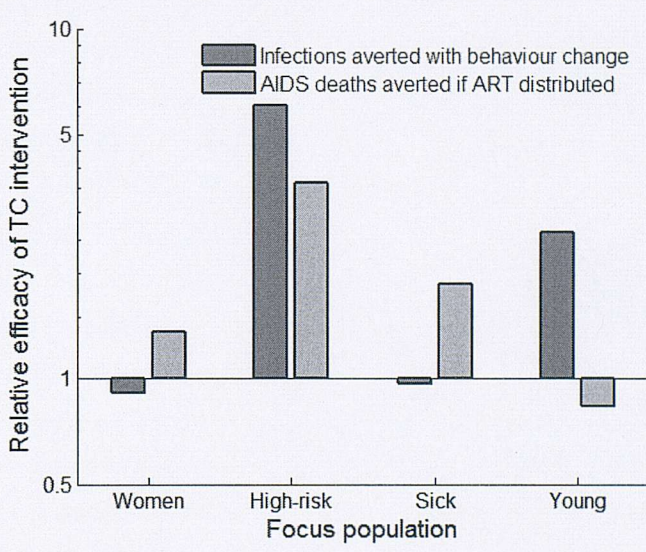


Figure 5.9 The impact of targeting. Two types of TC intervention are simulated: behaviour change following TC but no ART (dark bars), and (ii) ART offered to those receiving TC but individuals do not change their sexual behaviour (light bars). The efficacies of these interventions are measured as infections averted over twenty years and AIDS deaths averted over twenty years, respectively. The relative efficacy is the ratio of the efficacy of the intervention when uptake is ten-times higher among a particular sub-group (women, those at most risk of infection, those with symptoms of immune-suppression and younger individuals) to where uptake is ten-times higher among the alternative group (men, those at least risk of infection, those without symptoms and older individuals). In all scenarios, the number receiving TC is held constant. A value of more than one signifies that targeting that sub-group is advantageous, whereas a value less than one signifies that it would be better to target the alternative sub-group.

The expansion of TC services across countries in sub-Saharan Africa will be a primary tool in the fight against the HIV/AIDS epidemic [6, 284]. In Zimbabwe, TC services are set to be greatly expanded in the coming years. In the following projections it is assumed that the fraction that can access TC increases steadily to 80% over 10 years (2005-2015), and that uptake in the population is such that the average time between services becoming available and attending TC is 2.5 years. As stated above, this rate of expansion will be realistic if TC policies include routine 'opt-out' testing [146, 306], home-based services [307] or services integrated with antenatal care [308].

Based on recent epidemiological and demographic data [17, 91], the model projects that there will be ~2.9 million new infections among adults over 20 years (2005-2025) without further intervention. If the behavioural changes following TC are similar to those observed in a large efficacy trial in low-income settings [137] and last for 2 years on average, then ~4% of expected HIV infections would be averted over 20 years (116,000 infections) (Figure 5.10, scenario 2: blue solid line). If the changes lasted for 8 years instead, almost twice as many infections would be averted (218,000) (Figure 5.10, scenario 2: blue dashed line). Alternatively, if the behavioural changes observed in a rural Zimbabwean cohort [250] are repeated at the national level and last for two years, then the rapid expansion of TC across the country would avert less than 3% of infections over 20 years (84,000) (Figure 5.10, scenario 2: green solid lines). However, with the greater levels of protective behaviour change – including among uninfected individuals – generated by high quality HIV prevention counselling that are indicated in other studies (Figure 5.3), the model predicts that there could be 12%-23% (348,000-667,000) fewer infections over a 20 year period (Figure 5.10, scenario 3: red lines). The high HIV incidence rate in Zimbabwe (and other countries in the region) means that it is important to scale-up TC quickly. Assuming that these optimistic behavioural changes last 8 years, the model projects that if TC is scaled-up to 80% of the population over 5 years instead of 10 years, ~200,000 more infections could be averted (Figure 5.11).

An important goal of testing is to identify those who can benefit from treatment. Without an effective TC programme, the model projects that the total number of individuals that will be indicated for ART in Zimbabwe over 50 years will be ~6.8 million. With high quality HIV prevention counselling, protective behaviour change would lead to fewer people acquiring HIV and 1.8 million less would need to start ART (Figure 5.12). The difference in the number needing ART between the alternative scenarios increases over time as the epidemic is set to reach more and

more people if services are not optimised, but could be sent into decline if high-quality TC is implemented (Figure 5.12).

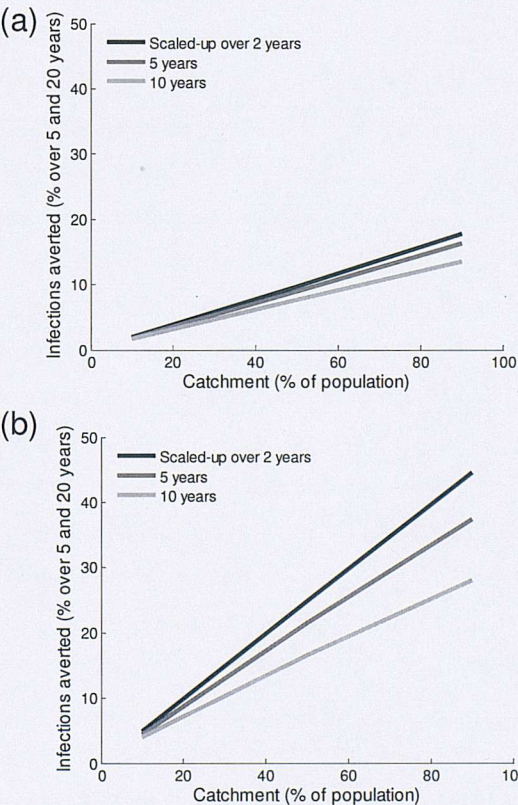
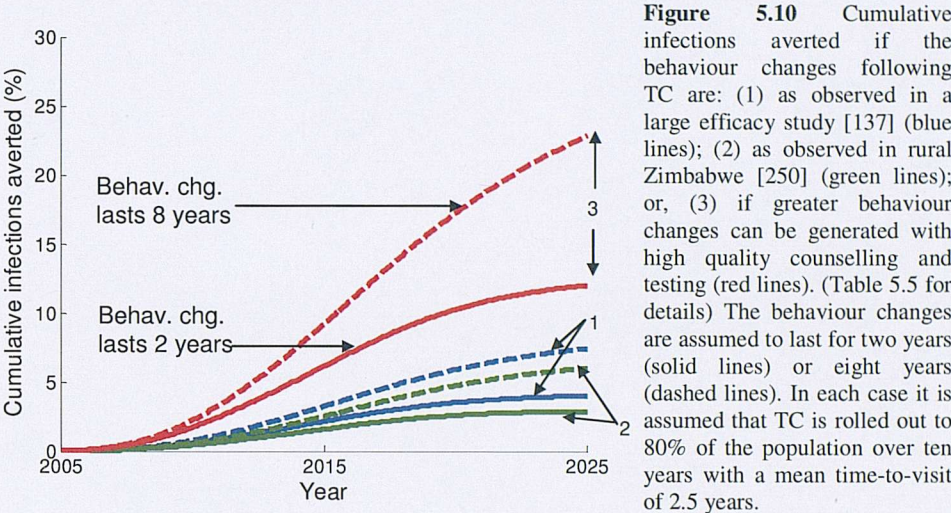


Figure 5.11 The influence of speed of scale-up on the impact of interventions. Infections averted over 20 years if TC is rolled out to the catchment population after 2 years (black lines), 5 years (dark grey lines) or 10 years (light grey lines). The assumed behaviour change following TC represents the effect of high quality prevention counselling (scenario 3: Table 5.5) which lasts for, on average (a) 2 years; and, (b) 8 years,

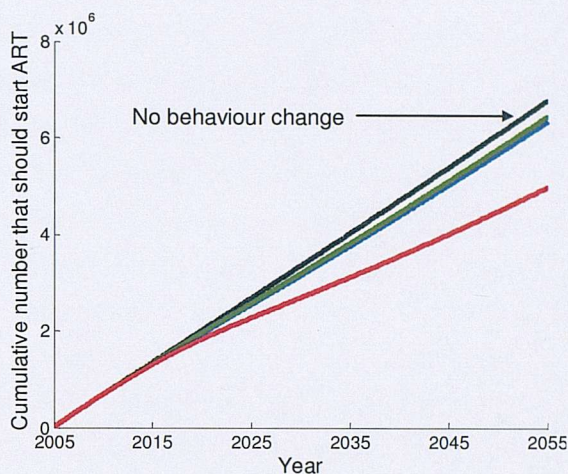


Figure 5.12 Cumulative number of individuals that are indicated for ART, if the behaviour changes following TC are: (1) as observed in a large efficacy study[137] (blue lines); (2) as observed in rural Zimbabwe [250] (green lines); or, (3) if greater behaviour changes can be generated with high quality counselling and testing (red lines). (Table 5.5 for details). The behaviour changes are assumed to last for two years (solid lines) or eight years (dashed lines). In each case it is assumed that TC is rolled out to 80% of the population over ten years with a mean time-to-visit of 2.5 years.

5.5 Discussion

Major changes in HIV risk behaviour throughout populations are required to reverse the HIV pandemic. The expansion of TC across Zimbabwe and other countries in sub-Saharan Africa [248, 284, 310] will be a primary tool in the fight against the HIV/AIDS epidemic, providing the gateway to ART and arguably the best chance to motivate behaviour change. Although treating existing HIV/AIDS patients is an urgent priority, tailoring TC services to those in need of ART will not substantially alter the course of the epidemic and eventually providing treatment may not be sustainable. These results, using a model specific to Zimbabwe, show that TC programmes that do not use available resources to provide high quality HIV prevention counselling and enable HIV-negative individuals to adopt less risky behaviours will certainly not achieve their full potential. The prevention impact of TC can be maximised by providing services to as many individuals as possible, focussing on those at most risk of acquiring and transmitting infection, urging the young to maintain less risky sexual behaviour, and warning against HIV-status based behaviour change for those that have not tested recently.

The duration of behaviour change was found to be extremely important in determining the prevention benefits derived from TC. Unfortunately, studies of behaviour change associated with TC have not extended beyond a few years, leaving considerable uncertainty about its long-term effect. It is unlikely that trials would be able to explore the duration of behaviour change, but observational studies should aim to examine first, whether behaviour does change and then how long it lasts. Ideally, exploring how best to promote a long lasting change, either at the primary counselling session itself, through follow-up visits or via community level work, should be a priority.

A major limitation of the model in exploring TC is its failure to represent couples in stable partnerships. Since this model does not include couples testing together, it may under-estimate the effect of condom use in discordant partnerships because TC delivered to couples together may be a more efficient way of finding discordant partnerships and facilitating behaviour change [309]. Further work using a simulation of individuals and the explicit representation of their partnerships would provide better insights into the potential epidemiological impact of providing testing and counselling to couples. However, if the scale-up of services is focussed on clinical settings [311], it will be more likely that individuals will be tested by themselves, than if dedicated stand-alone facilities become more widespread.

The recent emphasis on TC in the international community has attempted to normalise HIV as an infection where diagnosis is the key to accessing health care services [311]. The long-term success of changes in testing policy will depend on providing high quality HIV prevention counselling that can translate into effective behaviour change, preventing new infections to allow sustainable clinical care. As policies are adopted and TC coverage is expanded, high quality HIV prevention counselling must be provided consistently to ensure that the potential of the counselling intervention to change behaviour is maintained. Without such an approach, the good news stories associated with roll out of ART [284, 285] will merely prove a temporary period of remission in the tragic story of AIDS as the number of people requiring ART rises inexorably.

5.6 Participants at the Harare Workshop

Some elements of the model and the analysis were informed through consultation at a workshop held in Harare in July 2005. The participants are listed here alphabetically.

- E Chidombwe, Zimbabwe Aids Prevention Services Organisation
- S Dube, Imperial College London, UK
- GP Garnett, Imperial College London, UK
- E Gonese, Ministry of Health and Child Welfare, Zimbabwe
- S Greby, Centers for Disease Control and Prevention, Zimbabwe
- S Gregson, Imperial College London, UK and the Biomedical Research and Training Institute, Zimbabwe
- S Hader, Centers for Disease Control and Prevention, Zimbabwe
- T Hallett, Imperial College London, UK
- K Hatzold, Population Services International

- A Mahomva, Ministry of Health and Child Welfare, Zimbabwe
- C Makufa, PACT Zimbabwe
- S Makumbe, PACT Zimbabwe
- M Manyasha, PACT Zimbabwe
- S Moyo, Zimbabwe AIDS Prevention Project
- O Mugurungi, Ministry of Health and Child Welfare, Zimbabwe
- G Ncube, Ministry of Health and Child Welfare, Zimbabwe
- N Taruberekera, Population Services International

***Chapter 6: Measuring Effectiveness in
Community Randomised Trials of HIV
Prevention***

6.1 Introduction

Whilst a few individual-randomised controlled trials have recorded changes in behaviour [136, 137], demonstrations of successful interventions in reducing HIV incidence at the population level are rare. However, the translation of intervention activities into behavioural outcomes and then into a population-level impact on transmission is not inevitable and so the key measure of intervention success must be HIV incidence. Some success in reversing the HIV epidemic at a national level was detected in Uganda and Thailand through an evaluation of trends in prevalence and risk behaviours [24, 55, 73, 312] and more recently similar national trends have been observed in Zimbabwe [16, 17, 91], urban Haiti [236], parts of urban Kenya [237, 251], and south India [313]. In these circumstances the cause of behaviour change is uncertain. To justify the ongoing commitment and support for interventions, it is helpful if their effectiveness has been rigorously demonstrated [314] and the community-randomised controlled trial (CRCT) is the experimental design that provides a test of an intervention's effectiveness within the population [315]. Such trials at the community-level have been used initially to explore the impact of controlling bacterial sexually transmitted infections (STIs) on the incidence of HIV and latterly to explore interventions which additionally aim to reduce sexual risk behaviour.

The four reported CRCTs of HIV-prevention interventions have each employed different strategies to reduce transmission from and to those at most risk of infection (the “high-risk” groups – sex workers and their clients, those with STIs etc). In the Mwanza Trial in north-west Tanzania, syndromic management (treating those with symptoms) of STIs was found to reduce HIV incidence by 40% [107]. The Rakai Trial in Uganda attempted to improve on the control of STIs using mass antibiotic administration to target asymptomatic infections [109] and the Masaka Trial, also in Uganda, added a general population Information, Education and Communication (IEC) component to syndromic management of STIs [110]. Most recently, the Manicaland Trial focussed on peer-led education and awareness targeted to sex workers and their clients in a rural Zimbabwean community [94]. Unfortunately, none of the latter three (Rakai, Masaka and Manicaland) CRCTs found significant reductions in HIV incidence and in the Manicaland trial incidence may even have been higher in the intervention communities. Explanations as to why these trial results differ from the original success in Mwanza include the epidemiological context, with HIV having spread beyond the high-risk group where bacterial STIs play a critical role in transmission [119].

There are many problems in assessing how well complex multifaceted interventions have been implemented, in estimating how long they need to take effect and in discerning whether the changing epidemiology of HIV has influenced the results. In planning and interpreting trials of HIV prevention interventions, it is worth exploring the expected impact of behavioural change on HIV incidence over time to identify the circumstances when the effectiveness of an intervention would be apparent. Standard power calculations for CRCTs [316, 317] are available and elaborations have been suggested to optimise study design and analysis [318-321]. However, the implications of the dynamic response of incidence to a targeted intervention have not been considered. To examine this, a simulation model of the heterosexual spread of HIV was developed and used to investigate the chance of detecting a statistically significant effect of a powerful intervention in various trial conditions. Whilst this theoretical exploration provides general insights for community-randomised HIV intervention trials, in some cases the model is parameterised to represent aspects of the most recent trial (in Manicaland) in order to ground the analyses in an actual scenario.

6.2 Methods

6.2.1 Epidemic Simulation Model

The model used was a deterministic representation of the heterosexual transmission of HIV in a sex, age and sexual activity stratified population. The model is based on the first one described in Chapter 2 with the following modifications (details given at end of this chapter).

- 1) To better characterise targeted increases in condom use, the chance of infection through sexual partnerships was adapted to reflect the number of unprotected sex acts in the partnership and the transmission probability per sex act.

- 2) To reflect the recently recorded behavioural changes in Zimbabwe [17, 91], between year 19 and 24 of the epidemic, the mean number of sexual partnerships formed per year was reduced by 25% and the proportion of sex acts in which a condom is used was increased almost three-fold (Figure 6.1). Baseline values of these parameters are chosen such that, with these changes, the behaviour in 1998 matches reports from a sexual behaviour survey in Manicaland [40]. The timing of scale of this change is informed by the analyses in chapter 2.

- 3) The simulated intervention only directly affects female sex workers and their clients (the high-risk group) and generates a four-fold increase in the frequency with which they used condoms with any partner. These changes start in year 20 and

are completed within 3 years, but the speed of behaviour change is specified by the fraction of the change completed by time t , $f(t)$:

$$f(t) = \frac{e^{r(t-20)}}{(e^{3r}-1)} \quad \text{for } 20 \leq t < 23 \dots (6.1)$$

Here r determines the speed with which behaviour change takes place ($r < 0$ convex growth curve, $r > 0$ concave growth curve; unless otherwise specified $r = -3$) (Figure 6.2).

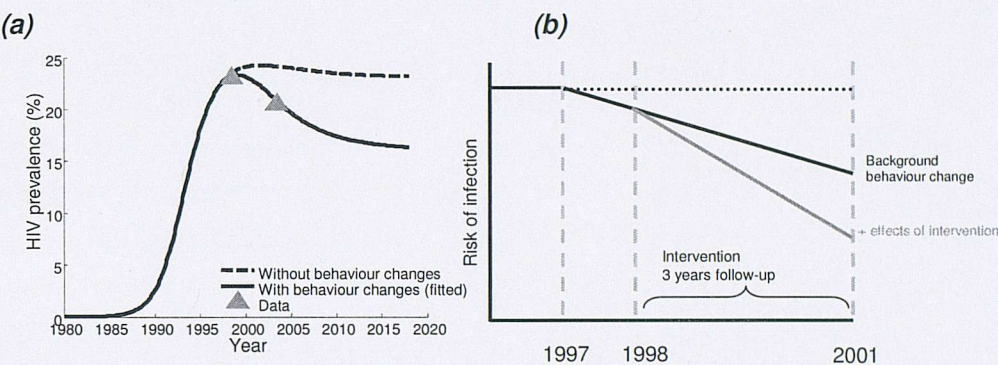


Figure 6.1 The epidemic context in Zimbabwe. (a) Model output showing prevalence over time in the absence of the intervention (b) Schematic diagram showing how the timing of the background behaviour change (from 1997) and the intervention (three years from 1998).

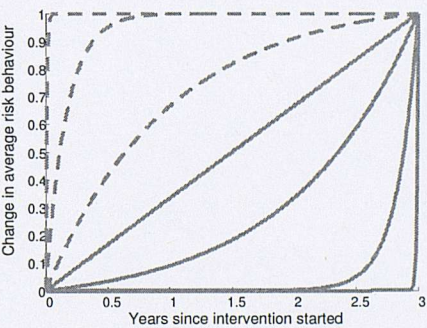


Figure 6.2 The development of the behaviour change due to the intervention. can accelerate ($r > 0$; solid lines) or decelerate ($r < 0$; dashed line) over time. In these simulations, from top-most line down, the values of r used are -10, -3, -1, 0.1, 1, 3 and 10.

Other minor changes to the model are listed at in the appendix to this chapter.

6.2.2 Power Calculations

The aim of the power calculation is to estimate the chance that, for a given deterministic change in incidence associated with the intervention, a statistically

significant difference between intervention and control communities could be detected. The problem is approached by running a series of stochastic realisations of the trial, and at the end of each, assessing whether the data that would have been collected would be sufficient to give a statistically significant result. Because incidence and losses to follow-up are experienced probabilistically, different trial outcomes are recorded each time, despite assuming the same underlying deterministic effect of the intervention. After a large number of repetitions (in this case, 5000), the proportion of simulations in which a significant result is obtained can be used to estimate the probability of detecting a statistically significant result in one real trial.

In each trial simulated trial, there are n pairs of communities; one is randomly assigned to the intervention arm and the other to the control arm. Let $c_{i,j,t}$ represent the number of infections that occur in each community at time t for the i^{th} pair in the j^{th} arm ($j=1$ for control community and $j=2$ for intervention communities). This is drawn from a Poisson distribution with mean equal to the expected the number of infections based on the deterministic simulations:

$$c_{i,j,t} \sim Po(\lambda_{i,j} Y_{i,j,t}) \dots (6.2)$$

Here $Y_{i,j,t}$ are the person-years at risk spent in that community during that time-step; incidence in the control communities is $\lambda_{i,1,t}$ and incidence in the corresponding intervention communities is $\lambda_{i,2,t}$. Incidence rates in both types of community (control and intervention) are assumed to be normally distributed with mean equal to the corresponding output from the dynamic simulation model: $I_{1,t}$ and $I_{2,t}$, respectively (see appendix for calculation). The variance of the distribution is parameterised with the coefficient-of-variation (CV) for the between-cluster variation in incidence, which is assumed to be the same in both arms of the trial.

$$\lambda_{i,j,t} = I_{j,t} + \varepsilon I_{j,t} CV$$

$$\dots (6.3)$$

$$\varepsilon \sim N(0,1)$$

The number of person-years spent at risk in that community during that time-step is given by:

$$Y_{i,j,t} = N_{i,j,t} \tau \dots (6.4)$$

where $N_{i,j,t}$ is the number of susceptible individuals in that community at that time and changes through time as:

$$N_{i,j,t} = N_{i,j,t-1} - c_{i,j,t-1} - Po(\tau g N_{i,j,t-1}) \dots (6.5)$$

where g is the rate at which individuals move out of the community or are otherwise lost from the study per year follow-up and τ is the duration of the time-step. The results of the modelling are not sensitive to the chosen distribution of true incidence rates (i.e. distribution of ε).

The overall measured incidence rate ratio (MIRR) after F years of follow-up ($MIRR_F$) is calculated as the geometric mean of the $MIRR$ in each pair:

$$r_{i,j,F} = \frac{\sum_{t=0}^F c_{i,j,t}}{\sum_{t=0}^F Y_{i,j,t}}$$

$$MIRR_F = \sqrt[n]{\prod_{i=1}^n \frac{r_{i,2,F}}{r_{i,1,F}}} \dots (6.6)$$

The hypothesis test is based on the statistic T being distributed under the null hypothesis as t with $n-1$ degrees of freedom [322]:

$$T = \frac{\sqrt{nd}}{s_d}$$

$$d_i = \sum_{i=1}^n (\log r_{i,2,F} - \log r_{i,1,F})$$

$$\bar{d} = \frac{\sum_{i=1}^n d_i}{n} \dots (6.7)$$

$$s_d = \sqrt{\frac{\sum_{i=1}^n (d_i - \bar{d})^2}{n-1}}$$

From simulations, it has been calculated that the type I error rate (significant result with no true difference between incidence in intervention and community sites) of this

test at the significance level of 5% is in the range 0.046-0.057 for all scenarios examined.

6.3 Contributions

In addition to my supervisors, I am grateful to Peter White and Nick Grassly (both Imperial College London) for useful discussion on this work.

6.4 Results

6.4.1 The Theoretical Effectiveness of an Intervention Targeted to High-risk Individuals

Behaviour change by the high-risk group of women and men (representing sex workers and their clients) can have a substantial impact on HIV incidence in the whole population: the dramatic behaviour change assumed (quadrupling condom use frequency and 90% reduction in prevalence of co-factor STIs) immediately generates ~70% reduction in incidence in the high-risk group (10% of population) and incidence in the whole population is reduced by ~35% after 10 years. An intervention targeted at the high-risk group is likely to have a bigger impact when implemented earlier in the epidemic than when implemented later because at the beginning most new infections occur in the high-risk groups (Figure 6.3(a)). The impact of behaviour change by the high-risk group is also sensitive to the structure of the sexual network. Behaviour change by the high-risk group will only be translated into a substantial reduction in incidence in the low-risk group if it is common for high-risk individuals to form sexual partnerships with low-risk individuals ("random mixing") (Figure 6.3(b)). If high-risk individuals rarely form partnerships with low-risk individuals ("assortative mixing") then any reduction in incidence in the high-risk group is not shared with the low-risk group.

The reduction in incidence in the whole population is not instantaneous – first, it takes time for average behaviour to change in the high-risk group, and second, there is a delay before the reduced risk behaviour by the high-risk group is translated into a reduction in incidence in the whole population (Figure 6.3(c)). The latter of these effects is probably the more important since, even with instantaneous behaviour change by the high-risk group, the full impact of the intervention is not realised for many years after the intervention starts (Figure 6.3(c) – black dotted line).

6.4.2 The Chance of Detecting a Statistically Significant Result for an Effective Intervention

In practice, the effect of an intervention in a CRCT is measured as the total number of events during follow-up divided by (estimated) person-years of observation. This will be identified as the ‘measured incidence rate ratio’ (MIRR). However, the potential usefulness of the intervention in programmes is indicated by the *instantaneous* incidence rate ratio (IRR) after the intervention has taken effect (Instantaneous incidence is the rate of new infections per person-year at risk). When rates of infection are low (as for HIV), MIRR will approximate the average of IRR over the follow-up period.

If the full effect of the intervention is exerted immediately, then MIRR would equal IRR. If the full effect of the intervention takes time to develop, MIRR will be closer to one than IRR, reflecting a smaller effect of the intervention at first (Figure 6.4(a-b)). The size of the discrepancy between the two measures is greatest when the reduction in incidence increases gradually over time. Although in the long-term the two measures converge, over the first years of the intervention, the difference between MIRR and IRR increases if the impact of the intervention grows very quickly.

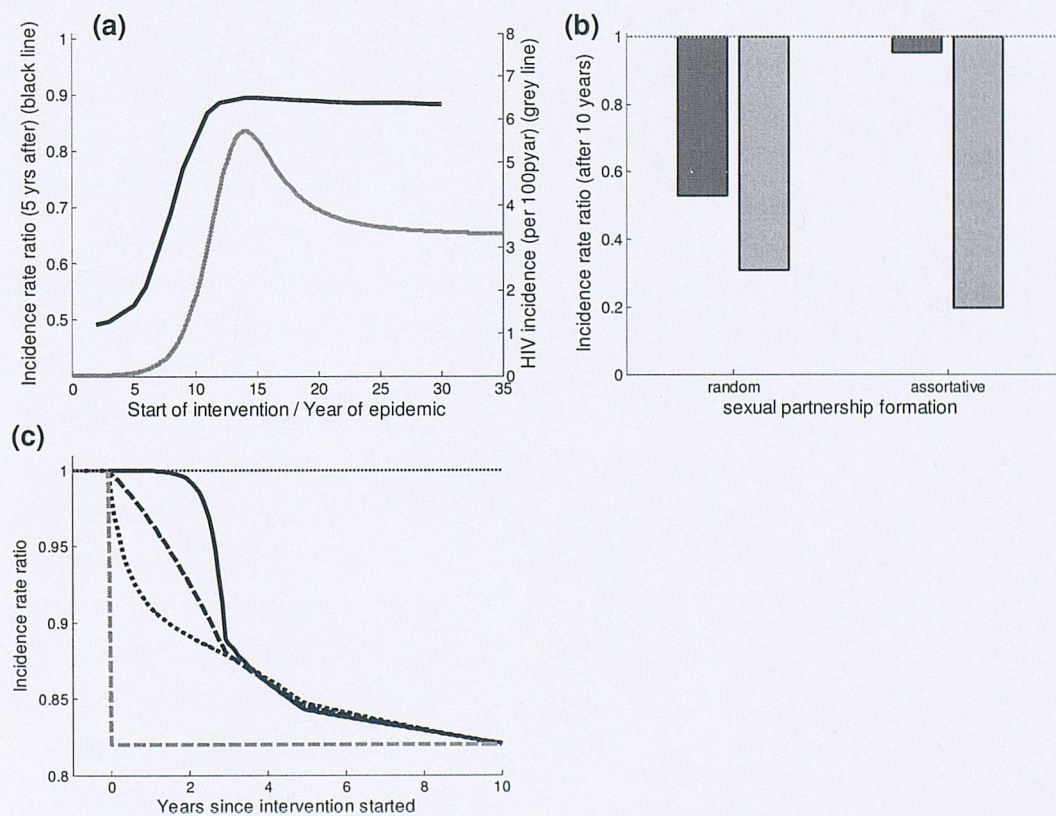


Figure 6.3 Theoretical Effectiveness of an Intervention Targeted to High-risk Individuals. (a) Predicted IRR 5 years after intervention starts as a function of the calendar year in which the intervention starts (solid black line on left-hand vertical axis) and modelled IRR in Manicaland between 1980 and 2015

(grey line on right-hand vertical axis) showing phase of epidemic. (b) Predicted IRR among low-risk (dark bars) and the high-risk (light bars) groups 10 years after the high-risk targeted intervention starts if the pattern of sexual partnership formation is “random” or “assortative”. (c) IRR as a function of time since intervention starts if behaviour change takes 3 years and progresses at a constant rate ($v=0.01$, black dashed line) or takes 3 years and the rate of change increases ($v=3$, solid black line) or decreases ($v=-3$, black dotted line). Shown as a comparison, the assumption about IRR made in standard power calculations: IRR is reduced instantaneously (grey dashed line).

These three factors (time for behaviour change, time for effect to spread from the high-risk group, measurement of MIRR not IRR) are not considered in most estimates of study power, which implicitly assume an instantaneous reduction in incidence (Figure 6.2(a) – dashed grey line). This simplifying assumption will lead to over-estimating the chance that the study returns a statistically significant result for an intervention that works (the power of the study) (Figure 6.4(c)). For example, the standard estimate of power for a theoretical five-year study with ideal study conditions (no loss to follow-up; six identical communities per arm with 1000 individuals per community) could exceed 0.99, but when the gradual reduction in incidence is allowed for, the estimate of power is reduced to approximately 0.71. Under more likely study conditions (3 years follow-up with 44% lost; 6 communities per arm with 788 individuals per community and between-community coefficient of variation 0.14 [94]), although power is estimated to be 0.82 with standard assumptions, it could be as low as 0.25 if incidence changes in the way predicted by the model.

Given the slow speed with which a substantial reduction in MIRR develops, the requirements for other aspects of the study design become more stringent if sufficient power is to be achieved with a short follow-up period (Figure 6.4(d)). Whilst traditional calculations would suggest that a wide range of study conditions would give a good chance of detecting an effect, these simulations suggest that only with very optimistic assumptions about the number of individuals in each community, between-community variation and the follow-up rate, would there be a good chance (probability > 0.8) of recording a statistically significant result within 5, or even 10 years. Of the key aspects of study design, between-community variation and length of follow-up have the strongest influence on study power. For a given total number of study participants, increasing the number of communities increases power more than increasing the number of participants per community [316] (Table 6.1).

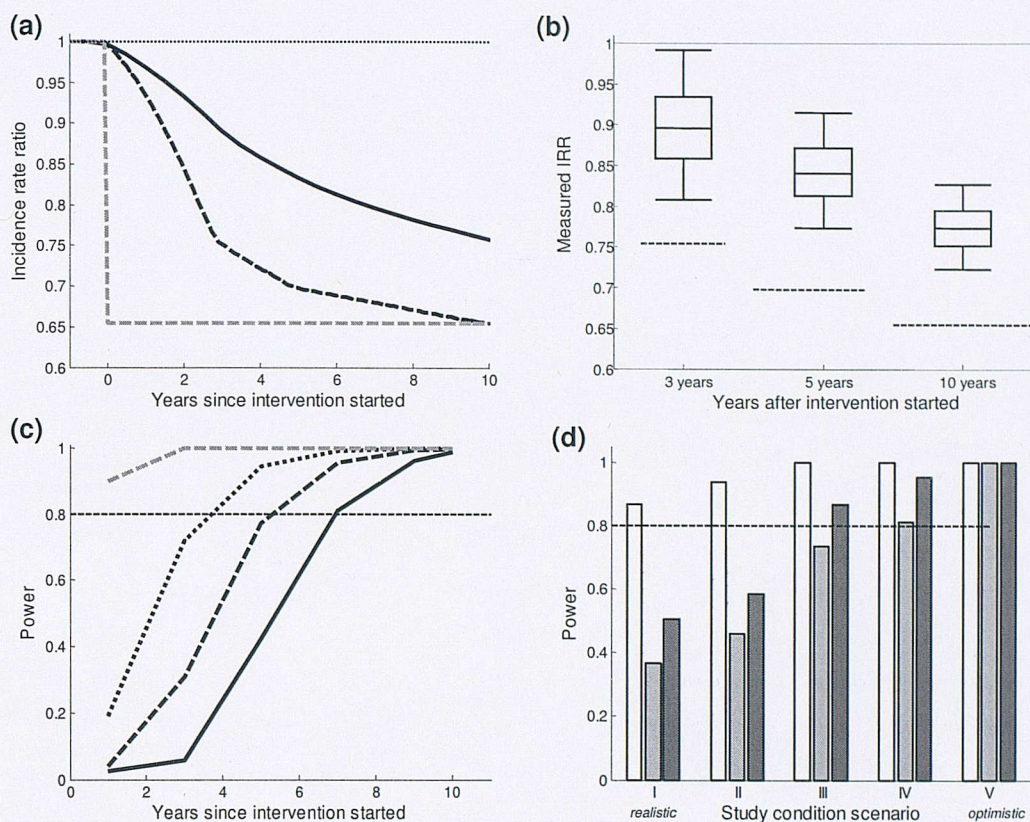


Figure 6.4 The Chance of Detecting a Statistically Significant Result for an Effective Intervention. (a) MIRR (black solid line) and IRR (black dashed line) as a function of time since intervention starts. Shown as a comparison, assumption about IRR made in standard power calculations: IRR is reduced instantaneously (grey dashed line). (b) Distribution of MIRR over 5000 stochastic runs after 3, 5 and 10 years follow-up, assuming no between-community variation and no losses to follow-up. Box shows inter-quartile range, horizontal tick indicates median and whiskers extend to 5th and 95th percentiles. Dashed horizontal lines show corresponding IRR. (c) Estimated power of the CRCT (two-tailed test at the 5% significance level) as a function of years of follow-up, assuming no between-community variation and no losses to follow-up if behaviour change is instantaneous (black dotted line), takes 3 years and progresses at a constant rate (black dashed line) or takes 3 years and the rate of change increases (solid black line) or if IRR is reduced instantaneously (grey dashed line). Other assumptions as in (a) and (c). (d) Estimated power of the CRCT for a range of study condition scenarios: (I) 6 communities per arm, 1000 individuals per community, CV of between-community variation = 0.15, 47% followed-up after 5 years; (II) as for I but with 3000 individuals per community; (III) as for II but with 12 communities per arm; (IV) as for III but with 100% followed-up after 5 years (V) as for IV but with CV=0.05. White bars show estimate using standard power calculations with 5 years follow-up; light grey bars show estimate based on gradual changes in incidence over time with 5 years follow-up; dark grey bars show estimate based on gradual changes in incidence over time with 10 years follow-up.

	Estimate of Power (± 2 standard deviations)	Relative Increase
Years of Follow-up		
3 years (r)	0.29 (0.27-0.30)	1.00
5 years	0.38 (0.37-0.39)	1.32
7 years	0.44 (0.42-0.45)	1.51
10 years	0.50 (0.49-0.52)	1.76
Variation between communities		
CV=0.15 (r)	0.27 (0.25-0.28)	1.00
CV=0.10	0.38 (0.36-0.39)	1.42
CV=0.05	0.52 (0.51-0.53)	1.96
CV=0.02	0.60 (0.59-0.61)	2.26
Follow-up rate (% after 5 years)		
47% (r)	0.27 (0.26-0.29)	1.00
61%	0.28 (0.27-0.30)	1.04
78%	0.31 (0.29-0.32)	1.12
100%	0.31 (0.30-0.33)	1.15
Number individuals per community		
1000 (r)	0.27 (0.25-0.28)	1.00
1500	0.31 (0.30-0.32)	1.16
2000	0.33 (0.32-0.35)	1.25
3000	0.34 (0.33-0.35)	1.27
Number of communities per arm		
6 (r)	0.27 (0.25-0.28)	1.00
8	0.32 (0.30-0.33)	1.18
10	0.38 (0.37-0.39)	1.42
12	0.45 (0.44-0.47)	1.69

Table 6.1: Elements of study design and study conditions that could improve study power. (CV=coefficient of variation). In each univariate analyses, other parameter values used are indicated by (r); these are based on the conditions of the recent trial in Manicaland, Zimbabwe [94].

6.4.3 The Influence of Epidemiological Context

The epidemiological background against which the intervention is tested can influence the magnitude of the impact of the intervention and the chance of detecting a statistically significant effect. The potential for epidemic spread can be summarised by R_0 , the basic reproductive number (the number of infections that occur when one infected individuals enters an entirely susceptible population [37]). The effect of an intervention that reduces R_0 is greater when R_0 is lower [37], so it is expected that background behaviour changes occurring during the follow-up period could enhance the reduction in incidence associated with the trial intervention (Figure 6.5(a) – left panel). Despite there being fewer incident infection observed, these simulations indicate that this could mean that background behaviour change increases the chance of detecting a statistically significant effect (Figure 6.5(a) – right panel).

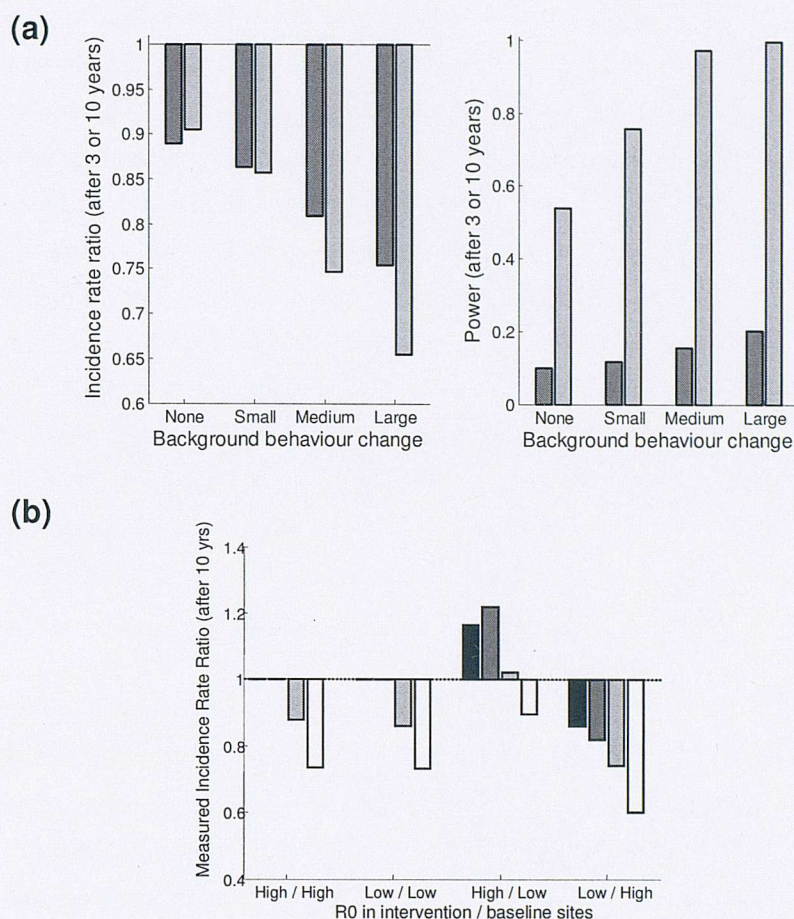


Figure 6.5: The Influence of Epidemiological Context. **(a)** Predicted IRR and the estimated power to detect a statistically significant effect of a high-risk targeted intervention (two-tailed test at the 5% significance level) after 3 (dark grey bars) or 10 (light grey bars) years assuming that there is no background behaviour change or that condom use increases by 30%, 100% or 280% and partner acquisition rate decrease by 5, 15 or 25% (“small”, “medium” and “large” amounts of behaviour change, respectively) linearly throughout the follow-up period equally in all communities. Study design and conditions assumed to be: 6 communities per trial arm, 1000 individuals per community, no variation between communities and no losses to follow-up. **(b)** Predicted MIRR after ten years when there are imbalances in R_0 between intervention and control communities. Assumptions made are: the intervention is not effective and there is no background behaviour change (black bars); the intervention is not effective but there is background behaviour change (dark grey bars); the intervention is effective but there is no background behaviour change (light grey bars); and, the intervention is effective and there is background behaviour change. High and low values of R_0 generate prevalence at the start of the trial of 24% and 21%, respectively.

Due to the small number of communities that are randomized it is likely that, by chance, HIV prevalence and incidence in the control and intervention communities is not equal. Such an imbalance means that, even before the intervention, IRR would not be equal to one. Moreover, if the differences reflect variation in the potential for epidemic spread, then the impact of behavioural changes – whether related to the trial or not – would be greater in communities with lower baseline incidence [37]. This means that the impact of an effective intervention would be under-estimated if R_0 is

initially higher in the intervention communities, and the impact of an ineffective intervention would be over-estimated if R_0 is initially lower in the intervention communities, especially if there are background behaviour changes. In the Manicaland trial, for instance, mean baseline HIV prevalence was 21% in the control communities and 24% in the intervention communities. Simulating this prevalence imbalance by varying R_0 between the control and intervention communities and assuming no background behaviour change, MIRR after ten years ($MIRR_{10}$) would be 0.86 if R_0 was the same in all communities, but 1.02 if R_0 was higher in intervention communities and 0.74 if R_0 was higher in control communities (Figure 6.5(b)). With background behaviour changes, the corresponding $MIRR_{10}$ estimates would be 0.75, 0.90 and 0.60. If the intervention was not effective but there were secular behavioural changes, $MIRR_{10}$ would be 1.22 if R_0 was higher in intervention communities and 0.82 if R_0 was higher in control communities (Figure 6.5(b)).

6.5 Discussion

The CRCT study design can provide strong evidence of the effectiveness of an intervention, although generalising the result to all contexts is not necessarily possible [86, 118]. However, in planning and interpreting trials of HIV prevention interventions it is worth exploring the expected impact of behavioural change on HIV incidence over time to identify the circumstances when the effectiveness of an intervention would be apparent. The scientific interpretation of a trial that returns a negative or null result must be informed by these considerations.

The model suggests that a tendency for random mixing (for example, high-risk men forming sexual partnerships with low-risk young women [40]) would allow a reduction in incidence among the high-risk group to spread throughout the population. However, in a CRCT, this would not necessarily be expected to be reflected in a substantial or statistically significant reduction in MIRR after a short follow-up period. The reasons for this are; 1) the intervention may take some time to get to scale or to change the behaviour of the high-risk group, and 2) there is a delay before the reduced risk behaviour by the high-risk group is translated into a reduction in incidence in the whole population. Delays in reductions in incidence will lessen the difference between measured incidence rates in the two study arms. This means that evidence for the effectiveness of interventions that reduce incidence gradually over a few years (such as those that operate through high-risk groups), and which could avert many infections in the longer terms in actual programmes, might not be found in CRCTs.

One of the purposes of CRCTs is to establish whether an intervention 'works' and should be included in programmes. Estimating the chance that an epidemiologically relevant reduction in incidence would be detected statistically is an integral part of CRCT study design and standard methods for power calculations have been published [316, 317]. However, the results show that these calculations can over-estimate power because they assume that the reduction in incidence in the whole population is immediate. This conclusion is likely to be conservative since the model of the transmission dynamics used here is deterministic and does not take account of the chance events which would likely further slow the impact of the intervention. Implicitly taking account of this effect when deciding the predicted effect size in standard power calculations can be misleading because it masks the assumptions (i.e. degree of optimism) about the actual long-term impact of the intervention. Over-estimating the power of a study may encourage the interpretation of a non-significant result as evidence for lack of effect, whereas these simulations suggest that a probable explanation for a non-significant result will often be the slow speed with which the effect of the intervention develops. Mathematical simulation modelling provides a convenient way to examine how the study power is related to study conditions, and consider the effect of incidence declining gradually over time, whether this is due to the intervention starting more slowly than planned or patterns of transmission changing gradually.

It is difficult to say which of the different ways a trial can improve its ability to detect a significant effect will be the most practical. The choice of communities will probably be determined by many practical matters besides their similarity and there may be a trade-off between using two similar communities close to each other or two that are less similar but further apart, which may reduce contaminating migration. There is also the danger that pairing of communities by attributes that do not correlate highly with the true incidence rate could be counter-productive when dealing with a small number of communities [323, 324]. Increasing the total number of individuals followed-up in a study will be associated with greater costs, but this will be spent more effectively if the number of communities is increased rather than the number of individuals in each community [316]. Increasing the number of communities also helps minimise the danger that, by chance, the two study arms do not have the same basic reproductive number (R_0) and the simulations show that even small differences at baseline can lead to large biases in MIRR. In the extreme cases, this could completely obscure the impact of truly efficacious intervention, or artificially generate a positive result for an ineffective intervention [219]. Generally, statistically controlling for differences in prevalence between sites will be insufficient

to eliminate this bias because not only does the value of R_0 determine the expected incidence rates under the null hypothesis, but it can also modify the actual the effect of the intervention and background behaviour changes. This leads lead to greater variation in the observed effects of the intervention than can be explained by variation in baseline prevalence, which itself will not fully capture variation in R_0 .

Losses at follow-up might be reduced by more frequent visits but these simulations suggest that, when taking other difficulties into account, a substantial increase in power is unlikely even with almost no losses to follow-up. Furthermore, if loss to follow-up is mostly accounted for by migration and mortality, as was the case in Manicaland [94], then extra visits will do little to help. On the other hand, having an interim round to recruit new migrants could help boost power and allow a measure of incidence later in the study, when the intervention is to scale and beginning to have an effect. Using detuned assays [64] at the follow-up round would also provide a way of measuring incidence later in the follow-up period, but the statistical uncertainty associated with estimates based on small numbers of recent seroconversions would limit the usefulness of this approach without following-up many more individuals.

Increasing the length of the follow-up period may be the most certain way to increase the chance that the study captures the effect of an intervention. However, commitment to a trial for a decade or longer may be difficult for funding agencies and investigators and runs the risk that the findings of the study will be out-of-date by the time it is complete. These difficulties may mean that, although a sufficiently powered CRCT is the best way to test the effectiveness of an intervention, observational studies based on sentinel surveillance may be increasingly relied upon to gauge the effect of on-going large-scale interventions without control groups [70, 118].

Some of the trials [94, 109, 110] were set against a background of generalised behaviour change that took place equally in all communities and was independent of the intervention. It has been assumed that a declining incidence of HIV would mask the impact of a successful intervention because there are fewer events in the control community which it is hoped will be prevented in the intervention community. Conversely, these results suggest that interventions can have a larger effect when other risk behaviour is reduced and this can outweigh the difficulties involved in establishing statistical differences between small numbers. Therefore, it is unlikely that secular changes in behaviour obscured the impact of the interventions in the African CRCTs, but this remains a concern in other settings where the incidence of HIV is lower.

CRCTs of HIV prevention interventions are more susceptible to these problems than other infectious diseases, particularly those that focus on individuals

with the riskiest sexual behaviour (e.g. those with STIs or involved in sex work). First, the private and psychologically substantive nature of sexual risk behaviour will tend to make changes slower. Next, the variation in sexual risk behaviour is greater and the pattern of contact with respect to risk may be more likely to be assortative than other forms of more casual contacts [325]. Both these factors slow the percolation of the effect of an intervention through the population. Third, the long duration of HIV infection delays the impact of intervention spreading beyond the highest-risk group, particularly if the changes reduce the chance of infection acquisition rather than transmission (e.g. treating ulcerative STIs among women [105], or male circumcision [30, 31, 226]). If the chance of acquisition is reduced and the infection lasted less time, prevalence among the high-risk group would decline faster, and the risk associated with contact with that group would reduce more quickly. If the chance of transmission is reduced, the spread of the impact is most limited by the extent of contact between high and low-risk individuals, and only to a lesser extent the duration of infection. Added to this is the fact that incident HIV infection is a relatively rare outcome in the general population and the chance of infection in intervention and control sites is sensitive to epidemic phase and subject to secular trends, driven by natural dynamics [251] and/or widespread behaviour change, which may differ slightly between superficially similar communities.

Other infectious diseases may share one or more of these attributes and therefore face a similar problem. For example, sexual behaviour change to reduce the incidence of other STIs may also take time to work, although the epidemiological response may be quick [22, 115]. The impact of interventions to prevent or treat tuberculosis will be slow to develop because there is a slow turnover of the infected population. On the other hand, interventions that aim to reduce the population of insect vectors of diseases such as malaria will be less affected by these issues since the turn-over of vectors is high and an effective reduction in the risk of infection to humans can develop quickly [37].

The CRCT is the gold-standard for demonstrating the effectiveness of an intervention in a specific context [314, 315]. If a negative or null result is obtained, after assessing how well the intervention was realised, one has to consider whether the intervention was not appropriate for the epidemiological context or whether the study design (as implemented) was able to detect a real effect. Mathematical descriptions of the transmission of HIV can help explore how efficacious the intervention could be, but to rule out the chance the study failed to detect an effect, CRCTs for the prevention of HIV infection in generalized epidemics may need to include more communities or run for much longer.

6.6 Appendix

Details of Changes to the Model Specification

Except in the ways detailed below, the model used to generate the simulations was the same as the first one described in Chapter 2.

1) *Force of infection re-written according to number of unprotected sex acts and transmission probability per sex act:*

Equation (2.3) in the original model specification was replaced with equation 6.8:

$$F_{k,i,m}(t) = \sum_{m'} \sum_{i'} (c_{k,i,m,i',m'}(t) \cdot (1 - (1 - P_{m',k',i',m'}(t))^{\psi_{i,m,i',m'}})) \dots (6.8)$$

where $c_{k,i,m,i',m'}$ is the number of partnerships formed by individuals of that gender, age and activity-group with individuals of the opposite gender of that age and activity-group, $P_{i',m'}$ is the risk per unprotected sex act of acquiring infection when forming partnerships with individuals of the opposite gender of that age and activity-group, and $\psi_{i,i'}$ is the number of unprotected sexual acts that comprise each sexual partnerships with individuals of the opposite gender of that age and activity-group.

The number of unprotected sexual acts per partnerships $\psi_{k,i,m,i',m'}$ is defined as:

$$\psi_{k,i,m,i',m'} = n_{i,m,i',m'}(1 - \xi_{k,i,m,i',m'}(t)) \dots (6.9)$$

where $n_{k,i,m,i',m'}$ is the total number of sexual acts per partnerships and $\xi_{k,i,m,i',m'}$ is the fraction of sexual acts in which a condom is used correctly and consistently. The parameterisation of $n_{i,m,i',m'}$ is simplified so that individuals have a “tendency” for number of sex acts based on their activity-group and in each partnership the individual from the higher activity-group “decides” how many acts that partnerships will comprise.

2) *Transmission probability varied by risk-group*

Equation 2.10 in the original model specification is replaced with equation 6.10;

$$P_{m,i',m'}(t) = \frac{(\beta^1 Y_{i',m'}^1 + \beta^2 Y_{i',m'}^2 + \beta^3 Y_{i',m'}^3)(1 + \nu_{\min(m,m')}(t))}{N_{i',m'}} \dots (6.10)$$

$P_{m,k',i',m'}(t)$ is the probability of infection through sexual partnerships with individuals of the opposite gender in the i^{th} age group and in sexual activity group m ; β^1 , β^2 , and β^3 are the per act probabilities of transmission of HIV during acute infection, latent infection and pre-AIDS, respectively; ν_m is the product of the chance that either partner has an STI and the associated multiplicative-increase in the transmission probability of HIV, to reflect a stable STI prevalence in the higher risk groups. This provides a very basic way to reflect that transmission within and from those with the riskiest sexual behaviour is likely to be enhanced by co-factor STIs [105].

3) Incidence calculation

Incidence (cases per person-years at risk) is calculated:

$$I(t) = \frac{\sum_{k=1}^2 \sum_{m=1}^3 \sum_{i=1}^8 \left(\lambda_{k,i,m}(t) \int_{L_i}^{U_i} X_{k,m}(a,t) \right)}{\sum_{k=1}^2 \sum_{m=1}^3 \sum_{i=1}^8 \left(\int_{L_i}^{U_i} X_{k,m}(a,t) \right)} \dots (6.11)$$

Where L_i and U_i are, respectively, the lower and upper age limits of the i^{th} age-group and $\lambda_{k,i,m}(t)$ is calculated from equation 2.3. This output is then discretised into units of duration τ . $I_{1,t}$ is calculated using on simulation runs where no interventions is assumed and $I_{2,t}$ is calculated using on simulations where an intervention is included (see below).

4) Background Behaviour Change

To reflect the recent behaviour and epidemic changes in Manicaland [91], between simulation year 19 and 24 the overall mean rates of partner change ($M_{k,i}$) and the overall frequency of condom use ($\xi_{i,m,i',m'}$) change linearly. In most simulations, the change are:

$$\begin{aligned} M_{k,i} &\rightarrow 0.85M_{k,i} \\ \xi_{i,m,i',m'} &\rightarrow 2.8\xi_{i,m,i',m'} \end{aligned}$$

The initial values of these parameters are fitted such that behaviour in the year 1998 matches that observed in the Manicaland behavioural survey [40]. The timing and scale of these changes are informed by the analyses in chapter 2.

When the effect of different degrees of background behaviour change are investigated, two others scenarios are devised – “small” and “medium” amounts of behaviour change, defined as:

$$\text{“small”}: M_{k,i} \rightarrow 0.95M_{k,i} \quad \& \quad \xi_{i,m,i',m'} \rightarrow 1.3\xi_{i,m,i',m'}$$

$$\text{“medium”}: M_{k,i} \rightarrow 0.85M_{k,i} \quad \& \quad \xi_{i,m,i',m'} \rightarrow 2\xi_{i,m,i',m'}$$

4) Simulated Intervention

When the intervention is simulated, it is assumed that for members of the highest risk group, the proportion of sex acts in which a condom is used increases A times and the chance that either they or any sexual partner has an STI decreases by a fraction B ; in all analyses, $A=4$ and $B=0.9$. These changes start in simulation year 20 and are completed within 3 years but the speed of behaviour change is specified by the fraction of the change completed by time t , $f(t)$ (see equation 6.1 and Figure 6.2).

$$\begin{aligned} \xi_{k,i,1,i',m'}(t) &= \xi_{k,i,1,i',m'}^{\text{pre-intv}} & \text{for } t \leq 20 \\ \xi_{k,i,1,i',m'}(t) &= (1 + Af(t))\xi_{k,i,1,i',m'}^{\text{pre-intv}} & \text{for } 20 < t \leq 23 \dots (6.12) \\ \xi_{k,i,1,i',m'}(t) &= (1 + A)\xi_{k,i,1,i',m'}^{\text{pre-intv}} & \text{for } t > 23 \end{aligned}$$

$$\begin{aligned} v_2 &= v_3 = 0 \\ v_1(t) &= v_2^{\text{pre-intv}} & \text{for } t \leq 20 \\ v_1(t) &= (1 - Bf(t))v_2^{\text{pre-intv}} & \text{for } 20 < t \leq 23 \dots (6.13) \\ v_1(t) &= (1 - B)v_2^{\text{pre-intv}} & \text{for } t > 23 \end{aligned}$$

5) Other changes made to the model

- Number of risk groups reduced from five to three, so that “high-risk” ($m=1$) and “low-risk” ($m=2,3$) groups can be easily identified.
- Age-groups width increased from one year to five years for computational speed.
- Method of integration changed from Runge-Kutta to Euler, for computational speed.
- Difference in rates of partner change by group, re-parameterised by arithmetic mean and proportional differences between groups (not geometric

mean). That is, equation 2.8 in the original specification is replaced with equation 6.14

$$C_{k,i,3} = \frac{M_{k,i}(t)}{\gamma_0 + \sum_{m=1}^2 \gamma_m \tau_m} \quad \dots(6.14)$$

$$C_{k,i,m} = \tau_m C_{k,i,1} \text{ for } m > 0$$

where $M_{k,i}$ is the gender- and age-specific arithmetic mean of partnership formation rate and τ_m independently determines the ratio of rate of partnership formation in each sexual-activity group relative to the lowest sexual-activity group (m=3).

Tables 6.2 to 6.5 give the parameters used in all simulations unless otherwise specified. Values not given here are the same as used in Chapter 2.

Parameter Value	Symbol (or formula)	Default Value	Justification or reference
Mortality rate	$\mu(a)$	Table 2.2	[292]
Fertility rate	$\phi(a)$	Table 2.2	[292]
Mean time in primary infection stage	$1/v_{12}$	3 months	[47]
Mean time in secondary infection stage	$1/v_{23}(a)$	8 years (all ages)	[47]
Mean time in tertiary infection stage	$1/g$	6 months	[47]
Additional hazard of death for those with AIDS	α	6 months	[47]
Transmission probability per unprotected sex act (latent infection)	β^2	0.001	<i>Fitted*</i>
Transmission probability (primary infection, pre-AIDS and full blown AIDS)	$10 \beta^2$	0.01	[97]
Product of prevalence of STI co-factor (by activity-group) and multiplicative increase in transmission of HIV.	$\nu_1^{pre-int \nu}$	0.5	<i>Predicted</i> [93]
Probability of vertical transmission	σ	0.35	[317]
Fraction of contacts made randomly with respect to sexual activity class	ϵ	0.5	<i>Fitted*</i>
Proportion of population born into each activity group (ascending)	γ_1	0.6	<i>Fitted*</i>
	γ_2	0.3	
	γ_3	0.1	
Relative rates of sexual partner change in sexual activity-groups 1 and 2 compared to group 3 (male and female).	τ_1	100	<i>Fitted*</i>
	τ_2	20	
Balance parameter (extent to which mixing pattern determined by males)	θ	0	<i>Fitted*</i>

Table 6.2: Default parameter values (used for baseline simulation and others unless otherwise stated). *These values were selected to give a realistic rate of spread and eventual epidemic magnitude. Where the effect is of interest to the current analysis, the sensitivity of the model to the value of these parameters is discussed in the main text.

Age-range	Estimated mean number of partnerships formed per year ($M_{k,i}(20)$)
15-19	2.8
20-24	4.2
25-29	4.2
30-34	4.2
35-39	3.5
40-44	2.8
45-49	1.5
50-54	0.7

Table 6.3: Estimated Mean number of partnerships formed per year in 1998. Based on fitting to age and gender-specific HIV prevalence for Manicaland study population at baseline (1998). Note, values change through time to simulate background behaviour change.

Number of sex acts per partnership		Female		
		m=0 (lowest)	m=1	m=2
Male	m=0 (lowest)	100	40	4
	m=1	40	40	4
	m=2 (highest)	4	4	4

Table 6.4: Number of sex acts per partnership.

		Proportion of sex acts in which condom used ($\xi_{i,m,i',m'}(20)$)	
Male activity- group	Male Age	Female aged <25	Female aged 25+
0 or 1	<30	0.25	0.4
	30+	0.1	0.1
2	<30	0.45	0.3
	30+	0.2	0.15

Table 6.5: Proportion of sex acts in which condom is used throughout correctly in 1998. Based on data collected from the Manicaland study population at baseline (1998). Note, values change through time to simulate background behaviour change.

***Chapter 7: Determining the Optimal Monitoring
of HIV Infected Patients Prior to ART in
Resource-poor Settings***

7.1 Introduction

For a decade, patients in developed countries that are advancing towards AIDS have been offered combination anti-retroviral therapy (ART) which has led to a sharp decline in the rate of AIDS-related deaths [150]. More recently, the humanitarian crisis associated with the general spread of HIV in many African countries has led to an unprecedented financial and logistical commitment to providing ART to those in need [124, 284, 285]. Initial planning focussed on identifying those currently requiring treatment rather than on how to monitor those with future treatment needs [177]. However, decisions need to be taken about how to care for all HIV infected patients, and these decisions will determine prognosis when ART is eventually initiated and the expected demand for ART and other health and social services across the population.

The potential for success of ART depends on the state of the immune-system when treatment is begun [8, 157]. Whilst, in western countries, the decision to initiate ART is informed by a range of high-technology tools [169, 170], in poorer countries, a more pragmatic public-health approach has been adopted [171]. The World Health Organisation (WHO) has recommended using CD4 counting machines (CD4 cells are the main target of the virus) to decide when treatment should be initiated [177] and in the “3 by 5” program, the campaign to get 3 million on therapy by 2005, almost all the focus countries followed these guidelines [178]. In many other settings, the decision to start therapy is taken without any laboratory support and will make use of standard symptom staging criteria [171]. However, studies from India and Africa show that although early signs of disease can be apparent within a few years of infection [172, 173], advanced immune depletion is not always associated with severe clinical symptoms [174-176].

The success and efficiency of ART delivery will be determined by the health-care environment into which ART provision is incorporated and the way in which patients are cared for before they need ART. Contextual factors, such as the effectiveness of referrals from ante-natal clinics (ANC) to ART specialists, uptake of voluntary testing and the availability of CD4 counting machines, will determine opportunities for initiating ART. The number of health-care workers that can clinically stage patients or use CD4 machines will determine how actively patients can be monitored. Providing a high-standard of care for HIV patients is a key objective in programmes such as PEPFAR [163, 284] (The (American) President’s Emergency Plan for AIDS Relief) and it has been suggested that synergies between care, prevention and treatment could alleviate future care needs (for example, caring for those with failing treatment and for AIDS-orphans).

Whilst a great deal of work has focussed on the optimal state at which to initiate ART [154, 155, 326, 327], the way in which the overall effectiveness is determined by other aspects of the health-care environment has not received close attention. In clinical trials it would be unethical to compromise patient management and impossible to compare the full range of management strategies. Understanding how the health-care environment influences the practical implementation of an initiation strategy and its effect on key health indicator outcomes will help inform best-practice guidelines and facilitate more accurate projections of future health-care needs. However, making predictions of the effect of ART at the population level is complicated by the variability between patients in the rate of disease progression, the uncertainty in CD4 measurement and other stochastic effects, such as unrelated causes of mortality, opportunities for diagnosing women during pregnancies and missed appointments. To address these complexities, a new mathematical simulation model was developed that follows a theoretical cohort of infected individuals as the disease progresses; tracking when symptoms occur; how they are diagnosed; how the clinician monitors the individuals' advancing disease; and the decision to initiate ART and the effect this has on survival.

7.2 Methods

The model stochastically simulates the progression to AIDS and death of a cohort of HIV-infected individuals and tracks the services they receive and key health indicator outcomes. Each individual is realised independently and the properties of the individual, the timing of events and outcomes are calculated based on a series of rules and random draws from probability distributions (described below). Random draws from particular distributions are simulated by transforming standard uniform deviates from the pseudo-random number generator in 'Matlab' software (The Mathworks). The data used to parameterise the disease-progression part of the model are taken from several African studies, and it was decided that the characteristics of the cohort would be parameterised to reflect the current epidemiological conditions in eastern Zimbabwe.

7.2.1 Characteristics of the simulated cohort

The composition of the cohort is based on the gender and age-distribution of newly infected individuals in the Manicaland cohort study (1998-2002) [91] (Table 7.1). To capture the range of possible outcomes, the number of people in the cohort is chosen to be 1000, which may be assumed to come from a total population of ~70,000 (e.g. the size of a small town in Zimbabwe). Mortality from non-HIV/AIDS

related causes among children are: 53 per 1000 live births for infants (0-1 years), and a total of 90 per 1000 live births die before their fifth birthday (deaths distributed exponentially with parameters 0.054 for 0-1 year-olds, and 0.010 for 1-4 year-olds) [328]. The chance of dying between ages 5 and 99 is Weibull distributed such that median life-expectancy in the absence of HIV/AIDS is 48.8 years for men and 52.5 years for women [263] (shape and scale parameters for males: 7 and 57.5; for females 7 and 61.8).

Age-group	Distribution of Incident Infections	
	Males	Females
15-19	0.047	0.111
20-24	0.095	0.146
25-29	0.100	0.148
30-34	0.089	0.032
35-39	0.084	0.026
40-44	0.025	0.016
45-49	0.033	0.013
50-54	0.034	0.111

Table 7.1 Distribution of incident infections with respect to age and gender, based on incident infection in Manicaland 1998-2002 [91].

7.2.2 Clinical progression

For the i^{th} individual, the CD4 count ($CD4_i(t)$) declines over time since infection (t) according to the function:

$$\begin{aligned} \sqrt{CD4_i(t)} &= a_i - b_i t \\ a_i &\sim N(\mu_a, \sigma_a) \\ b_i &\sim N(\mu_b^0, \sigma_b) \quad \text{if infected when age} < 35 \text{ years} \\ b_i &\sim N(\mu_b^1, \sigma_b) \quad \text{if infected when age} \geq 35 \text{ years} \end{aligned} \qquad \dots(7.1)$$

The unit of $CD4_i(t)$ is the number of cells per microlitre of peripheral blood $(\mu l)^{-1}$. A steady decline in the square-root of CD4 count is theoretically [329] and clinically [179] justified and makes use of parameters that are directly comparable to those evaluated in several statistical analyses [330-332]. Although this is not likely to be a good description of CD4 decline immediately after infection, it should be sufficient for our analyses, which involve using CD4 count information once the infection is established.

The values of $\mu_a = 25.91$, $\sigma_a = 0.61$ and $\mu_b^0 = 1.32$ are taken from a study of populations in Western and West-Central Africa [333]. The value $\sigma_b = 1$ matches a Bayesian shrinkage estimate [331] of the variance in the rate of decline of CD4 counts. This means that, in the model, 68% of individuals younger than 35 years are assigned rates of CD4 decline within one standard deviation of the mean (0.3 to 2.3) and, of the rest, half are assigned a rate of decline less than 0.3 (slow-progressors) and half are assigned a rate of decline greater than 2.3 (fast-progressors) (Figure 7.1(a)). The value of $\mu_b^1 = 2.0$ is chosen to reproduce shorter survival times for older people [230, 234].

Each measurement of CD4 count is modelled as an observation of $CD4_i(t)$ plus random error (with standard deviation σ_m). The error derives partly from technical factors [334], but mostly from short-timescale physiological fluctuations in the true CD4 count [335-337]. In laboratory studies where counts have been repeated on the same blood sample and on blood samples taken within the same few weeks, the combined variation is estimated to have a standard deviation of approximately 50. In the model, it is assumed that this variation is distributed uniformly, with mean zero. The value upon which the clinical decision is taken ($m_i(t)$) can be a function (f) of several ($1, 2, \dots, j, \dots, n$) measurements that are taken on separate occasions.

$$\begin{aligned} \varepsilon_j &\sim U(-\sqrt{3}\sigma_m, +\sqrt{3}\sigma_m) \\ m_i(t) &= CD4_i(t) + f(\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n) \end{aligned} \quad \dots(7.2)$$

Figure 7.1(b) show successive CD4 measurements for five randomly-chosen individuals.

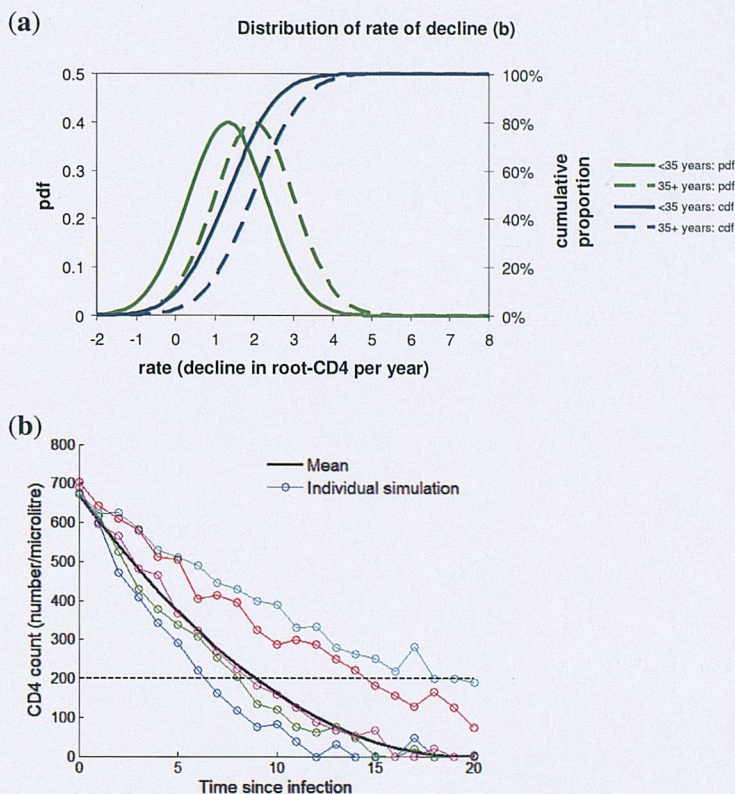


Figure 7.1 Decline in patients' CD4 counts in the model. (a) The distribution of rate of decline of CD4 count (root transform of value in number per microlitre) for those infected when younger than 35 years (solid lines) and when 35 years or older (dashed lines). Green line (left axis) give probability density function (pdf) and blue line (right axis) give cumulative distribution. (b) Change in CD4 count over time since infection. Thick line gives mean trend and other lines show the progression of five randomly-chosen individuals observed once a year.

It is not clear how closely clinical signs of immune-suppression (WHO stage III or IV) are correlated with severe immune-suppression. To incorporate this uncertainty into the model, three alternative scenarios were defined (Figure 7.2). Scenario I (the default) is based on observations from Uganda [174] and Ethiopia [175] (Double Weibull distribution with first shape and scale parameters 2.2 and 80.0 and second shape and scale parameters 12.4 and 399.3, respectively, weighting to first 0.53). The precise shape of this distribution is chosen for its biological plausibility, as well as the fit to the data. In scenario II, 90% of individuals develop symptoms by the time their CD4 count has dropped below $200 (\mu\text{l})^{-1}$ (Weibull distribution shape parameter 3, scale parameter 355) and in scenario III, 15% of individuals develop symptoms by

the time their CD4 count has dropped below $200 (\mu\text{l})^{-1}$ (Weibull distribution shape parameter 1.5, scale parameter 130).

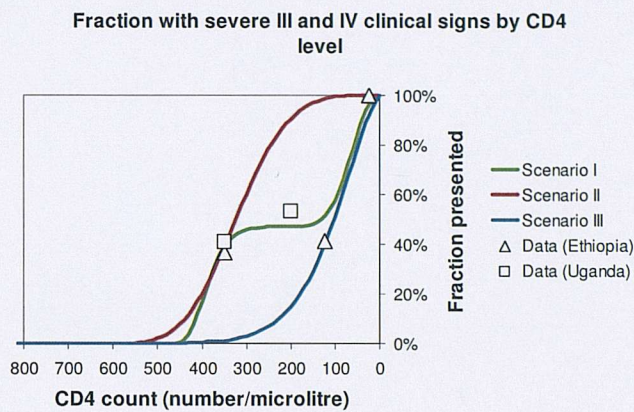


Figure 7.2 Fraction with severe stage III and stage IV clinical signs by CD4 count. Scenario I (green line) and scenario II (red line) for CD4 level when symptoms of severe symptoms of immune-suppression (WHO stage III and IV) develop. Squares show data points from studies in Uganda [174] and triangles show data points from Ethiopia [175].

Survival after CD4 count falls below $200 (\mu\text{l})^{-1}$ is assumed to be exponentially distributed with a median survival of 11 months, in accordance with a review of studies from resource-poor settings [338]. Survival from infection to death for individuals infected when 30 years-old has been estimated to be 10.9 years in Western populations [234] and 9.8 years in Uganda [230], although other studies have suggested lower survival rates in African populations (reviewed by Jaffar *et al.* [247]). Despite being based on independent data sources, the model is in good agreement with these results; in the model survival of people infected when younger than 35 years had a median of ~9.5 years (Figure 7.3) and follows a similar distributional form. There are few data on survival of people infected when older than 35 years, but in the model the median is ~7 years.

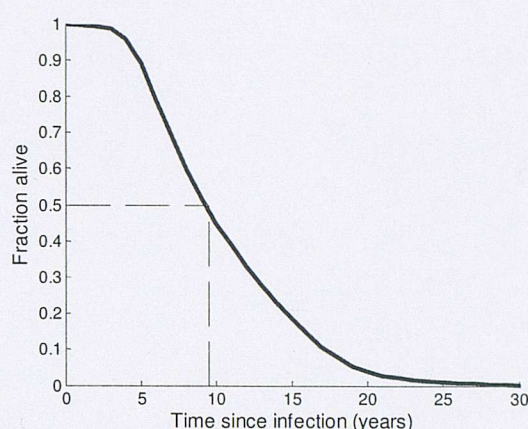


Figure 7.3 Modelled survival distribution for infected cohort in the absence of treatment (median 9.5 years).

7.2.3 Diagnosis of infection

Individuals may be diagnosed with HIV in one of three ways, whichever comes first. Once the infection is diagnosed, clinical monitoring of the individual can begin (see below).

1. Individual falls pregnant and attends ante-natal clinic (ANC).

Recent estimates of fertility rates in Zimbabwe [297, 339] and measurements of sub-fertility over the course of infection [47] are used to capture patterns of ANC attendance (Table 7.2). For each pregnancy, the probability that the woman will attend an ante-natal clinic, have her infection diagnosed and be referred to the anti-retroviral treatment (ART) programme can be 10% (“poor referral” scenario; estimated to currently be the case in Zimbabwe) or 90% (“good referral” scenario). It is assumed that attendance at ANC is exactly six months before delivery.

2. Individuals go for voluntary counselling and testing (VCT).

It is assumed that the probability that an individual goes for VCT is constant over time. “Low VCT uptake” means that 5% of individuals (randomly selected) go for VCT and are referred and “High VCT uptake” means that 70% of individuals go for VCT and are referred. Individuals go for VCT at some time (uniformly distributed) before they would otherwise present at a clinic (see below). It is assumed that individuals that do not go for VCT are either geographically isolated from services or unwilling to attend for other reasons. High VCT uptake could be achieved following scale-up of services

[248], including home-based testing [307], or if policies are changed to allow routine 'opt-out' testing at all medical facilities [146, 306].

3. Individual develops symptoms and goes to a health-service provider

The CD4 level at which an individual develops symptoms sufficiently severe to seek medical attention is determined by when the depletion of the immune-system reaches a predetermined threshold. This threshold varies between individuals and is drawn stochastically from a distribution based on the CD4 levels of those attending a clinic in Cote d'Ivoire [340]: Weibull distribution, shape parameters 0.8, scale parameter 194.1 (Figure 7.4). Two alternative scenarios are also included, whereby individuals present at the clinic earlier (e.g. in response to minor symptoms [172, 173]: Weibull distribution, shape parameters 2.2, scale parameter 400.0) or later (Weibull distribution, shape parameters 0.9, scale parameter 80.0).

Age group	Fertility rate in general population ^{†*} [339]	Zimbabwe HIV Prevalence (2002) [17]	Average sub-fertility [297]	Estimated fertility of uninfected women ^{†!!}	Assumed fertility for infected women, by years before AIDS [§]			
					4+ (RR=0.79)	2-3 (RR=0.45)	0-1 (RR=0.27)	AIDS (RR=0.19)
15-19	112	0.15	0.84	115	91	52	31	22
20-24	199	0.25	0.85	207	163	93	56	39
25-29	180	0.36	0.78	195	154	88	53	37
30-34	135	0.33	0.65	153	121	69	41	29
35-39	108	0.31	0.63	122	96	55	33	23
40-44	46	0.21	0.65	50	39	22	13	9
45-49	15	0.15 [‡]	0.65	16	13	7	4	3

Table 7.2 Assumed fertility of HIV-infected women in the model cohort. [†]Fertility rate expressed as number of live births per 1000 women per year. ^{*}These rates based on all women in Zimbabwe, some of whom will be infected. [‡] Data not available for this age-group: value interpolated. ^{!!}Fertility of uninfected women calculated assuming that observed fertility in DHS survey is composed of infected and uninfected women in proportion to HIV-prevalence at nationally representative antenatal clinics in 2002, and that sub-fertility among all infected-women is as measured in rural areas between 1995 and 2000. [§]Fertility has been shown to decrease with progressing infection [47]. RR is the observed ratio of fertility of infected women relative to uninfected women in Uganda, and this was used to estimate fertility of infected women in Zimbabwe for the model. In the model, AIDS is defined as when CD4 count falls below 200. It is assumed that women on ART have the same fertility as women with AIDS.

CD4 distribution for symptoms at presentation

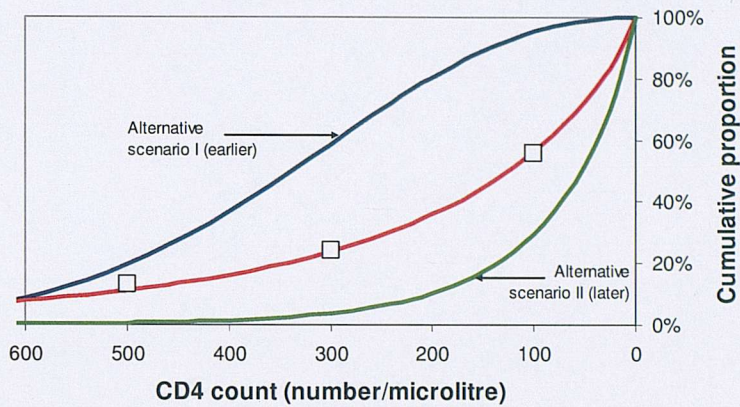


Figure 7.4 The assumed distributions of CD4 level at which individuals present at a clinic if they have not already been diagnosed. The red line is the default scenario and is based on CD4 counts among those presenting at an urban clinic in Cote d'Ivoire [340] (white squares). The blue and the green lines are alternative scenarios, whereby individuals present at a clinic earlier or later, respectively.

7.2.4 Clinical Monitoring

Once the infection is diagnosed, individuals can visit a health service provider so that their need for ART can be assessed. It is assumed that when an individual is first diagnosed (whether at VCT, ANC or when they develop symptoms sufficiently severe to seek care), they immediately visit the health service provider. At each visit to a health service provider the date of the next appointment is arranged. Following others [341], the scheduled interval between appointments can depend on the stage of HIV infection; a patient not eligible for ART should return after τ_1 , which depends on age and the CD4 measurement (Table 7.3), whereas a patient on therapy should return after $\tau_2 = 6$ months. Individuals may be lost-to-follow-up while not receiving ART and do not attend the next or any subsequent appointment (e.g. due to out-migration, incapacity, forgetting etc.). The hazard of loss to follow-up is constant, (with the exponential parameter $h = 0.05$) and such that ~5% of individuals are lost in the first year.

	CD4 measurement (number/microlitre) $m_i(t)$	Time until next scheduled appointment	
		Infected when aged < 35 years	Infected when aged 35+ years
Scenario I	Any	1 year	1 year
Scenario II	Any	6 months	6 months
Scenario III	Any	3 months	3 months
Scenario IV	$m_i(t) \leq 350$	3 months	3 months
	$350 \leq m_i(t) \leq 500$	6 months	6 months
	$m_i(t) \geq 500$	1 year	1 year
Scenario V	$m_i(t) \leq 350$	6 months	3 months
	$350 \leq m_i(t) \leq 500$	1 year	6 months
	$m_i(t) \geq 500$	2 years	1 year
Scenario VI	Any	1 year	6 months
Scenario VII	Any	None scheduled [‡]	

Table 7.3 Possible strategies for scheduling the next appointment. ‡Individuals may attend another appointment when they develop symptoms.

7.2.5 Decision to Start ART

At each visit to the health service provider a decision is taken about whether to offer ART to the individual if they are not already on ART and have not used ART in the past. The algorithm is to start ART if certain criteria regarding clinical symptoms and, where available, CD4 measurements are met (Table 7.4). The recommendations of the WHO [177] are to start ART if the CD4 count is below $200(\mu\text{l})^{-1}$ or below $350(\mu\text{l})^{-1}$ if the patient already has severe symptoms (code 7 in Table 7.4).

7.2.6 The effect of ART

When starting ART, an individual is assigned a duration of time until they die as a result of treatment failure and/or AIDS (in the absence of other competing causes of mortality not related to HIV/AIDS). A meta-analysis of cohort studies from high-income settings (ART-Cohort Collaboration: <http://www.art-cohort-collaboration.org/>) has quantified three-year survival for individuals starting therapy, stratified by baseline CD4 and the presence of WHO stage III/IV symptoms [157]. The ART-LINC collaboration of cohorts also finds evidence that the risk of death is higher in low-income settings in the first few months of ART, but similar to the rate in high-income countries later [8]. In the absence of a systematic aggregation of survival rates over a longer period from African cohorts, three survival scenarios were defined (“best”, “medium” and “worst”). These scenarios are parameterised in the following way:

- i. First-year survival is equal to aggregated estimates from low-income settings[8]. The “medium” scenario uses the point estimate and the “best” and “worst” scenarios use the limits of the 95% confidence intervals.

- ii. The relationship between CD4 count, symptoms and hazard of death after the first year is based on data from high-income countries[157]. In the “best” scenario, the hazard of mortality observed in the first three years of therapy is assumed to stay constant; in the default scenario it increases gradually; and in the pessimistic scenario the hazard of death increases sharply with time on ART.

Survival time is Weibull distributed for all scenarios (Figure 7.5). The parameters for the survival time scenarios are given in Table 7.5. The “medium” scenario, which is used in simulations unless otherwise stated, produces four-year survival rates of ~75% for those starting with CD4 count below 50 and 90% for those starting with CD4 count between 200 and 349, which is in good agreement with longer-term analyses of the ART-LINC cohort data, which have not yet been published [342].

WHO stage III/IV & high viral load at baseline	CD4 count when treatment started*	Optimistic scenario			Default Scenario			Pessimistic Scenario		
		Shape	Scale	First- year failure	Shape	Scale	First- year failure	Shape	Scale	First- year failure
Yes	0-50	1.0	34.2	8.7%	1.6	13.7	10.9%	2.5	7.9	12.1%
	50-99	1.0	43.7	5.3%	1.6	16.0	6.7%	2.5	8.8	7.4%
	100-199	1.0	47.8	3.6%	1.6	16.9	4.6%	2.5	9.1	5.1%
	200-349	1.0	79.7	1.4%	1.6	23.3	1.7%	2.5	11.1	1.9%
	350+	1.0	141.0	1.4%	1.6	33.3	1.7%	2.5	14.0	1.9%
No	0-50	1.0	85.86	8.7%	1.6	24.4	10.9%	2.5	11.5	12.1%
	50-99	1.0	109.70	5.3%	1.6	28.4	6.7%	2.5	12.7	7.4%
	100-199	1.0	119.92	3.6%	1.6	30.1	4.6%	2.5	13.1	5.1%
	200-349	1.0	199.97	1.4%	1.6	41.4	1.7%	2.5	16.1	1.9%
	350+	1.0	353.84	1.4%	1.6	59.1	1.7%	2.5	20.2	1.9%

Table 7.5 Parameters for Weibull distribution of survival time from start of ART to death. These rates do not take into account mortality from causes unrelated to HIV/AIDS. *Number per microlitre of peripheral blood.

Code	ART Initiation rule	Number of CD4 measurements		Decision to initiate ART	
		Symptoms	No Symptoms	Symptoms	No Symptoms
1	Syndromic initiation	0	0	Start	Do not start
2	Initial CD4 measurement, thereafter symptomatic initiation	0*	0*	Start	Start if CD4<200*
3	SI + CD4 confirmation if symptomatic	1	0	Start if CD4<350	Do not start
4	SI + CD4 confirmation if asymptomatic	0	1	Start	Start if CD4<200
5	CD4 monitoring: high blanket threshold	1	1	Start if CD4<350	Start if CD4<350
6	CD4 monitoring: low blanket threshold	1	1	Start if CD4<200	Start if CD4<200
7	WHO-CD4 recommendations	1	1	Start if CD4<350	Start if CD4<200
8***	WHO recommendations with 2 CD4 measurements (take mean)	2	2	Start if CD4<350	Start if CD4<200
9***	WHO recommendations with 2 CD4 measurements (take min) if first close**	1-2	1-2	Start if CD4<350	Start if CD4<200

*No measurement after the first appointment.

**A measurement is "close" if it is no more than 20cells/microlitre greater than the appropriate initiation threshold.

***If a second measurement is made, another appointment is required

Table 7.4 Possible decision rules for ART initiation used in the model.

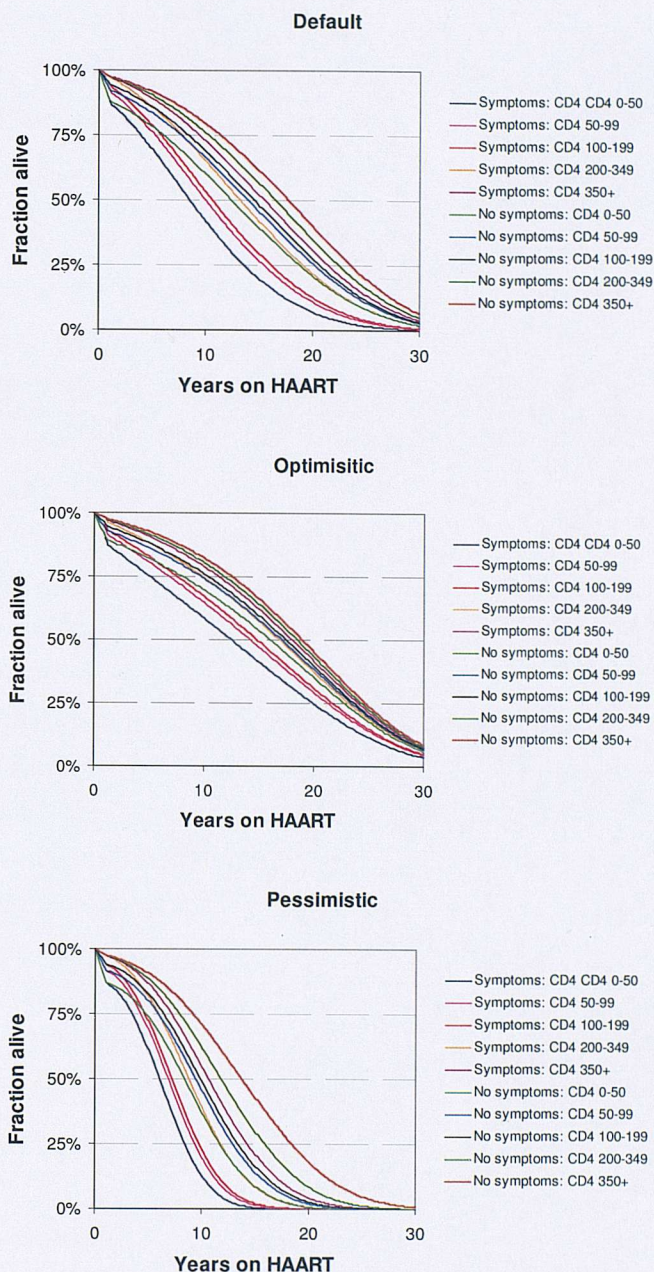


Figure 7.5 Survival from commencement of ART with default, optimistic and pessimistic assumption, by presence or absence of symptoms and true-time averaged CD4 count at commencement. Background survival is included for a male starting ART aged 35 years.

7.2.7 Pregnancy and mother-to-child transmission

Pregnant women that have had their infection diagnosed and have not been lost to follow-up are eligible to receive treatment to prevent mother-to-child transmission

(PMTCT) if they are not already on ART. Following other analyses for Zimbabwe [328], it is assumed that the probability that a woman who has had her infection diagnosed, is able to receive treatment to prevent mother-to-child transmission is $\kappa_1 = 0.3$ and the probability of acceptance is $\kappa_2 = 0.5$. The probability that the baby is infected from its mother is $\beta^+ = 0.24$ if she has been received PMTCT and $\beta^- = 0.32$ if she has not. This approximates the case for 7-17 months of breastfeeding and treatment being a single dose of Nevirapine [343, 344]. The probability that a baby is infected from its mother who is permanently on ART is $\beta^{++} = 0.04$ [344]. Following the recommendations of UNAIDS [344], the additional mortality hazard of an infected baby in the absence of any treatment is taken to be distributed as a double-Weibull (first shape and scale parameters 0.97 and 1.52, second shape and scale parameters 5.39 and 10, respectively, weighting to first 0.65) [345]. This distribution has two components; the first represents the fast progressors, who are infected inutero and intrapartum; the second represents the slow progressors, who are infected during breast feeding. HIV infected babies of mothers that had been diagnosed at the time of delivery are assumed to be eligible to receive ART. In one African cohort study [346], mean age of starting ART was 7.2 years and survival after one year was 91% and, in the model it is assumed that this chance of yearly survival remains constant over the next years of life. It is implicitly assumed that infected babies of women that were not diagnosed at delivery but are subsequently diagnosed whilst the baby is still alive do not receive the benefits of ART because the opportunity to initiate ART at the appropriate time has been missed. A “child death” is counted if they die before their 15th birthday and a child is assumed to be (maternally) orphaned if their mother dies whilst they are alive and before their eighteenth birthday.

7.2.8 Distribution Notation

If U_i are uniform random deviates between 0 and 1, then:

- E_i are exponentially distributed with mean μ :

$$E_i = \frac{\ln(U_i)}{-\mu} \quad \dots(7.3)$$

- W_i are Weibull distributed with shape parameter k and scale parameter λ :

$$W_i = \lambda(-\ln(U_i))^{1/k} \quad \dots(7.4)$$

- D_i are distributed as a double Weibull with first shape and scale parameters k_1 and λ_1 and second shape k_2 and scale λ_2 parameters and weighting to first w :

$$\begin{aligned} D_i &= \lambda_1 (-\ln(U_i))^{1/k_1} \quad \text{if } U_i < w \\ D_i &= \lambda_2 (-\ln(U_i))^{1/k_2} \quad \text{otherwise} \end{aligned} \quad \dots(7.5)$$

7.3 Contributions

This work has benefited from useful discussion with Peter White, T Deirdre Hollingsworth (both Imperial College London), Frank de Wolfe (Imperial College London & HIV Monitoring Foundation) and my supervisors. Sources for some data used in the model parameterisation were suggested by Stacie Greby and Eileen Burke (both at the Centers for Disease Control and Prevention).

7.4 Results

The model predicts that, in the absence of treatment, infected individuals will each lose, on average, ~22 years of life (range over stochastic realisations $\pm$ two standard deviations from mean: 21.4-22.6) and die aged 39 (38.6-39.6) years having experienced severe symptoms for ~700 (638-774) days (Table 7.6).

If patients are initiated on ART only when they develop symptoms of immune-suppression (syndromic initiation), referral of infected women from ANC to the ART programme is low and uptake of VCT is low, then the impact of ART on these population level indicators is small (Table 7.6: column A). Although the life of those treated is extended by between six and seventeen years (depending upon the effect of ART assumed), the average life-years saved among all those infected (treated or not) is equivalent to only two to five years per person. The effect of ART is limited by the failure to diagnose many individuals and by starting treatment late when the immune system is already weakened. Cumulative mortality in the first few years of infection is similar to the scenario where treatment is not available because most fast-progressors die without being treated and the opportunity to save life-years is only available for those with advanced disease (Figure 7.6(a)).

A CD4 count can provide an early warning of immune system depletion before symptoms develop. When a CD4 count is used to help decide when to initiate ART in the manner recommended by WHO [177], ~60% more individuals are started

on ART and the extension of life for those treated rises to between seven and nineteen years (Table 7.6: column B and Figure 7.6(b)).

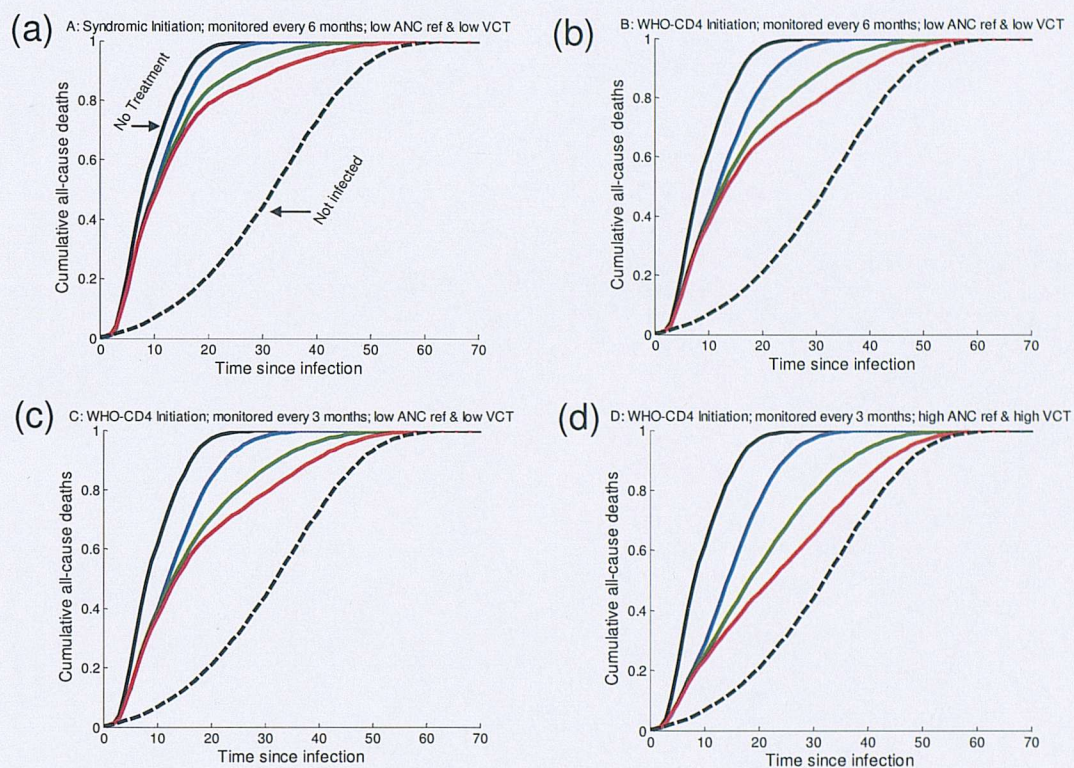


Figure 7.6: Survival distribution of an infected cohort if there is no treatment available (solid black line) or if ART is available and its assumed effect is worst (blue line), middle (green line) or best (red line) (See Table 7.5 and Figure 7.5 for details). The survival of an age and gender-matched cohort that is not infected is shown for comparison (dashed black line).

Our model shows that the frequency with which patients are monitored also determines the impact of ART (Table 7.6: column C and Figure 7.6(c)). With more frequent monitoring there is a better chance that ART can be started at the right time, and with the same initiation rule, patients that are monitored every three months instead of every six months, are expected to live approximately half a year longer (Table 7.6 and Figure 7.7).

		No treatment	A Syndromic Initiation Monitoring every 6 months Low ANC referral Low VCT uptake			B WHO-CD4 initiation Monitoring every 6 months Low ANC referral Low VCT uptake			C WHO-CD4 initiation Monitoring every 3 months Low ANC referral Low VCT uptake			D WHO-CD4 initiation Monitoring every 3 months High ANC referral High VCT uptake		
			ART effect:											
<i>Per 1000 infected</i>			worst	med	best	worst	med	best	worst	med	best	worst	med	best
Person-years lost to HIV/AIDS (1000s)	22		20	18	17	19	16	13	19	16	13	17	12	8
Mean age at death	39		41	43	44	42	45	48	43	46	48	45	49	53
Number of "sick days" (1000s)	717		504	490	471	519	502	465	516	497	461	335	297	253
Number of child deaths (<15 years)	172		171	173	171	175	176	176	172	174	176	167	172	172
Number of maternal orphanings	300		286	253	237	275	208	184	267	216	182	250	151	98
Life-years saved (1000s)	<i>n/a</i>		1.8	3.4	5.0	3.4	6.3	8.6	3.5	6.5	9.0	5.6	10.4	14.4
Years on ART (1000s)	<i>n/a</i>		2.5	4.1	5.7	4.3	7.2	9.5	4.5	7.5	9.9	7.3	12.1	16.1
Percent ever diagnosed	<i>n/a</i>		51	51	51	51	51	51	51	51	52	81	81	81
Number of monitoring appts (1000s)	<i>n/a</i>		4.0	4.1	4.1	3.7	3.7	3.8	6.7	6.6	6.7	17.4	17.3	17.2
CD4 tests per person diagnosed	<i>n/a</i>		0	0	0	7	7	7	13	13	13	21	21	21
Number treated	<i>n/a</i>		292	293	288	466	464	474	482	484	486	765	762	757
Life-years saved per person diagnosed	<i>n/a</i>		3.5	6.7	9.7	6.7	12.3	17.0	7.0	12.8	17.4	6.8	12.8	17.7
Years on ART per person treated	<i>n/a</i>		8.4	14.1	19.6	9.2	15.4	20.5	9.3	15.5	20.3	9.5	16.0	21.1
Life-years saved per person treated	<i>n/a</i>		6.0	11.7	17.1	7.3	13.4	18.5	7.4	13.5	18.3	7.3	13.8	18.8

Table 7.6 Key indicator outcomes for alternative initiation decision rules and health-care system parameters.

The effect of the ART delivery programme is further improved if referral from ANC and uptake of VCT is improved so that more individuals are diagnosed and monitored from earlier in the infection (Table 7.6: column D and Figure 7.6(d)). The model predicts that with achievable levels of referral from ANC and VCT uptake, almost all HIV-infected individuals would enter care. In this scenario, the total number of person-years saved is almost double compared to the case when referral is low. With earlier diagnosis of infection, there are also fewer sick days because clinical signs can be used to initiate ART promptly.

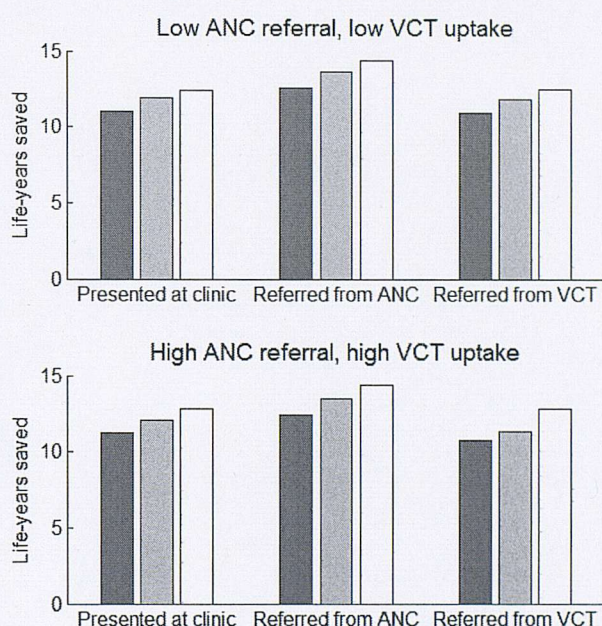


Figure 7.7 The impact of increasing the frequency of monitoring individuals in care on average life-years saved per person diagnosed, by the route through which they enter care. Individuals in care are monitored every 12 months (dark grey bars), every 6 months (light grey bars) or every 3 months (white bars). In the upper panel, it is assumed that referral from ANC is low and uptake of VCT is low; in the lower panel, it is assumed that referral from ANC is high and uptake of VCT is high. ART is initiated with CD4 counts in the manner recommended by WHO (code 7; Table 7.4).

Increasing opportunities for early diagnosis has two benefits: first, it allows more people to enter care and receive ART before they die; and second, it increases the chance that ART can be initiated at the right time. To quantify the latter effect, alternative cohorts are compared where either all individuals enter care through referral (from ANC or VCT) or individuals can only enter care by presenting at a clinic with symptoms. With referral, the CD4 count at which ART is started tends to be higher (Figure 7.8(a-b)) and the life-years saved by ART is greater (Figure 7.8(c-d)).

Referral of women from ANC is especially productive because they are typically young and disease-free (Figure 7.9(a)). However, the apparent effectiveness of ART at the population level may not improve when more individuals are diagnosed earlier through VCT (Figure 7.9(b)). This is because those progressing to AIDS fastest, who would otherwise die outside of the ART programme, will start ART when already immune-suppressed and die within the programme, bringing down measures such as average survival time on ART.

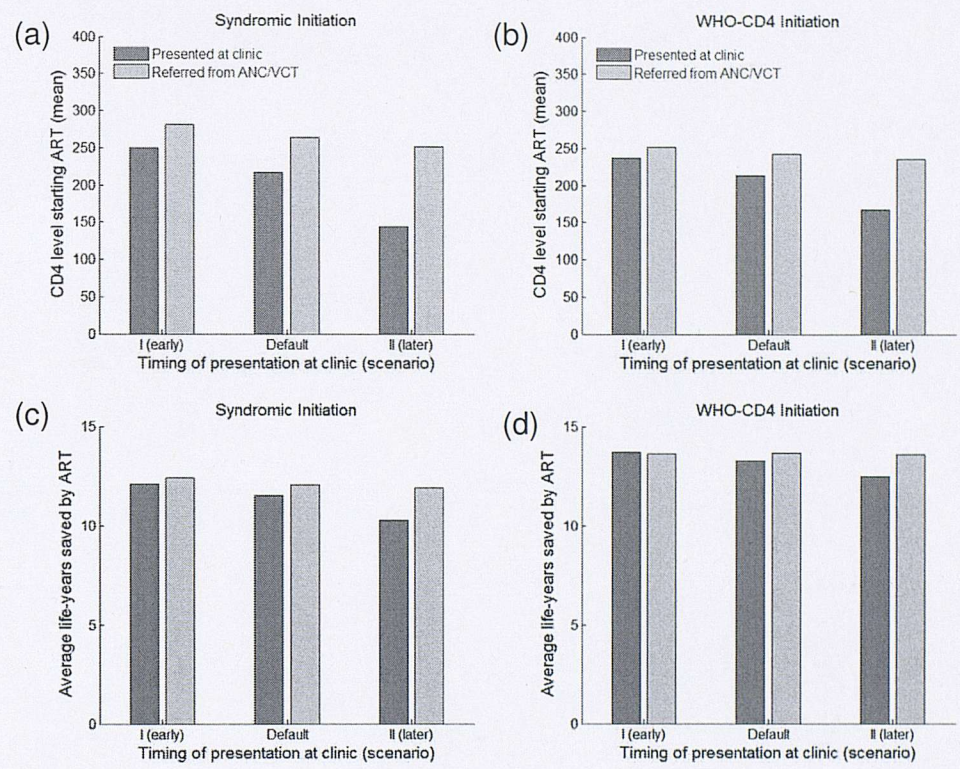


Figure 7.8 Alternative cohorts are compared where either all individuals enter care through referral (from ANC or VCT; light grey bars) or individuals can only enter care by presenting with symptoms (dark grey bars). Different assumptions are made about when individuals present at clinic (Figure 7.4): the ‘default’ scenario is based on data [340], the ‘early’ scenario represents individuals presenting at clinic in response to minor symptoms and the ‘later’ scenario represents individuals presenting at clinic after a longer delay. The measured outcome is the mean CD4 count at which ART is begun (a–b), and the mean number of life-years saved per person that is treated (c–d). Treatment is initiated syndromically (code 1; Table 7.4) (a,c) or using CD4 counts in the manner recommended by WHO (code 7; Table 7.4) (b,d). Individuals in care are monitored every six months.

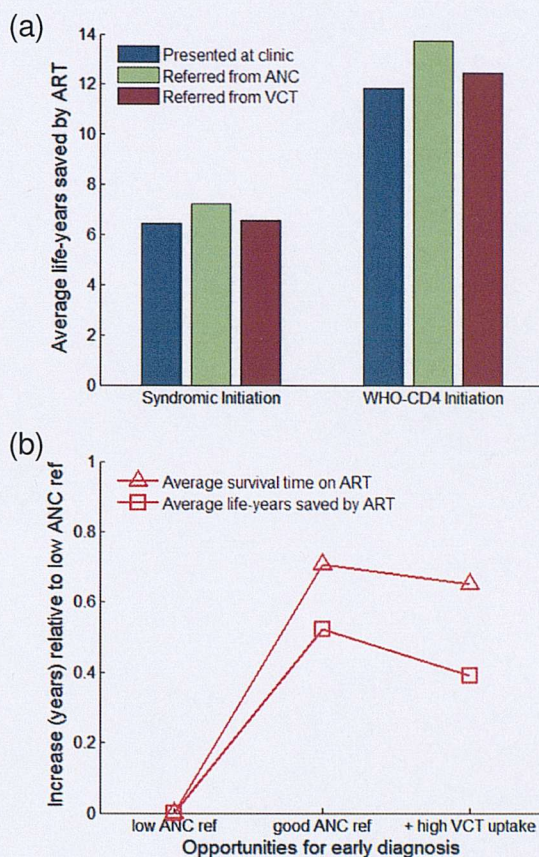


Figure 7.9 The impact of ART, by route of entry to care. **(a)** Average life-years saved by ART for those who enter the ART programme through ANC referral (blue bars), VCT referral (green bars) and those who present at clinic with symptoms (red bars), when ART is initiated syndromically or using CD4 counts in the manner recommended by WHO (codes 1 and 7; Table 7.4). **(b)** The effect of increasing opportunities for diagnosis on the average survival time on ART (triangles) and average life-years saved by ART (squares). Values shown are the difference (in years) relative to where referral from ANC is low and VCT uptake is low. The initiation rule is the WHO recommendations (code 7). In both panels, individuals are monitored every 6 months; ANC referral is assumed to be high and VCT uptake is assumed to be low.

Altogether, these three factors - the way in which ART is initiated, the opportunities for early diagnosis of infection and the frequency with which patients in care are monitored - combine to determine the improvement in life-expectancy at infection due to the availability of ART (Figure 7.10). Upgrading from syndromic initiation with low ANC referral rates, low VCT uptake and monitoring every twelve months will allow more individuals to enter care, more individual in care to be started on ART, and individuals on ART to have better survival chances (Figure 7.11). In total, this could save six more life-years per person treated, and improve overall life-expectancy at infection by seven years (Figure 7.10).

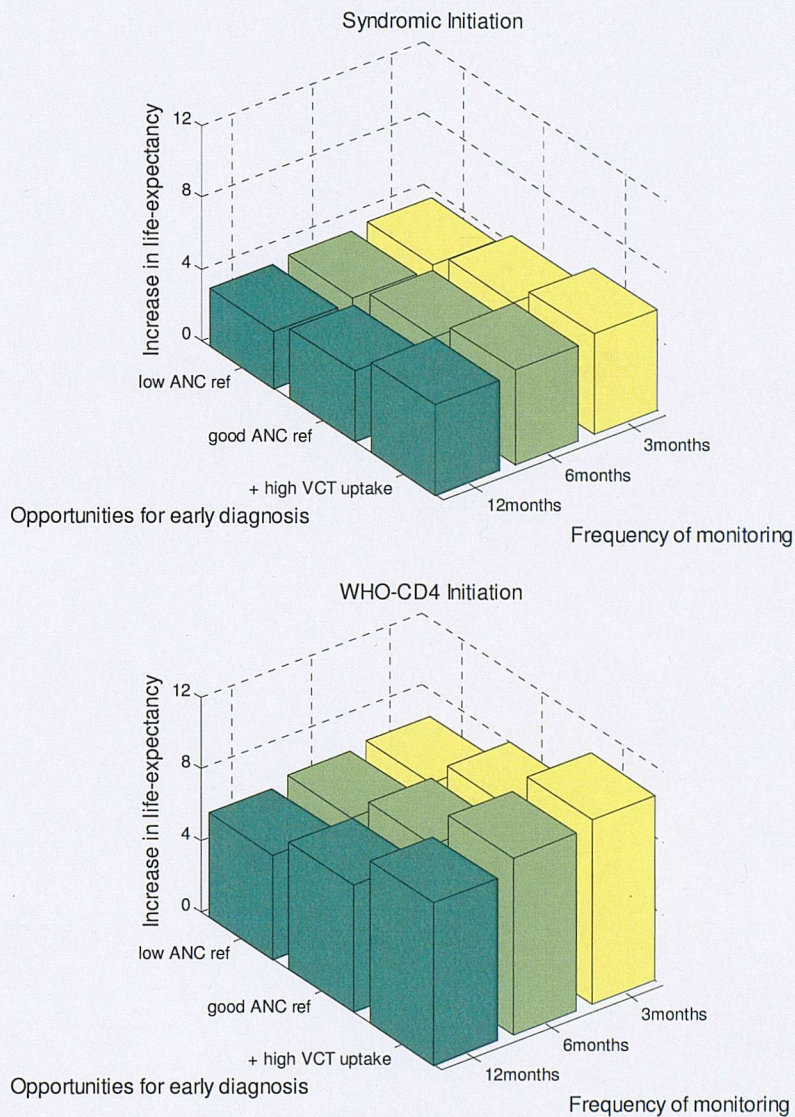


Figure 7.10 Improvements in life-expectancy at infection due to the availability of ART. In the upper panel only symptoms are used to initiate ART (code 1); in the lower panel one CD4 measurement is used in the way WHO recommend (code 7).

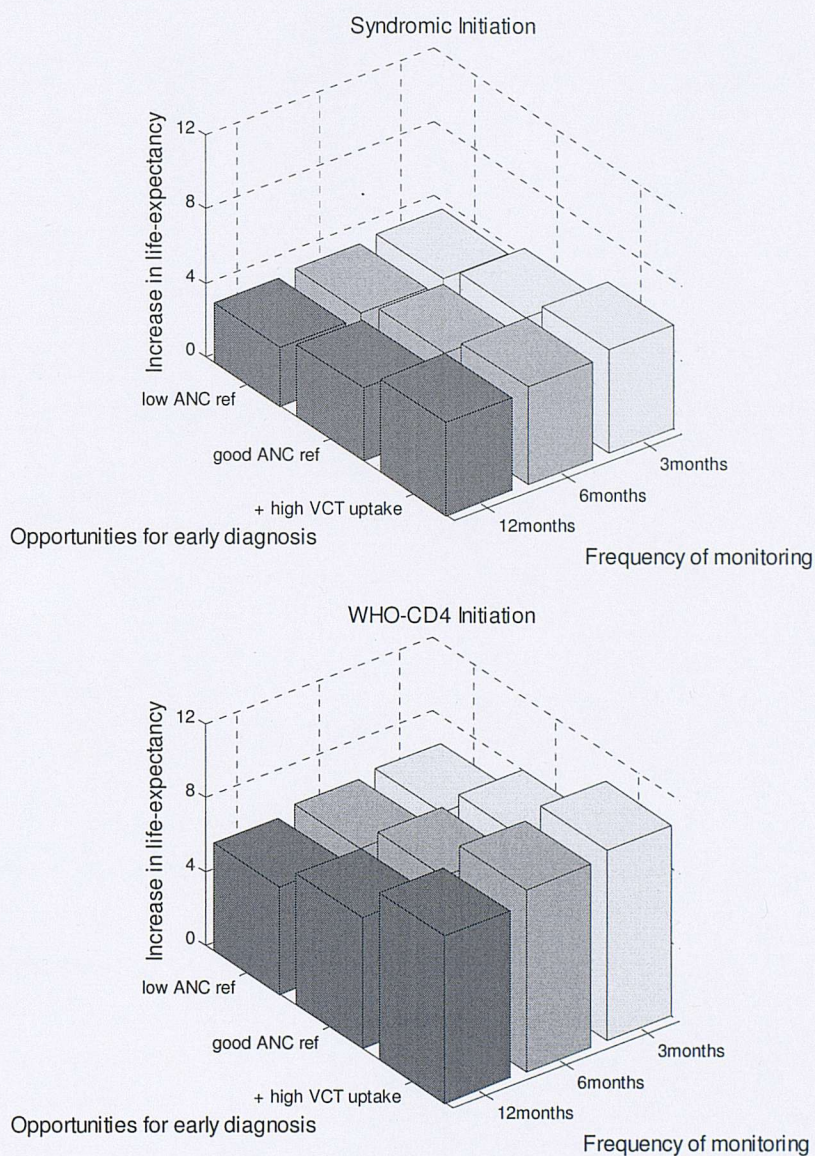


Figure 7.10 Improvements in life-expectancy at infection due to the availability of ART. In the upper panel only symptoms are used to initiate ART (code 1); in the lower panel one CD4 measurement is used in the way WHO recommend (code 7).

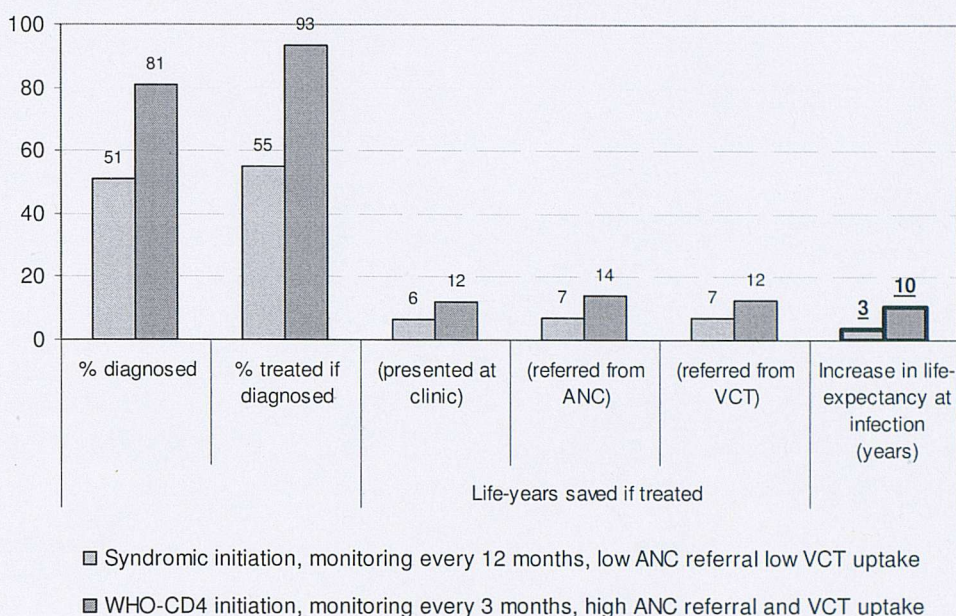


Figure 7.11 “Best” (dark grey bars) and “worst” (light grey bars) alternative ART programmes are compared. These scenarios are equivalent to the lowest and highest bars in Figure 7.10, but here the components of the reported increase in life-expectancy at infection are quantified. With CD4 initiation and more frequent monitoring from earlier, more individuals can enter care, more individuals in care can start ART, and individuals on ART can have better survival chances.

When more individuals are diagnosed and diagnosed at an earlier stage, there will be a greater case-load for the ART programme (Table 7.6). This will increase out of proportion to the overall benefit (life-years saved) because individuals that do not immediately need ART and would not otherwise enter care (slow-progressors and those at an early stage of infection) are unnecessarily monitored for many years. The efficiency of ART, as measured by the number of life-years saved per year on ART, also decreases if infections are diagnosed earlier, because some patients will start ART too soon (due to random error in CD4 measurement or early symptoms), when they would survive for some years more without.

Alternative strategies were investigated that could use the resources of the ART programme more efficiently (Tables 7.3, 7.4 and 7.7). In terms of life-years saved per person diagnosed and life-years saved per year of ART (a measure of efficiency), there is a clear advantage of using CD4 counts to check that asymptomatic individuals are not severely immune suppressed (Figure 7.12: codes 1-3 versus 4-7). If treatment is initiated at a higher CD4 level than WHO recommends (code 5) then more life-years are saved but with less efficiency since many individuals would survive for years after reaching this threshold without ART. The

opposite is true if ART is used more selectively by initiating at lower CD4 levels (code 6), where fewer life-years are saved but with greater efficiency.

Years saved per person diagnosed

Initiation Strategy	Interval between appointments (months)						
	I	II	III	IV	V	VI	VII
	12	6 [II]	3 [III]	12-3 (depn CD4) [IV]	6-24 (depn CD4 & age) [V]	6-12 (depn age) [VI]	On symptoms [VII]
1	6.5	6.9	7.3	6.6	6.0	6.6	2.8
2	5.8	6.4	6.8	6.4	6.1	5.8	0.9
3	6.5	6.7	6.8	6.5	6.1	6.5	2.7
4	11.9	12.8	13.5	13.4	12.6	11.8	5.1
5	15.3	15.2	15.2	15.2	15.3	15.4	8.8
6	9.3	11.0	11.9	11.9	11.1	9.6	3.3
7	11.8	12.3	13.2	13.0	12.7	11.9	4.9
8	12.0	13.5	14.5	14.5	13.4	12.2	5.1
9	12.7	14.0	14.8	14.9	13.9	12.8	5.2

Years spent on ART (1000s)

Initiation Strategy	12	6 [II]	3 [III]	12-3 (depn CD4) [IV]	6-24 (depn CD4 & age) [V]	6-12 (depn age) [VI]	On symptoms [VII]
1	4.887	5.235	5.503	4.889	4.390	4.948	2.051
2	4.390	4.823	5.220	4.828	4.463	4.411	0.618
3	4.835	5.126	5.179	4.883	4.516	4.898	1.983
4	8.414	9.201	9.643	9.616	8.930	8.469	3.561
5	11.293	11.342	11.449	11.465	11.284	11.479	6.362
6	6.296	7.611	8.054	8.106	7.613	6.609	2.263
7	8.335	8.896	9.446	9.454	9.065	8.421	3.472
8	8.589	9.648	10.378	10.358	9.485	8.739	3.523
9	8.977	10.004	10.607	10.728	9.988	9.069	3.621

Years saved per year on ART

Initiation Strategy	12	6 [II]	3 [III]	12-3 (depn CD4) [IV]	6-24 (depn CD4 & age) [V]	6-12 (depn age) [VI]	On symptoms [VII]
1	0.8	0.8	0.8	0.8	0.8	0.8	0.9
2	0.8	0.8	0.8	0.8	0.8	0.8	0.9
3	0.8	0.8	0.8	0.8	0.9	0.8	0.9
4	0.9	0.9	0.9	0.9	0.9	0.9	0.9
5	0.8	0.8	0.8	0.8	0.8	0.8	0.9
6	0.9	0.9	0.9	0.9	0.9	0.9	0.9
7	0.9	0.9	0.9	0.9	0.9	0.9	0.9
8	0.9	0.9	0.9	0.9	0.9	0.9	0.9
9	0.9	0.9	0.9	0.9	0.9	0.9	0.9

Number of appointments (1000s)

Initiation Strategy	12	6 [II]	3 [III]	12-3 (depn CD4) [IV]	6-24 (depn CD4 & age) [V]	6-12 (depn age) [VI]	On symptoms [VII]
1	4.0	7.0	13.2	3.9	2.6	4.2	1.0
2	4.1	7.2	13.3	5.1	3.2	4.4	1.0
3	3.9	7.1	13.2	4.0	2.6	4.2	1.0
4	3.7	6.5	12.2	6.6	3.9	4.0	1.0
5	2.9	5.0	9.2	3.8	2.4	3.1	0.9
6	4.2	7.8	14.6	8.9	5.2	4.6	1.0
7	3.7	6.5	12.2	6.8	4.0	3.9	1.0
8	7.5	12.8	23.4	12.2	7.5	8.0	1.9
9	3.7	6.4	11.4	5.9	3.7	4.0	1.0

Number of CD4 tests per person diagnosed

Initiation Strategy	12	6 [II]	3 [III]	12-3 (depn CD4) [IV]	6-24 (depn CD4 & age) [V]	6-12 (depn age) [VI]	On symptoms [VII]
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3	0.5	0.6	0.8	0.5	0.5	0.6	0.2
4	5.5	9.9	19.3	10.2	5.9	5.9	1.3
5	4.7	8.0	14.8	6.1	3.8	5.0	1.5
6	6.8	12.3	23.6	14.3	8.3	7.3	1.6
7	6.1	10.4	19.6	10.8	6.5	6.4	1.6
8	12.1	20.7	37.7	19.7	12.1	12.8	3.1
9	6.0	10.3	18.5	9.4	5.9	6.4	1.6

Table 7.7 Key indicator outcomes for alternative initiation rules and intervals between scheduled appointments. In all cases, the values relate to a cohort of 1000 HIV-infected individuals. ANC referral is assumed to be high and VCT uptake is assumed to be low.

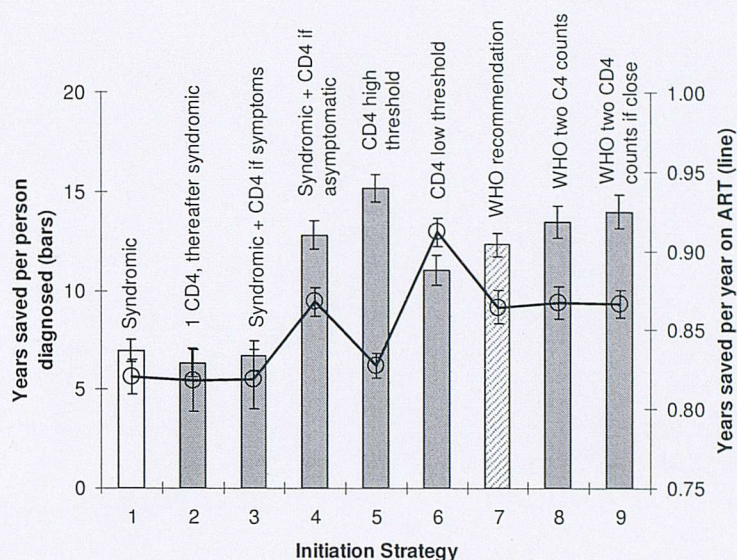


Figure 7.12 Comparison of possible initiation strategies (details in Table 7.4) in years saved per person diagnosed (grey bars on left axis) and years saved per year on ART (circles on right axis). Appointments are scheduled for every 6 months. Errorbars show ± 2 standard deviations from 20 stochastic runs.

Comparing all strategies together, those which use more CD4 counts tend to save more life-years and are more efficient. The advantage of CD4 counts is greater when the association between CD4 level and symptoms is weak (Figure 7.13). However, the model suggests that CD4 counts remains advantageous under a variety of scenarios for this relationship (Figure 7.13). The alternative strategies of testing everyone (code 7), and only testing those without symptoms (code 4) are similarly effective and efficient, although the latter requires up to 20% fewer CD4 counts, depending on the timing of entry to the health-care system and the functional relationship between symptoms and CD4 level (Table 7.7).

The physiological variability of CD4 counts means that taking two measurements instead of one could lead to better clinical decision making (Figure 7.12 and 7.14). In the model, when the decision to initiate ART (in the manner recommended by WHO) is based on the average of two measurements, approximately one extra life-year is saved per person diagnosed. However, this requires double the number of monitoring appointments and CD4 count laboratory resources. A more efficient way to overcome the variability in CD4 counts is to only make a second count if the first is just above the initiation threshold. Compared to using only one count, with this strategy on average there are 1.5 more life-years saved per person diagnosed. Moreover, the resources required (appointments and number of CD4 counts) is no greater than when only one count is made, since some border-line individuals start ART sooner and therefore require less pre-ART monitoring (Figure 7.14).

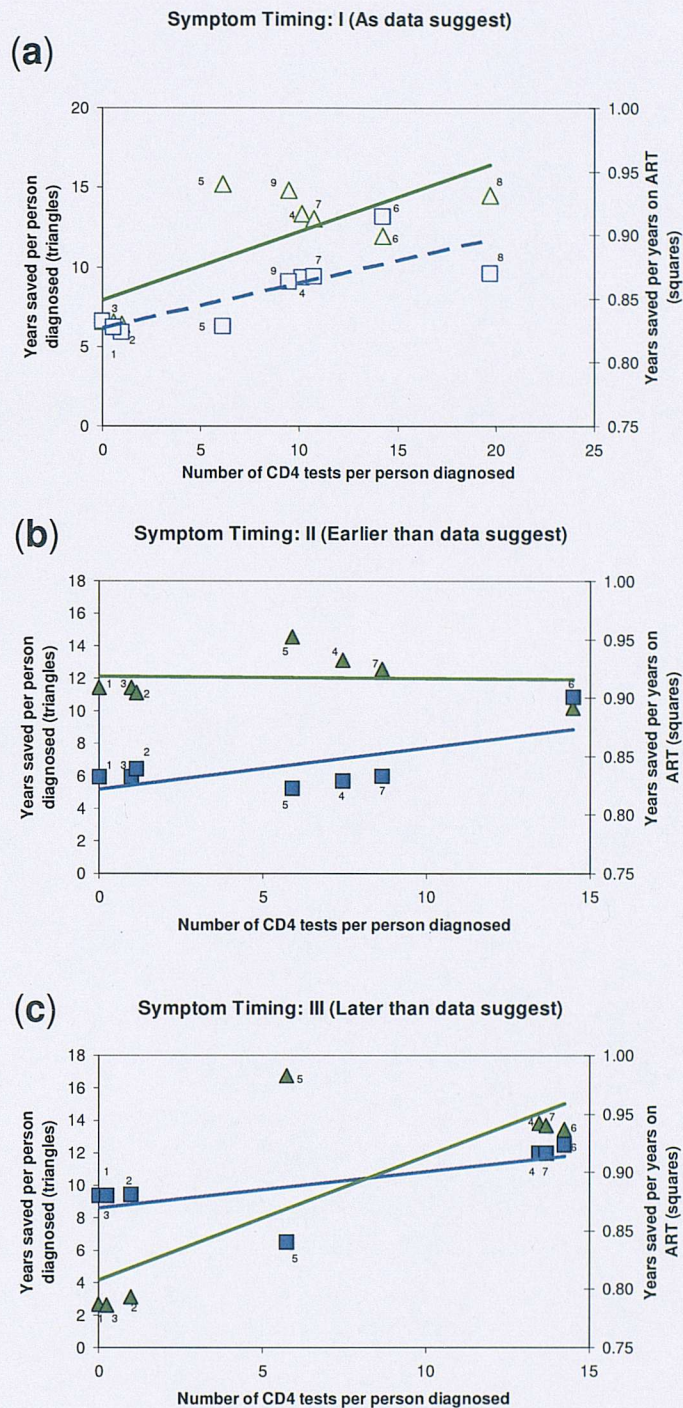


Figure 7.13 Comparison of possible initiation strategies in years saved per person diagnosed (triangles and solid line on left axis) and years saved per year on ART (squares and dashed line on right axis) plotted against the number of CD4 test used per person diagnosed. Lines are linear trends for ease of reading. The panels show the result when different assumptions on the timing of symptoms are made (see Figure 7.2): (a) Scenario I (default); (b) Scenario II (symptoms earlier than data suggest); (c) Scenario III (symptoms later than data suggest). Points are labelled with the initiation code (Table 7.4) to which they refer.

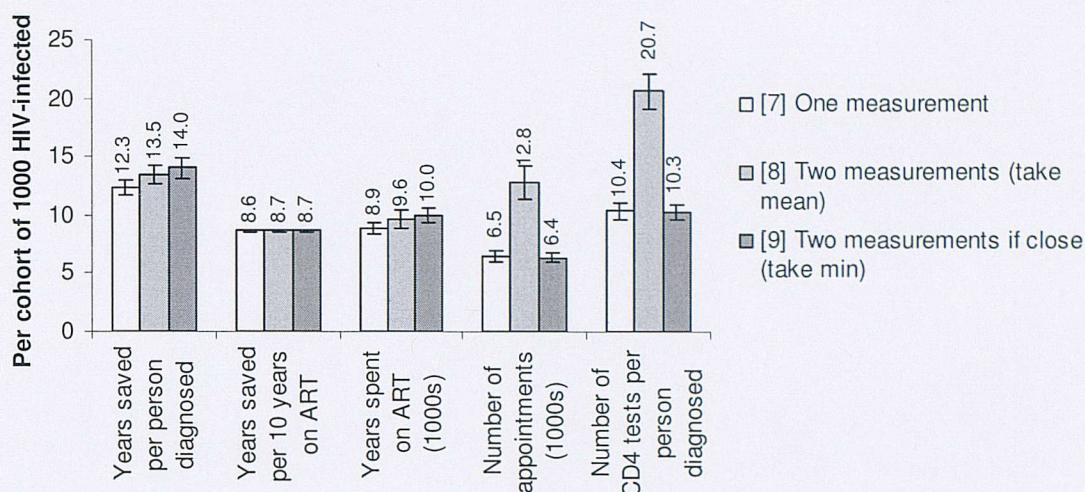


Figure 7.14 Key indicator outcomes for alternative initiation rules. Rule 7 is initiation as per WHO recommendation using one CD4 count (code 7; Table 7.4); rule 8 is the same but uses the mean of two CD4 counts; and, rule 9 instead only uses a second CD4 count if the first is close to the appropriate threshold (see Table 7.4). Appointments are scheduled for every 6 months, ANC referral is assumed to be high and VCT uptake is assumed to be low.

With frequent monitoring, the chosen ART initiation strategy can be implemented more accurately and more life-years can be saved (Figure 7.15). Scheduling appointments is essential because relying on individuals to attend when they experience symptoms excludes the advantages of early diagnosis. However, the incremental benefit of increasing the frequency of monitoring more than every six months is small although the additional number of appointments required is great. An efficient allocation of appointments is to schedule patients with high CD4 count to be monitored less frequently than those with low CD4 counts (code IV). The number of appointments is reduced further without a substantial reduction in the life-years saved if the scheduling system also takes account of age (code V), where young people are monitored less frequently than older people. The model predicts that in this system, there would be almost the same number of diagnostic appointments (0.3 more, per person infected) as if everyone is monitored every twelve months, but with 7-10% more life-years saved per person diagnosed.

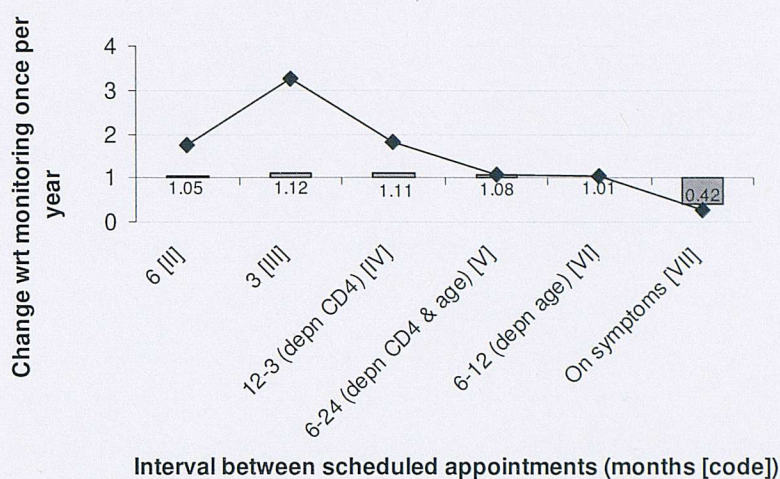


Figure 7.15 Comparison of different monitoring strategies (details in Table 7.4) in years saved per person (bars and numbers) and total number of appointments (line), each given relative to scheduling appointment every 12 months. The initiation scenario is the WHO recommendation with CD4 counts (code 7), ANC referral is assumed to be high and VCT uptake is assumed to be low.

7.5 Discussion

There is great potential for ART to alleviate premature death due to AIDS in resource-poor settings but poor management of those not yet needing treatment could prevent this potential from being realised. This modelling shows that using CD4 count to initiate ART could greatly increase the number of life-years saved because it enables individuals to receive ART before the immune system is severely weakened, when the effect of therapy is greatest [8, 157]. However, the full benefits of using CD4 counts will not be realised unless the health care system is competent at finding those in need of treatment and then monitoring patients regularly. Individuals tend to present at clinics once they have developed severe symptoms [340] which means that many will die before they are diagnosed or that they can only be given ART after their immune system is weakened. Regularly monitoring patients from early in their infection improves their prognosis because there will be the opportunity to start ART at the right time. Rates of early diagnosis may be improved by encouraging individuals to attend testing centres and in some settings, testing is now routine [306, 347]. Another way to start monitoring infected individuals early is by effectively referring women that have tested positive at ANCs.

These changes will dramatically increase the number of appointments with health-care workers and the amount of ART required, and without careful management this could be out of proportion to the benefits derived. The CD4 count is a more reliable indication of need for ART than the presence of symptoms, so CD4

initiation is expected to enable a more efficient use of ART. However, starting patients at higher CD4 thresholds than the WHO recommends (below 350 CD⁺ T-cells per microlitre of peripheral blood for those with symptoms and below 200 otherwise) will save fewer life-years per years on therapy. Avoiding testing those who have already developed symptoms could reduce the number of tests required without sacrificing effect because seldom do individuals have symptoms and a CD4 count higher than 350 (μl)⁻¹. With more frequent monitoring, it is more likely that ART can be initiated at the right time, whether syndromic or CD4-based initiation is used. The efficiency of appointment scheduling can be improved by prioritising older and more immune-suppressed patients to be monitored more frequently than others, since they will need ART first. Relying on individuals to return to the clinic when they develop symptoms would reduce the number of appointments required but is not an effective way to manage patients because symptoms unreliably predict the need for ART.

Early diagnosis and close monitoring of patients, though burdensome to the health-care system in the short-term, can help reduce future health-care needs. There will be less morbidity before therapy because it can be initiated promptly when required. Treating patients before symptoms develop could also help limit the onward transmission of HIV [222] and other infectious diseases that are enhanced by HIV infection, such as malaria [217], tuberculosis [218] and sexually transmitted infections [105], which may have not been diagnosed otherwise. Treatment of opportunistic infections from an earlier point could also help reduce the rate of immune-system deterioration, extending life-years before ART is required.

The model is limited by the lack of data on the relationship between the WHO staging criteria and CD4 count, which underlies the quantitative estimation of the benefits of different type of initiation. Although the average CD4 count among patients with certain conditions has been reported in many studies [172, 173, 348], it is not possible to know which of these patients a clinician would have staged as indicating for ART. The data that were used to parameterise the model come from a large study in Uganda [174] and a smaller study in Ethiopia [175] which both indicate that many individuals with low CD4 count would not be indicated for ART under WHO guidelines, although the exact functional relationship is not known. The sensitivity of the conclusions to the assumed relationship was investigated (Figure 7.9) and the model indicates that CD4 counting is still advisable even if symptoms develop before severe immune-suppression in the majority of people. In the absence of more detailed data, the model does not differentiate between WHO stage 3 and 4 disease and cannot replicate the clinical judgement which should be used in assessing how

soon patients with stage 3 symptoms should be started on ART [177]. Instead it identifies individuals that develop “severe symptoms of immune-suppression” which is analogous to WHO stage 3 and we explore the effects of using different CD4 thresholds for starting ART. Under the WHO recommendations, patients with stage 4 disease should be started on ART regardless of their CD4 level but in the model they will only be started if their CD4 count falls below the threshold being used for starting any symptomatic patient. However, patients with stage 4 disease will seldom have higher CD4 counts than this so we expect the model to only slightly underestimate the effect of following WHO recommendations. Another limitation is that the model does not capture other advantages and disadvantages to the timing of ART initiation besides survival, such as the chance of drug resistance developing or the impact of treatment on HIV transmission [154, 222].

A public-health approach to delivering ART has to consider how to initiate ART and organise the health-care delivery system to maximise the benefit for the population overall. Diagnosing infections earlier (through referrals from ANC or VCT), regularly monitoring patients and using CD4 counts to initiate ART will save more life-years and reduce future health-care needs. Without caring for patients at all stages of infection in this way, the long-awaited chance to substantially reduce AIDS-mortality with ART could be squandered.

Chapter 8: Discussion

8.1 Introduction

The unfolding HIV pandemic has been remarkably different in populations across the globe and across Africa, with the most extensive spread in southern Africa. As with any infectious disease there is a threshold combination of epidemiological parameters which allow for the spread of the virus. The differences between populations generating the very different epidemics have been subtle and difficult to measure reliably, but it appears that a combination of high transmission probabilities associated with other sexually transmitted infections and a lack of male circumcision and the contact patterns provided by commercial sex or by many with long standing overlapping casual partnerships allow for devastating epidemics. Much previous work has been done on how to capture the epidemiology of HIV in models and illustrating the relationship between interventions and control of the virus. However, much of this work has been broad in scope with qualitative insights into the pattern of effect of interventions. In this thesis, the focus has been on the application of models to practical policy related questions. The thesis illustrates how through the synthesis of questions posed by policy makers, empirical data and carefully tailored models, theoretical analyses can generate important insights.

Three inter-related areas have been covered: surveillance, behavioural interventions and anti-retroviral therapy (ART). What emerges is the need for more concerted efforts in prevention if the gains in treatment are to be capitalised upon. However, much still needs to be done to understand HIV prevention. Advocates, taken up by the emergency of a pandemic, have often said that 'we know what works'. In reviewing the evidence in this thesis it is clear that not only do we not know what works, but also that our epidemiological tools to evaluate what works are underdeveloped. This thesis provides a step in developing more appropriate evaluation of HIV interventions. In this Chapter some of these themes arising from earlier chapters are expanded upon, along with some examples of how this work might be further developed.

8.2 Discussion on Themes Arising From All Chapters

➤ *HIV testing could be the most important determinant of the success of prevention and treatment interventions.*

In Chapter 1, several hypotheses for why HIV has spread widely in southern Africa and have so far escaped control were discussed; one important factor is that HIV can be transmitted by apparently healthy people [286]. This means that neither the infected person nor those uninfected persons, with whom they form sexual

partnerships, is aware that there is risk of transmission. This sets HIV apart from most other infectious diseases, where infectious individuals show symptoms, enabling actions to be taken that limit opportunities for transmission [38]. With HIV infection, symptoms may not develop until the individual is severely immune-suppressed [174], by which time they have typically put others at risk for over a decade. Furthermore, by the time symptoms develop, the potential impact of ART on survival is much less than if ART had been started sooner [8].

Diagnostic tests indicating an HIV infection are now cheap and simple to use, and testing services are being scaled-up in many African countries [143, 149, 248, 347]. With HIV testing, individuals can find out whether they could transmit the infection or if they are at risk of acquiring it. The greater efficacy of behaviour change counselling that accompanies a test result, or that is conducted with couples found to be sero-discordant, has been demonstrated in trials [136, 303]. In a mathematical model of heterosexual transmission in Zimbabwe (Chapter 5), it was shown that if testing and counselling (TC) could generate long-lasting protective behavioural changes, then over the next decades, more than 20% of infections could be averted and the total number of patients starting ART could be reduced by several million.

The other important role of testing is that, following a positive test result, individuals can enter the health-care system. Compared with individuals that present at clinics and are diagnosed with HIV when already ill, those attending VCT whilst healthy stand a much better chance of surviving on ART for longer [8, 340]. Africa is not the only setting where delaying being tested is bad for one's health; in the Netherlands, the chance of dying in the first three years of ART was found to be half the national average in the hospital which admits men who are regularly tested for HIV in a cohort study [349]. Models of disease progression (Chapter 7) showed the advantage of monitoring individuals from earlier in the infection is especially great when CD4 counting machines are used; they can provide an early warning for immune-suppression while the potential impact of ART is greatest. Although these have become cheaper and easier to use [334], some countries still choose to rely on the symptoms of the patient alone [178].

Cheap HIV tests could provide a powerful way to reduce the insidious spread of HIV. However, data suggest that currently VCT is not serving either of these purposes very well [139, 146, 250]. This may be to do with the perceived antagonism between the two roles; in the rush to deliver ART to as many people as possible, behaviour change counselling of those not yet infected is neglected, and the profile of VCT clients is shifting towards those that already have severe symptoms [350]. Thus, uninfected individuals are not effectively counselled to change their behaviour, and

infected but healthy individuals are not entering care early enough. Two studies in Zimbabwe have indicated, alarmingly, that uninfected individuals receiving VCT services have increased their risk behaviour [146, 250]. Importantly, the VCT services used in these situations were quite minimal – in the study where VCT was not provided in a formal trial, 30% reported not having received any post-test counselling, and a further 45% reported having ten minutes or less. Whilst this highlights the need for higher quality services, official guidelines from the Centers for Disease Control and Prevention [351] are now more focussed on providing VCT in a clinical setting and substantially reducing the counselling training for those that administer the tests. This will allow more infected individuals to be monitored from earlier in their infection, but will do little to bolster behaviour change counselling for the greater part of patients who are not infected.

In another development, new prevention initiatives have been focussed on people living with HIV/AIDS (PLWHA), with the rationale that this efficiently directs efforts to the minority in the population that will transmit infection [352]. This seems like a promising step, and brings HIV control interventions into line with traditional epidemiological methods of 'case-finding'. Indeed, modelling alternative patterns of increasing condom use (Chapter 5) suggests that near consistent condom use in partnerships known to be sero-discordant could drive greater reductions in transmissions than substantial changes in condom use irrespective of sero-status. However, this limitation is that this requires very high levels of sero-status knowledge and currently the vast majority (75-92%) of PLWHA do not know they are infected [145]. This is an approach for the future, when testing is universal, re-testing is frequent, and highly-infectious new ('window period') infections can be detected [353]. For now, as VCT services are scaled-up, most clients counselled will be HIV negative and, modelling in this thesis makes it clear that the population level impact of VCT rests on behavioural changes amongst this group.

With the vast resources devoted to VCT, and the remarkable global increases in service availability [164], the results here illustrate that serious programmatic changes need to be made to balance providing increased opportunities for HIV diagnosis and enhancing the behaviour change counselling delivered to the uninfected majority.

➤ ***The population level impact of interventions cannot be inferred from individual level observational analysis of risk or be predicted accurately***

Ideas for behavioural interventions are often based on statistical analyses of risk factors for infection. However, it not always appreciated that individual level changes

do not necessarily translate into similar population level epidemiological effects. The impact of behavioural changes depends on many (unmeasured) variables, such as the distribution of risk behaviour, the phase of the epidemic and extent of contact between high and low risk populations. These factors have been summarised as the “epidemiological context” [86].

In this thesis, the impact of several potential behaviour change interventions on the heterosexual spread of HIV was studied. Delaying first sex, choosing sexual partners of the same age (Chapter 4) and choosing sexual partners on the basis of sero-status (Chapter 5), were all found to have minimal effects on overall transmission in the population. This is despite clear evidence that young women that start sex early and have older partners are more likely to be infected [40, 127], and contradicts our intuition about the benefit of selectively forming sero-concordant partnerships. It seems that the individual protective effects of these changes are small, and the benefit can be overwhelmed by behavioural adjustments in other parts of the population [135]. In the case of sero-sorting, infrequent testing can lead to inaccurate knowledge of sero-status, so that some individuals could selectively form sero-discordant partnerships (having been infected since their last negative test).

In other instances, the impact of behaviour change can be enhanced at the population level if young individuals and/or those with the highest risk behaviour are selectively targeted (Chapters 5 and 6). These groups contribute disproportionately to the onward spread of the epidemic, and, for this reason, it can be efficient to focus intervention effort on patients with sexually transmitted infections, mobile populations, sex workers and their clients. Although the contribution to transmission of high-risk groups is greatest in the early phase of the epidemic, models of the mature Zimbabwean epidemic indicate that these groups can still play an important part in sustaining high endemic levels (Chapter 6).

The epidemiological impact of an intervention can also be greater when the overall level of risk is lower, meaning that interventions can operate synergistically, and that crediting one intervention with a particular epidemiological outcome can be misleading. In Uganda several behavioural changes occurred at once, but reduction in concurrent partners has been singled out as the most important in driving the declines in incidence and prevalence [24]. In Zimbabwe, it seems that the situation is further complicated because sexually transmitted infections were successfully controlled and condom use reached high levels before prevalence data were systematically collected [17] (Chapter 2).

The impact of other interventions could be large or small depending on the pattern of partnership formation (e.g. in the case of interventions targeted to high-risk

groups; Chapter 6) and the degree to which this is controlled by men or women (e.g. in the case of young women delaying first sex; Chapter 4). These rather abstract properties of models cannot be measured directly, so the predicted impact of these interventions remains somewhat uncertain. Although it can be inconvenient, it is important to recognise this uncertainty and quantify it as far as possible. Over-estimating the impact of an intervention could lead, for example, to recruiting too few individuals to a community-randomised control trial, meaning that it would be under-powered (Chapter 6). On the other hand, under-estimating the potential impact of an intervention could lead to the credit for reduced incidence being wrongly attributed to another intervention.

Other types of uncertainty in the projected impact of interventions could be reduced through observational studies. The impact of VCT is very sensitive to how long any behavioural changes last but, since the trials have lasted only a few years, this is not known. Given the ongoing debate about the best policy direction for VCT, it is important to refine these predictions so that the potential impact of VCT can be properly compared with those of other types of intervention. This is an example of how mathematical modelling can highlight investigations that could contribute most to resolving pressing dilemmas in public health policy [201, 275].

➤ ***Population benefits versus individual benefits***

Although the impact of public health interventions must be maximised for the population, it can be difficult to set aside individual needs. In these circumstances, mathematical models are useful decision-making tools because they can quantify individual and population benefits in the short and longer term [201]. In this thesis, models have been used to develop several recommendations that apparently go against the benefit of the individual, but could be advantageous if the spared resources go elsewhere:

- i. VCT centres should not aim to repeatedly test 'low-risk' individuals (Chapter 5);
- ii. VCT centres should not devote their resources to finding individuals that have already developed severe symptoms of immune-suppression (Chapter 5 and 7);
- iii. Individuals with CD4 counts higher than 350 should not start ART (Chapter 7);
- iv. Young patients should not be the priority for intensive monitoring for ART needs (Chapter 7).

The common theme is that, at the expense of others, those groups that contribute most to the transmission of HIV should be prioritised for infection-prevention interventions and that those who could benefit most from health-care system resources should be prioritised for treatment interventions.

With new interventions (such as providing emotional support services for PLWHA, male circumcision or any new approach/technology), it is repeatedly stated that they should not be funded at the expense of other interventions [354]. With the exponentially increasing funds available [83, 164, 355], this may actually be theoretically possible, although when funding reaches a plateau, some tougher choices will have to be made. This is routine for other institutions like the National Institute for Health and Clinical Excellence (NICE) in the UK that seeks to optimise public spending on new medicines and has restricted proven life-saving treatments that are considered to be too expensive [356, 357]. However, the task is more formidable in the case of HIV interventions, where the benefits of interventions averting infections are theoretical and uncertain, and trade-offs between averting future infections or current morbidity and mortality are central.

Misalignments between the individual and population levels can be identified and quantified, if not resolved, with the help of the mathematical modelling. An important current debate is about whether HIV testing should be compulsory [306, 358]. Models quantify the benefit - the more people that are tested, the better prevention and intervention programmes can operate (Chapters 4 and 7) - but it must be left to others to consider how this compares with the cost of limiting the individuals' right 'not to know'. The 'Siracusa Principles' [359, 360] set out conditions under which it may be acceptable to restrict individual rights for the population benefit (for example, that restrictions must be strictly provided for by law, neither arbitrary nor discriminatory, based on objective considerations, necessary to respond to a pressing social need, proportional to the social aim, and no more restrictive than necessary to achieve the intended purpose). These were met when individuals were forcibly quarantined in the 2003 SARS epidemic [361], and in 2007 when a man arrived in America with a highly-resistant strain of Tuberculosis [362]. A British HIV-infected man was convicted in 2005 of causing grievous bodily harm to a woman whom he knowingly placed at risk of infection [363]. But, does this mean it is time for testing to become compulsory i.e. no longer voluntary? In South Africa, public opinion may be heading in that direction [364] but this seems premature. A key issue is whether every non-mandatory strategy as been exhausted – which for testing in Africa is not yet the case.

➤ ***Measuring the effectiveness of interventions is difficult in trials, but may be possible through analysis of sentinel surveillance.***

In the light of the complicated relationship between individual behaviour and population level epidemiological impact, it is essential that the success of interventions is properly assessed. Two types of methods for doing this are explored in this thesis: analysis of sentinel surveillance data (Chapter 2), and conducting formalised cluster/community-randomised control trials (CRCTs) (Chapter 6). Whilst the latter is recognised to provide a higher standard of evidence, a number of practical factors can limit the usefulness of this type of study.

Modelling in Chapter 6 showed that, in response to an intervention, HIV incidence can reduce slowly at first and gather pace over time. Targeting high-risk groups can further slow the reduction in incidence in the general population because it takes time for prevalence in high-risk groups to subside. This means that for a trial to be sufficiently powered, the constraints on the similarity between clusters, the follow-up rate of participants, the number of participants in each community and the duration of follow-up are more stringent than at first it appears. Therefore, most feasible 3 or 4 year CRCTs would be underpowered, allowing few conclusions to be drawn from a negative result. Although high-quality, adequately powered trials are in the public interest so that resources can be invested efficiently, running long duration CRCTs could be considered to go against the interest of individuals, because those in the control arm are denied access to the intervention for longer. It also takes longer for society to benefit from the lessons of the trials.

In fact, even with a positive trial result, it would not necessarily be clear that the intervention would work in another setting [86, 119]. The epidemiological context will modulate its impact and it is unlikely the intervention could be applied as assiduously when scaled-up as it can be in a trial. For these reasons, using data collected at the national level, when an intervention is already to scale, seems like a promising option [70, 118].

Monitoring the evolution of the HIV epidemic has relied on sentinel surveillance estimates of HIV prevalence among women attending antenatal clinics, and latterly, also on behavioural surveys [53, 365]. Unfortunately, sufficient credence is not always lent to analyses based on such data. This may be for several reasons. First, the comparison is “ecological”, meaning that regionally-aggregated prevalence and behavioural trends are used, potentially obscuring confounding variables at the

individual level. Second, it has been recognised that the diminishing availability of susceptible individuals in the population and the shifting risk distribution can mean that declines in either incidence or prevalence do not necessarily signify behavioural changes [54]. Lastly, prevalence among pregnant women may not represent prevalence in the general population as HIV infection and fertility could be positively associated (because they arise from similar behaviours) or negatively associated (because HIV-infection can lead to sub-fertility) and this could change over time [17, 48, 49].

However, work in this thesis has shown that greater use could be made of sentinel surveillance data by incorporating these complexities (in so far that they modulate the result of the interest) in mathematical models and comparing simulated output with observations. By simulating an epidemic scenario that included, to extreme levels, all those factors that could potentially contribute to a prevalence decline not related to behavioural changes, a conservative conclusion could be drawn that behaviour change had played a role in observed prevalence downturns in Zimbabwe, Kenya and Haiti (Chapter 2). Further weight is lent to such findings if concomitant behavioural surveys indicate substantial behavioural changes, and this was the case for Zimbabwe and Kenya.

It is important that conclusions drawn about prevalence declines are robust and conservative, lest the furore that surrounded the declines observed in Uganda [82, 85] be repeated. The greatest magnitude of prevalence decline can be generated by maximising the initial heterogeneity in risk behaviour (to ignite a large epidemic), by allowing AIDS mortality to deplete the population of those with the greatest risk (so that incidence settles to a lower level), and by minimising the survival time with HIV (so that prevalence trends follow more closely the sharp decline in incidence). The modelling work also suggested that although biases in the sample of pregnant women probably lead to inaccurate estimates of the absolute prevalence level in the general populations, trends in prevalence are not obscured or artificially generated. This is because fertility declines with early HIV infection, meaning that the subfertility bias will have excluded infected women from the ANC sample since the earliest records.

Furthermore, in Chapter 3, methods to estimate incidence from successive measures of prevalence were developed from previous work [67, 69, 255] and their performance was tested using simulated data and actual data from three community-based cohort studies in Africa. These methods could be used with the new rounds of Demographic and Health Surveys (DHS) that measure HIV prevalence in the general

population. With these methods, changes in incidence could be detected sooner and characterised more accurately than when using prevalence data only.

8.3 Future Work

Two lines of research emerge from this work that could usefully be pursued; further development of existing theoretical frameworks and the development of a new framework. These are now briefly discussed in turn.

8.3.1 Development of Existing Theoretical Frameworks

The analysis of prevalence trends in the future will contend with further complications than are considered here. As access to ART increases, prevalence in the general population will increase as those infected live longer [222], but long-term survival on ART is not known, and it seems likely that it will change as methods of initiation and patient management evolve. Whether prevalence rises in ANC measures will also depend on how fertility rates recover on therapy. Prevalence trends among young people may escape these biases but these data can have smaller sample sizes and be distorted by shifting patterns of sexual debut [49]. Also, as the coverage of sentinel surveillance sites has expanded, the disparity between urban and rural epidemics has become clear, raising new issues for interpreting aggregated trends in prevalence. Only by aggregating trends over multiple sites do we get the statistical precision required to detect changes, but how will these changes be altered if sub-regional epidemics are out of phase?

For simplicity and generalisability, the contribution of STIs to HIV transmission has not been explicitly described in the models used here. This is despite evidence that some infections can increase the chance of acquisition and transmission of HIV [105]. It was hoped that by varying the average chance of transmission of HIV between different settings (to match greater epidemic prevalence in Kenya than Haiti, for example: Chapter 2) and allowing the risk of infection and transmission to vary within a population (between the risk groups), would implicitly capture different compositions and rates of STIs in those population and sub-populations, that are thought to have contributed to alternative epidemic trajectories. However, it is possible that an explicit description of STI transmission in maturing epidemics would reveal processes that could contribute to observed downturns in prevalence. If STI epidemics are more likely to fade-out when the riskiest part of the population is depleted then transmission from that group would decline further than these models have predicted. The much greater-than-observed heterogeneity in risk used in these models, though, is likely to have exaggerated possible declines in prevalence (so that

conservative conclusions can be drawn in comparison with observation), even though this particular effect has not been included.

In the ART era, the age-specific mortality rates that can be used to estimate HIV incidence from successive measures of prevalence will also have to be updated and the performance of these methods re-evaluated. Although it is unlikely to be the case in the short-term [9], if the pattern of ART access is similar in many countries in the long-term, standard mortality rates could still be used.

The predicted impact of interventions will also have to take account of an increasing fraction of the population receiving ART. For instance, transmission between older men and younger women may decrease as more of the older men start ART. Alternatively, increased survival of older men on ART could generate more demand for sexual partnerships with young women, increasing transmission overall. ART could prolong marriages, but could mean that more orphans are left behind, who can be the most likely to fall into riskier sexual behaviours, such as starting sex early and forming partnerships with older men [366]. Increased survival amongst those with the riskiest sexual behaviour could also sustain higher endemic levels of STIs, indirectly promoting HIV transmission [367, 368] and offsetting the direct advantages in reduced HIV transmissibility [286].

With an increasing number of expensive options for preventing new infection (including ART, circumcision, vaginal microbicides), it will be more important to develop priorities and make effectiveness and cost-effectiveness comparisons between a variety of intervention 'packages'. Analysing the impact of new 'bio-medical' interventions will require greater understanding of how these options would be used together and whether this leads to behavioural disinhibition. In the same way that people who use sunscreen tend to over-compensate for the reduced risk of melanoma by spending much more time in the sun [369], women may start to use microbicides gels instead of condoms, putting themselves at greater risk [195]. By the same token, if a male is circumcised and his perception of the reduced risk of infection and transmission leads to riskier sexual practices, then, at the population level, the benefit of circumcision interventions will be undermined and the burden of infection will be shifted further onto women [27, 370], which has important implications for the demographic impact of the epidemic [354]. More complicated interventions introduce further uncertainties to estimates and projections, and, as before, these can be best identified with the help of models, but only fully quantified with further data collection.

8.3.2 A New Theoretical Framework: The Influence of the Changes in Risk over the Life-Course

In this thesis, it was important to restrict as far as possible the complexity of the models used, to avoid unnecessary details interfering with the particular analysis of interest. However, in comparing these models with behavioural data and considering further analyses concerning long-term projections and demographic and epidemiological feedback mechanisms, an intriguing limitation was apparent; existing models fail to identify how an individual's risk (in terms of the types of partnerships they form) can change over the lifetime, and how this personal journey will be responsive to life-course events that happen to the individuals and to others in the community.

As discussed in Chapter 1, heterogeneity in the risk of infection is an important factor in the generalised spread of HIV [37] and the extent of contact between “high” and “low” risk groups partly determines the speed and extent of epidemic spread and the potential effect of behaviour change interventions [42, 371]. In concentrated epidemics, where most transmission is driven by high-risk behaviour, simple descriptions of risk have had great explanatory power [72]. However, in the mature generalised epidemics of Africa, a more detailed account of risk may now be needed. A minority of infections are attributed to paid-for sex [371, 372] and the large number of sero-discordant marital partnerships [307, 373, 374] indicates that in the coming years most new infections could occur within mutually-faithful monogamous marital partnerships. The models in this thesis aim to qualitatively capture the range of types of sexual partnerships (casual partnerships of short duration and a small number of unprotected sex acts versus regular partnerships of longer duration and a large number of unprotected sex acts) but partners are not explicitly identified, fertility is not linked to partnership status, parenthood is not traced, and the mixture of partnerships formed by each individual is constant over their life or changes according to the prevailing population structure.

Observations from cross-sectional studies, longitudinal studies and trials have accumulated that are not readily explained by existing transmission models. A substantial proportion (in some settings, a majority) of discordant partnerships in Africa include an infected women and an uninfected man [374], whilst standard ideas predict that men should typically be the source of infection to their wives [40, 375]. In the Manicaland HIV/STD intervention trial, protective behavioural changes among men attending beer halls, did not translate into reduce incidence in their communities as expected [94]. Community-based cohort studies in Uganda, Tanzania and Zimbabwe show that there are two periods when women are most at risk of infection;

when they are young and when they are middle-aged (unpublished analyses from the ALPHA Network group of cohort studies [376]). These regularities are also detected in other African settings, where incidence is estimated from DHS sero-surveys (Chapter 3).

Sexual behaviour changes substantially over the life-course. Among young people, different risk behaviours can be associated [127, 377] and this can be linked to the socio-economic circumstances of the immediate family [92], having relocated [377] and being orphaned [366]. In general, however, indicators of recent risk behaviour are not correlated with long-term indicators [378] and whilst long-term indicators do roughly predict the distribution of infection [127, 378], marital status is always a key modifying variable [377, 379]. Many young unmarried women tend to form concurrent partnerships with much older men, but they typically marry men of a more similar age to their own [40]. In recent times, young men have started marrying later, possibly because they cannot afford the bride price, and, in the interim, they may be forming more casual partnerships [372]. Although most married men do not pay for sex directly, many have long-term extramarital partnerships [375].

The HIV epidemic could also directly interact with the life-course through its effect on fertility [47], which could increase the likelihood of divorce [380], and mortality, which could alter the demographic composition of the population and drive trends in the age difference between sexual and marital partners. Following the death of their husband, formerly “low-risk” women may form new short-term partnerships [270] – putting others at risk if they are already infected, or themselves at risk if not.

An important prediction of existing models (that was central to Chapter 2) is that in maturing epidemics, incidence may decrease because those with the riskiest sexual behaviour will be selectively removed by AIDS mortality [54, 91, 231]. On the other hand, if being widowed forces women to seek new partners, orphaning leads to increased risk and sub-fertility promotes marital instability, then epidemics may be fuelled rather than slowed as they mature. Understanding which of these alternative scenarios is more likely will contribute to the interpretation of observed epidemiological trends; for instance, it could be that stable HIV prevalence is the hallmark of protective behavioural changes counterbalancing the natural tendency for epidemics to ‘self-excite’.

Optimising and prioritising interventions will be clearer from the perspective of the life-course so that the effect of gaps, overlaps and dynamic interactions can be identified. Interventions to change sexual behaviour are often directed towards particular life-courses stages (e.g. abstinence for young people, faithfulness for married couples [284]) and their effects could be modified by behaviour at other life-

stages [381]. Interventions may even alter the life-course: voluntary counselling and testing aimed at married/pre-marital couples [382] can lead to separation if they are sero-discordant [142]. Furthermore, for many, the point of entry to testing and treatment will be at a key life-course event – pregnancy, marriage or the death of a spouse – and understanding the position of individuals in the sexual network at these times will help predict where demand will arise and the potential effect of treatment on transmission. Understanding how ART will reshape the overall demographic impact of the epidemic also demands an explicit account of behaviour, transmission and disease progression in the partnerships that produce children and leave behind orphans.

8.4 Final Remarks

The HIV epidemic is accelerating into its second quarter-century but funding, data and technical insights are accumulating that could finally bring it under control. Uganda and Zimbabwe have shown that interventions that encourage ordinary people to change their sexual behaviour can turn back the epidemic. In the next twenty-five years, several high-tech tools will be added to the public health arsenal, which, in combination with existing efforts in testing and counselling for behaviour changes, may be sufficient to drive the epidemic down to much lower levels throughout the world. The public health research agenda between now and then will be focussed on carefully assessing interventions – perhaps in small trials or on a larger scale using sentinel surveillance – and finding programmatic strategies that optimally share resources between interventions to protect individual and communities. Mathematical modelling will be at the centre of this research, providing a precise framework that can incorporate all the necessary biological and behavioural processes to guide policy in the short and long term.

References

1. *Pneumocystis pneumonia* - Los Angeles. MMWR Morb Mortal Wkly, 1981. **30**: p. 250-2.
2. UNAIDS, *2006 Report on the global AIDS epidemic*. 2006: Geneva. p.
http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.
3. Sarngadharan, M.G., et al., *Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS*. Science, 1984. **224**(4648): p. 506-8.
4. Popovic, M., et al., *Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS*. Science, 1984. **224**(4648): p. 497-500.
5. Gallo, R.C., et al., *Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS*. Science, 1984. **224**(4648): p. 500-3.
6. Stover, J., et al., *Can we reverse the HIV/AIDS pandemic with an expanded response?* Lancet, 2002. **360**(9326): p. 73-7.
7. Stover, J., et al., *The global impact of scaling up HIV/AIDS prevention programs in low- and middle-income countries*. Science, 2006. **311**(5766): p. 1474-6.
8. Braitstein, P., et al., *Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries*. Lancet, 2006. **367**(9513): p. 817-24.
9. Boerma, J.T., et al., *Monitoring the scale-up of antiretroviral therapy programmes: methods to estimate coverage*. Bull World Health Organ, 2006. **84**(2): p. 145-50.
10. Salomon, J.A., et al., *Integrating HIV prevention and treatment: from slogans to impact*. PLoS Med, 2005. **2**(1): p. e16.
11. U.S. Census Bureau International Data Base, *Midyear Population, by Age and Sex*. available from <http://www.census.gov/ipc/www/world.html>, 2007.
12. UNICEF, *Monitoring the situation of children and women*. <http://www.childinfo.org/>, 2007.
13. UNAIDS, UNICEF, and USAID, *Children on the Brink - A joint report of new orphan estimates and a framework for action*. 2004.
14. Birmingham, K., *UN acknowledges HIV/AIDS as a threat to world peace*. Nat Med, 2000. **6**(2): p. 117.
15. Asamoah-Odei, E., J.M. Garcia Calleja, and J.T. Boerma, *HIV prevalence and trends in sub-Saharan Africa: no decline and large subregional differences*. Lancet, 2004. **364**(9428): p. 35-40.
16. Mahomva, A., et al., *HIV prevalence and trends from data in Zimbabwe, 1997-2004*. Sex Transm Infect, 2006. **82 Suppl 1**: p. i42-7.
17. UNAIDS, *Evidence for HIV decline in Zimbabwe: a comprehensive review of the epidemiological data*. 2005. p. www.epidem.org.

18. Shelton, J.D., D.T. Halperin, and D. Wilson, *Has global HIV incidence peaked?* Lancet, 2006. **367**(9517): p. 1120-2.
19. Carael, M., *Sexual behaviour*, in *Sexual behaviour and AIDS in the developing world*, J. Cleland and B. Ferry, Editors. 1995, Taylor and Francis: London.
20. Halperin, D.T. and H. Epstein, *Concurrent sexual partnerships help to explain Africa's high HIV prevalence: implications for prevention*. Lancet, 2004. **364**(9428): p. 4-6.
21. Wellings, K., et al., *Sexual behaviour in context: a global perspective*. Lancet, 2006. **368**(9548): p. 1706-28.
22. Boily, M.C., C.M. Lowndes, and S. Gregson, *Population-level risk factors for HIV transmission and 'the 4 Cities Study': temporal dynamics and the significance of sexual mixing patterns*. Aids, 2002. **16**(15): p. 2101-2.
23. Morris, M. and M. Kretzschmar, *Concurrent partnerships and the spread of HIV*. Aids, 1997. **11**(5): p. 641-8.
24. Stoneburner, R.L. and D. Low-Beer, *Population-level HIV declines and behavioral risk avoidance in Uganda*. Science, 2004. **304**(5671): p. 714-8.
25. Ferry, B., et al., *Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection*. Aids, 2001. **15 Suppl 4**: p. S41-50.
26. Auvert, B., et al., *Male circumcision and HIV infection in four cities in sub-Saharan Africa*. Aids, 2001. **15 Suppl 4**: p. S31-40.
27. Williams, B.G., et al., *The potential impact of male circumcision on HIV in Sub-Saharan Africa*. PLoS Med, 2006. **3**(7): p. e262.
28. Weiss, H.A., M.A. Quigley, and R.J. Hayes, *Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis*. Aids, 2000. **14**(15): p. 2361-70.
29. Siegfried, N., et al., *HIV and male circumcision--a systematic review with assessment of the quality of studies*. Lancet Infect Dis, 2005. **5**(3): p. 165-73.
30. Auvert, B., et al., *Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial*. PLoS Med, 2005. **2**(11): p. e298.
31. Bailey, R.C., et al., *Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial*. Lancet, 2007. **369**(9562): p. 643-56.
32. Gray, R.H., et al., *Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial*. Lancet, 2007. **369**(9562): p. 657-66.
33. Aidsmap, *Women may be at heightened risk of HIV infection immediately after male partner is circumcised* <http://www.aidsmap.com/en/news/3CBF12A3-A1AC-4A0E-A79C-54FC6EF93E28.asp> (accessed 14th August 2007), 2007.
34. Kapiga, S.H., et al., *The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania*. Aids, 1998. **12**(1): p. 75-84.
35. de Gourville, E.M., et al., *Risk factors for concordant HIV infection in heterosexual couples in Trinidad*. Int J STD AIDS, 1998. **9**(3): p. 151-7.

36. Gray, R.H., et al., *Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. Rakai Project Team. Aids*, 2000. **14**(15): p. 2371-81.
37. Anderson, R.M. and R.M. May, *Infectious diseases of humans*. 1991, Oxford: Oxford university press.
38. Fraser, C., et al., *Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A*, 2004. **101**(16): p. 6146-51.
39. French, K., S. Riley, and G. Garnett, *Simulations of the HIV epidemic in sub-Saharan Africa: sexual transmission versus transmission through unsafe medical injections. Sex Transm Dis*, 2006. **33**(3): p. 127-34.
40. Gregson, S., et al., *Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet*, 2002. **359**(9321): p. 1896-903.
41. Luke, N. and K.M. Kurz, *Cross-generational and transactional sexual relationships in Sub-Saharan Africa*. 2002, International Centre for Research on Women: Washington, D.C.
42. Garnett, G.P. and R.M. Anderson, *Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. Philos Trans R Soc Lond B Biol Sci*, 1993. **342**(1300): p. 137-59.
43. Museveni, Y.K., *AIDS is a socioeconomic disease*, in *What is Africa's problem?*, E. Kanyogonya, Editor. 2000, University of Minnesota Press: Minneapolis. p. 247-255.
44. Chin, J., *Public health surveillance of AIDS and HIV infections. Bull World Health Organ*, 1990. **68**(5): p. 529-536.
45. Chin, J. and J. Mann, *Global surveillance and forecasting of AIDS. Bull World Health Organ*, 1989. **67**(1): p. 1-7.
46. Zaba, B. and S. Gregson, *Measuring the impact of HIV on fertility in Africa. Aids*, 1998. **12 Suppl 1**: p. S41-50.
47. Ross, A., et al., *HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. Aids*, 2004. **18**(5): p. 799-804.
48. Garnett, G.P. and S. Gregson, *Monitoring the course of the HIV-1 epidemic: the influence of patterns of fertility on HIV-1 prevalence estimates. Mathematical Population Studies*, 2000. **8**(3): p. 251-277.
49. Zaba, B., T. Boerma, and R. White, *Monitoring the AIDS epidemic using HIV prevalence data among young women attending antenatal clinics: prospects and problems. Aids*, 2000. **14**(11): p. 1633-45.
50. Gregson, S. and G.P. Garnett, *Contrasting gender differentials in HIV-1 prevalence and associated mortality increase in eastern and southern Africa: artefact of data or natural course of epidemics? Aids*, 2000. **14 Suppl 3**: p. S85-99.
51. Glynn, J.R., et al., *Factors influencing the difference in HIV prevalence between antenatal clinic and general population in sub-Saharan Africa. Aids*, 2001. **15**(13): p. 1717-25.

52. Gregson, S., et al., *Study of bias in antenatal clinic HIV-1 surveillance data in a high contraceptive prevalence population in sub-Saharan Africa*. *Aids*, 2002. **16**(4): p. 643-52.
53. Ghys, P.D., et al., *Measuring trends in prevalence and incidence of HIV infection in countries with generalised epidemics*. *Sex Transm Infect*, 2006. **82**(suppl_1): p. i52-56.
54. UNAIDS Reference Group on Estimates Modelling and Projections, *Trends in HIV incidence and prevalence: natural course of the epidemic or results of behavioural change?*, in *UNAIDS Best practice collection*. 1999: Geneva, Switzerland.
55. Kilian, A.H., et al., *Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda*. *Aids*, 1999. **13**(3): p. 391-8.
56. World Health Organization/United Nations Joint Programme on AIDS, *Second Generation Surveillance for HIV: the Next Decade*. 2000: Geneva.
57. Zaba, B., et al., *The role of behavioral data in HIV surveillance*. *Aids*, 2005. **19 Suppl 2**: p. S39-52.
58. Garnett, G.P., et al., *Behavioural data as an adjunct to HIV surveillance data*. *Sex Transm Infect*, 2006. **82**(suppl_1): p. i57-i62.
59. UNAIDS Reference Group on Estimates Modelling and Projections, *Improved methods and assumptions for estimation of the HIV/AIDS epidemic and its impact: Recommendations of the UNAIDS Reference Group on Estimates, Modelling and Projections*. *Aids*, 2002. **16**(9): p. W1-14.
60. Stover, J., *Projecting the demographic consequences of adult HIV prevalence trends: the Spectrum Projection Package*. *Sex Transm Infect*, 2004. **80 Suppl 1**: p. i14-18.
61. *Demographic and Health Surveys - Providing information for informed decisions in population, health and nutrition*. <http://www.measuredhs.com>.
62. Boerma, J.T., P.D. Ghys, and N. Walker, *Estimates of HIV-1 prevalence from national population-based surveys as a new gold standard*. *Lancet*, 2003. **362**(9399): p. 1929-31.
63. McDougal, J.S., et al., *Surveillance for HIV-1 incidence using tests for recent infection in resource-constrained countries*. *Aids*, 2005. **19 Suppl 2**: p. S25-30.
64. Parekh, B.S., et al., *Quantitative detection of increasing HIV type 1 antibodies after seroconversion: a simple assay for detecting recent HIV infection and estimating incidence*. *AIDS Res Hum Retroviruses*, 2002. **18**(4): p. 295-307.
65. McDougal, J.S., et al., *Comparison of HIV type 1 incidence observed during longitudinal follow-up with incidence estimated by cross-sectional analysis using the BED capture enzyme immunoassay*. *AIDS Res Hum Retroviruses*, 2006. **22**(10): p. 945-52.
66. UNAIDS, *Statement on the use of the BED-assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring. Report of a meeting of the UNAIDS*

- Reference Group on Estimates, Modelling and Projections. Athens, Greece, 13-15th Decemeber 2005. 2005, UNAIDS: Geneva.
67. Batter, V., et al., *High HIV-1 incidence in young women masked by stable overall seroprevalence among childbearing women in Kinshasa, Zaire: estimating incidence from serial seroprevalence data*. *Aids*, 1994. **8**(6): p. 811-7.
 68. Ades, A.E. and G.F. Medley, *Estimates of disease incidence in women based on antenatal or neonatal seroprevalence data: HIV in New York City*. *Stat Med*, 1994. **13**(18): p. 1881-94.
 69. Gregson, S., et al., *Demographic approaches to the estimation of incidence of HIV-1 infection among adults from age-specific prevalence data in stable endemic conditions*. *Aids*, 1996. **10**(14): p. 1689-97.
 70. Hallett, T.B., P.J. White, and G.P. Garnett, *The appropriate evaluation of HIV prevention interventions: from experiment to full scale implementation*. *Sex Transm Infect*, 2007.
 71. UNAIDS, *Evaluation of the 100% condom program in Thailand*. available from http://data.unaids.org/Publications/IRC-pub01/JC275-100pCondom_en.pdf, 2000.
 72. Morris, M., et al., *Bridge populations in the spread of HIV/AIDS in Thailand*. *Aids*, 1996. **10**(11): p. 1265-71.
 73. Nelson, K.E., et al., *Changes in sexual behavior and a decline in HIV infection among young men in Thailand*. *N Engl J Med*, 1996. **335**(5): p. 297-303.
 74. Nelson, K.E., et al., *HIV infection in young men in northern Thailand, 1991-1998: increasing role of injection drug use*. *J Acquir Immune Defic Syndr*, 2002. **29**(1): p. 62-8.
 75. Hearst, N. and S. Chen, *Condom promotion for AIDS prevention in the developing world: is it working?* *Stud Fam Plann*, 2004. **35**(1): p. 39-47.
 76. STD/AIDS Control Program - Ministry of Health Uganda, *STD/HIV/AIDS Surveillance Report*. available from: <http://www.health.go.ug/docs/hiv0603.pdf>, 2003.
 77. Okware, S., et al., *Revisiting the ABC strategy: HIV prevention in Uganda in the era of antiretroviral therapy*. *Postgrad Med J*, 2005. **81**(960): p. 625-8.
 78. Hogle, A.J., *What happened in Uganda? Declining HIV prevalence, behavior change and the national response*. 2002, U.S. Agency for International development,.
 79. STD/AIDS Control Program - Ministry of Health Uganda, *National condom policy and strategy - draft*. 2003: Kampala.
 80. Asiimwe-Okiror, G., et al., *Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda*. *Aids*, 1997. **11**(14): p. 1757-63.
 81. Mbulaiteye, S.M., et al., *Declining HIV-1 incidence and associated prevalence over 10 years in a rural population in south-west Uganda: a cohort study*. *Lancet*, 2002. **360**(9326): p. 41-6.
 82. Parkhurst, J.O., *The Ugandan success story? Evidence and claims of HIV-1 prevention*. *Lancet*, 2002. **360**(9326): p. 78-80.

83. The Global Fund to Fight AIDS Tuberculosis and Malaria, *The Global Fund to Fight AIDS, Tuberculosis and Malaria*. www.theglobalfund.org.
84. *The President's Emergency Plan for AIDS Relief. U.S. Five-year global HIV/AIDS strategy*. www.pepfar.gov.
85. Gill, P., *Body Count: Fixing the Blame for the Global AIDS Catastrophe*. 2006: Thunder's Mouth Press. 208.
86. Grassly, N.C., et al., *The effectiveness of HIV prevention and the epidemiological context*. Bull World Health Organ, 2001. **79**(12): p. 1121-32.
87. Halperin, D.T., et al., *The time has come for common ground on preventing sexual transmission of HIV*. Lancet, 2004. **364**(9449): p. 1913-5.
88. Human rights watch. *II. The United States' "War on Comdoms"*. 2004 [cited 2005 February 22].
89. American Foundation for AIDS Research, *The effectiveness of condoms in preventing HIV transmission*. 2005, American Foundation for AIDS Research,.
90. Shafer, L.A., et al. *HIV prevalence and incidence are no longer falling in Uganda – a case for renewed prevention efforts: evidence from a rural population cohort 1989-2005, and from ANC surveillance (THLB0108)*. in *XVI International AIDS Conference*. 2006. Toronto, Canada.
91. Gregson, S., et al., *HIV decline associated with behavior change in eastern Zimbabwe*. Science, 2006. **311**(5761): p. 664-6.
92. Gregson, S., H. Waddell, and S. Chandiwanana, *School education and HIV control in sub-Saharan Africa: From discord to harmony?* Journal Of International Development, 2001. **13**: p. 467-485.
93. UNAIDS. *Follow-up to the declaration of commitment on HIV/AIDS (UNGASS)*. http://data.unaids.org/pub/Report/2006/2006_country_progress_report_zimbabwe_en.pdf 2006 [cited 2006 16th October].
94. Gregson, S., et al., *Impact and Process Evaluation of Integrated Community and Clinic-Based HIV-1 Control: A Cluster-Randomised Trial in Eastern Zimbabwe*. PLoS Med, 2007. **4**(3): p. e102.
95. McKusick, L., W. Horstman, and T.J. Coates, *AIDS and sexual behavior reported by gay men in San Francisco*. Am J Public Health, 1985. **75**(5): p. 493-6.
96. Holmes, K.K., R. Levine, and M. Weaver, *Effectiveness of condoms in preventing sexually transmitted infections*. Bull World Health Organ, 2004. **82**(6): p. 454-61.
97. Pinkerton, S.D. and P.R. Abramson, *Effectiveness of condoms in preventing HIV transmission*. Soc Sci Med, 1997. **44**(9): p. 1303-12.
98. Bracher, M., G. Santow, and S.C. Watkins, *Assessing the potential of condom use to prevent the spread of HIV: a microsimulation study*. Stud Fam Plann, 2004. **35**(1): p. 48-64.
99. Baggaley, R., et al., *Systematic review of HIV-1 transmission probabilities in absence of antiretroviral therapy*. In preparation.

100. Garnett, G.P. and R.M. Anderson, *Strategies for limiting the spread of HIV in developing countries: conclusions based on studies of the transmission dynamics of the virus*. J Acquir Immune Defic Syndr Hum Retrovirol, 1995. **9**(5): p. 500-13.
101. Albert, A.E., et al., *Condom use among female commercial sex workers in Nevada's legal brothels*. Am J Public Health, 1995. **85**(11): p. 1514-20.
102. Magnani, R.J. and A.M. Karim, *ABCs: The Youth Perspective*. available at http://www.synergyaids.com/Documents/6_Robert_magnani.pdf, 2002.
103. Mills, S., et al., *HIV risk behavioral surveillance in Bangkok, Thailand: sexual behavior trends among eight population groups*. Aids, 1997. **11 Suppl 1**: p. S43-51.
104. Hearst, N., et al., *Reducing AIDS risk among port workers in Santos, Brazil*. Am J Public Health, 1999. **89**(1): p. 76-8.
105. Rottingen, J.A., D.W. Cameron, and G.P. Garnett, *A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known?* Sex Transm Dis, 2001. **28**(10): p. 579-97.
106. Pepin, J., et al., *The interaction of HIV infection and other sexually transmitted diseases: an opportunity for intervention*. Aids, 1989. **3**(1): p. 3-9.
107. Grosskurth, H., et al., *Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial*. Lancet, 1995. **346**(8974): p. 530-6.
108. Grosskurth, H., et al., *Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials*. Lancet, 2000. **355**(9219): p. 1981-7.
109. Wawer, M.J., et al., *Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group*. Lancet, 1999. **353**(9152): p. 525-35.
110. Kamali, A., et al., *Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial*. Lancet, 2003. **361**(9358): p. 645-52.
111. Orroth, K.K., et al., *Higher risk behaviour and rates of sexually transmitted diseases in Mwanza compared to Uganda may help explain HIV prevention trial outcomes*. Aids, 2003. **17**(18): p. 2653-60.
112. Orroth, K.K., et al., *Comparison of STD prevalences in the Mwanza, Rakai, and Masaka trial populations: the role of selection bias and diagnostic errors*. Sex Transm Infect, 2003. **79**(2): p. 98-105.
113. Wald, A. and K. Link, *Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis*. J Infect Dis, 2002. **185**(1): p. 45-52.
114. Freeman, E.E., et al., *The proportion of new HIV infections attributable to HSV- 2 increases over time: simulations of the changing role of sexually transmitted infections in sub-Saharan African HIV epidemics*. Sex Transm Infect, 2007.

115. Boily, M.C., C.M. Lowndes, and M. Alary, *Complementary hypothesis concerning the community sexually transmitted disease mass treatment puzzle in Rakai, Uganda*. *Aids*, 2000. **14**(16): p. 2583-92.
116. Hudson, C.P., *Community-based trials of sexually transmitted disease treatment: repercussions for epidemiology and HIV prevention*. *Bull World Health Organ*, 2001. **79**(1): p. 48-58.
117. Orroth, K.K., et al., *Empirical observations underestimate the proportion of human immunodeficiency virus infections attributable to sexually transmitted diseases in the Mwanza and Rakai sexually transmitted disease treatment trials: Simulation results*. *Sex Transm Dis*, 2006. **33**(9): p. 536-44.
118. Alary, M., C.M. Lowndes, and M.C. Boily, *Community randomized trials for HIV prevention: the past, a lesson for the future?* *Aids*, 2003. **17**(18): p. 2661-3.
119. White, R.G., et al., *Can Population Differences Explain the Contrasting Results of the Mwanza, Rakai, and Masaka HIV/Sexually Transmitted Disease Intervention Trials?: A Modeling Study*. *J Acquir Immune Defic Syndr*, 2004. **37**(4): p. 1500-1513.
120. White, R.G. *Treating STIs to prevent HIV in Africa: Still an effective control strategy?* in *17th ISSTD*. 2007. Seattle, USA.
121. Laga, M., et al., *To stem HIV in Africa, prevent transmission to young women*. *Aids*, 2001. **15**(7): p. 931-4.
122. Genuis, S.J. and S.K. Genuis, *Adolescent behaviour should be priority*. *Bmj*, 2004. **328**(7444): p. 894.
123. Green, E.C. and J. Berman, *Liaisons fueling AIDS in Africa*, in *The Washington Times*. 2003.
124. UNAIDS, *2004 Report of the global AIDS epidemic*. 2004: Geneva.
125. AIDSMark, *Cross-generational sex fueling the HIV/AIDS epidemic in sub-Saharan Africa*. 2003, International Centre for Research on Women (ICRW) and Population Services International (PSI).
126. Kelly, R.J., et al., *Age differences in sexual partners and risk of HIV-1 infection in rural Uganda*. *J Acquir Immune Defic Syndr*, 2003. **32**(4): p. 446-51.
127. Pettifor, A.E., et al., *Early age of first sex: a risk factor for HIV infection among women in Zimbabwe*. *Aids*, 2004. **18**(10): p. 1435-1442.
128. Drain, P.K., et al., *Correlates of National HIV Seroprevalence: An Ecologic Analysis of 122 Developing Countries*. *J Acquir Immune Defic Syndr*, 2004. **35**(4): p. 407-420.
129. Hallett, T.B., et al., *Age at first sex and HIV infection in rural Zimbabwe*. *Stud Fam Plann*, 2007. **38**(1): p. 1-10.
130. Population Services International, *Dangerous Liasons*, in *PSI Research Brief*. 2003.
131. Cohen, J., *Asia and Africa: on different trajectories?* *Science*, 2004. **304**(5679): p. 1932-8.
132. Konings, E., et al., *Sexual behaviour survey in a rural area of northwest Tanzania*. *Aids*, 1994. **8**(7): p. 987-93.

133. Longfield, K., et al., *Relationships between older men and younger women: implications for STIs/HIV in Kenya*. Stud Fam Plann, 2004. **35**(2): p. 125-34.
134. Buve, A., K. Bishikwabo-Nsarhaza, and G. Mutangadura, *The spread and effect of HIV-1 infection in sub-Saharan Africa*. Lancet, 2002. **359**(9322): p. 2011-7.
135. Boily, M.C. and B. Masse, *Mathematical models of disease transmission: a precious tool for the study of sexually transmitted diseases*. Can J Public Health, 1997. **88**(4): p. 255-65.
136. Kamb, M.L., et al., *Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group*. JAMA, 1998. **280**(13): p. 1161-7.
137. The Voluntary HIV-1 Counseling and Testing Efficacy Study Group, *Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomised trial*. Lancet, 2000. **356**(9224): p. 103-12.
138. Sweat, M., et al., *Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania*. Lancet, 2000. **356**(9224): p. 113-21.
139. Weinhardt, L.S., et al., *Effects of HIV counseling and testing on sexual risk behavior: a meta-analytic review of published research, 1985-1997*. Am J Public Health, 1999. **89**(9): p. 1397-405.
140. Corbett, E.L., et al., *HIV incidence during a cluster-randomized trial of two strategies providing voluntary counselling and testing at the workplace, Zimbabwe*. Aids, 2007. **21**(4): p. 483-9.
141. Sherr, L., et al., *Voluntary counselling and testing: Uptake and impact on sexual behaviour and HIV incidence in a rural Zimbabwean prospective cohort*. in preparation.
142. Grinstead, O.A., et al., *Positive and negative life events after counselling and testing: the Voluntary HIV-1 Counselling and Testing Efficacy Study*. Aids, 2001. **15**(8): p. 1045-52.
143. Oberzaucher, N. and R. Baggaley, *HIV Voluntary Counselling and Testing: a gateway to prevention and care*. 2002, Joint United Nations Programme on HIV/AIDS (UNAIDS).
144. Population Services International, *Marketing HIV Counseling and Testing*. available at <http://www.psi.org/resources/pubs/New-Start-august-06.pdf>, 2006.
145. WHO, UNAIDS, and UNICEF, *Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector Progress Report (available from http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf)*. April, 2007: Geneva.
146. Corbett, E.L., et al., *Uptake of workplace HIV counselling and testing: a cluster-randomised trial in Zimbabwe*. PLoS Med, 2006. **3**(7): p. e238.

147. Weiser, S.D., et al., *Routine HIV testing in Botswana: a population-based study on attitudes, practices, and human rights concerns*. PLoS Med, 2006. 3(7): p. e261.
148. Dube, S., et al., *Optimising the Population Level Impact of Voluntary Counselling and Testing in Zimbabwe: Insights from Mathematical Models*. 2005, Department of infectious Disease Epidemiology, Imperial College London; Centers for Disease Control and Prevention (CDC), Atlanta, USA.
149. Nyamato, E., et al. *VCT+: The Road to ART (abstract 178)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
150. Sepkowitz, K.A., *AIDS--the first 20 years*. N Engl J Med, 2001. 344(23): p. 1764-72.
151. Hammer, S.M., et al., *A controlled trial of two nucleoside analogues plus zidovudine in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team*. N Engl J Med, 1997. 337(11): p. 725-33.
152. Staszewski, S., et al., *Efavirenz plus zidovudine and lamivudine, efavirenz plus zidovudine, and zidovudine plus lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team*. N Engl J Med, 1999. 341(25): p. 1865-73.
153. Carr, A. and D.A. Cooper, *Adverse effects of antiretroviral therapy*. Lancet, 2000. 356(9239): p. 1423-30.
154. Wood, E., et al., *When to initiate antiretroviral therapy in HIV-1-infected adults: a review for clinicians and patients*. Lancet Infect Dis, 2005. 5(7): p. 407-14.
155. Lane, H.C. and J.D. Neaton, *When to start therapy for HIV infection: a swinging pendulum in search of data*. Ann Intern Med, 2003. 138(8): p. 680-1.
156. Ho, D.D., *Time to hit HIV, early and hard*. N Engl J Med, 1995. 333(7): p. 450-1.
157. Egger, M., et al., *Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies*. Lancet, 2002. 360(9327): p. 119-29.
158. Deeks, S.G., *Treatment of antiretroviral-drug-resistant HIV-1 infection*. Lancet, 2003. 362(9400): p. 2002-11.
159. Yeni, P.G., et al., *Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel*. Jama, 2004. 292(2): p. 251-65.
160. Quinn, T.C., et al., *Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group*. N Engl J Med, 2000. 342(13): p. 921-9.
161. Baggaley, R.F., N.M. Ferguson, and G.P. Garnett, *The epidemiological impact of antiretroviral use predicted by mathematical models: a review*. Emerg Themes Epidemiol, 2005. 2: p. 9.
162. Kabugo, C., et al., *Long-term experience providing antiretroviral drugs in a fee-for-service HIV clinic in Uganda: evidence of extended virologic and CD4+ cell count responses*. J Acquir Immune Defic Syndr, 2005. 38(5): p. 578-83.

163. Office of the United States Global AIDS Coordinator, *The President's Emergency Plan for AIDS Relief. U.S. Five-year global HIV/AIDS strategy*. 2004.
164. Office of the United States Global AIDS Coordinator, *The United States President's Emergency Plan for AIDS Relief*. <http://www.pepfar.gov>, accessed 8th March, 2007.
165. Schwartlander, B., et al., *AIDS. Resource needs for HIV/AIDS*. Science, 2001. **292**(5526): p. 2434-6.
166. *The G8 Gleneagles communique on Africa. Climate change, energy, sustainable development. G8 Summit 2005*. available at http://www.fco.gov.uk/Files/kfile/PostG8_Gleneagles_Communique.0.pdf, 2005.
167. Attaran, A., *Adherence to HAART: Africans take medicines more faithfully than North Americans*. PLoS Med, 2007. **4**(2): p. e83.
168. Mills, E.J., et al., *Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis*. Jama, 2006. **296**(6): p. 679-90.
169. Gazzard, B., *British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005)*. HIV Med, 2005. **6 Suppl 2**: p. 1-61.
170. United States Department of Health and Human Services (DHHS), *Guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents*. 2006, Available from: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (accessed 26th September, 2006).
171. Gilks, C.F., et al., *The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings*. Lancet, 2006. **368**(9534): p. 505-10.
172. Morgan, D., et al., *Early manifestations (pre-AIDS) of HIV-1 infection in Uganda*. Aids, 1998. **12**(6): p. 591-6.
173. Morgan, D., et al., *Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study*. Bmj, 2002. **324**(7331): p. 193-6.
174. Kagaayi, J., et al. *WHO Staging Criteria Versus CD4 Screening for Antiretroviral Eligibility in Rural Rakai District, Uganda*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
175. Kassa, E., et al., *Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers*. Aids, 1999. **13**(3): p. 381-9.
176. Attili, V.S., et al., *Validity of existing CD4+ classification in north Indians, in predicting immune status*. J Infect, 2005. **51**(1): p. 41-6.
177. World Health Organization, *Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance: Africa Region*. 2005: Geneva.
178. Beck, E.J., et al., *National adult antiretroviral therapy guidelines in resource-limited countries: concordance with 2003 WHO guidelines?* Aids, 2006. **20**(11): p. 1497-502.
179. Margolick, J.B., et al., *Failure of T-cell homeostasis preceding AIDS in HIV-1 infection. The Multicenter AIDS Cohort Study*. Nat Med, 1995. **1**(7): p. 674-80.

180. Mukherjee, J.S., et al., *Tackling HIV in resource poor countries*. Bmj, 2003. **327**(7423): p. 1104-6.
181. Merson, M.H., *The HIV-AIDS pandemic at 25--the global response*. N Engl J Med, 2006. **354**(23): p. 2414-7.
182. UNAIDS, *Statement On South African Trial Findings Regarding Male Circumcision And Hiv*. 2005.
183. UNAIDS, *Statement on Kenyan and Ugandan trial findings regarding male circumcision and HIV*. available at http://data.unaids.org/pub/PressStatement/2006/20061213_Male_Circumcision_joint_PR_en.pdf, 2006.
184. UNAIDS, WHO and UNAIDS announce recommendations from expert meeting on male circumcision for HIV prevention. available at http://data.unaids.org/pub/PressRelease/2007/20070328_pr_mc_recommendations_en.pdf, 2007.
185. Kahn, J.G., E. Marseille, and B. Auvert, *Cost-effectiveness of male circumcision for HIV prevention in a South African setting*. PLoS Med, 2006. **3**(12): p. e517.
186. Koelle, D.M. and L. Corey, *Recent progress in herpes simplex virus immunobiology and vaccine research*. Clin Microbiol Rev, 2003. **16**(1): p. 96-113.
187. Freeman, E.E., et al., *Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies*. Aids, 2006. **20**(1): p. 73-83.
188. Watson-Jones, D., et al. *Impact of HSV-2 suppressive therapy on HIV incidence in HSV-2 seropositive women: a randomised controlled trial in Tanzania*. in 4th IAS Conference on Pathogenesis, Treatment and Prevention. 2007. Sydney, Australia.
189. Nagot, N., et al., *Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus*. N Engl J Med, 2007. **356**(8): p. 790-9.
190. Bailey, G.P. *Impact of episodic acyclovir therapy on genital ulcer duration and HIV shedding from herpetic ulcers among men in South Africa*. in 17th ISSTD. 2007. Seattle, USA.
191. Paz-Bailey, G., et al., *Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease*. Clin Infect Dis, 2005. **41**(9): p. 1304-12.
192. Weber, J., K. Desai, and J. Darbyshire, *The development of vaginal microbicides for the prevention of HIV transmission*. PLoS Med, 2005. **2**(5): p. e142.
193. Balzarini, J. and L. Van Damme, *Microbicide drug candidates to prevent HIV infection*. Lancet, 2007. **369**(9563): p. 787-97.
194. Foss, A.M., et al., *Shifts in condom use following microbicide introduction: should we be concerned?* Aids, 2003. **17**(8): p. 1227-37.
195. Smith, R.J., et al., *Evaluating the potential impact of vaginal microbicides to reduce the risk of acquiring HIV in female sex workers*. Aids, 2005. **19**(4): p. 413-21.

196. *The Global HIV/AIDS Vaccine Enterprise: scientific strategic plan*. PLoS Med, 2005. **2**(2): p. e25.
197. Anderson, R.M. and G.P. Garnett, *Low-efficacy HIV vaccines: potential for community-based intervention programmes*. Lancet, 1996. **348**(9033): p. 1010-3.
198. Blower, S.M., H.B. Gershengorn, and R.M. Grant, *A tale of two futures: HIV and antiretroviral therapy in San Francisco*. Science, 2000. **287**(5453): p. 650-4.
199. International AIDS Vaccine Initiative, *Estimating the Impact of an AIDS Vaccine in Developing Countries (Policy briefing)*. Available at <http://www.iavi.org/file.cfm?fid=42539>, 2006.
200. Cassell, M.M., et al., *Risk compensation: the Achilles' heel of innovations in HIV prevention?* Bmj, 2006. **332**(7541): p. 605-7.
201. Anderson, R.M. and G.P. Garnett, *Mathematical models of the transmission and control of sexually transmitted diseases*. Sex Transm Dis, 2000. **27**(10): p. 636-43.
202. Bernoulli, D., *Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir*. Mém Math Phys Acad R Sci Paris, 1760: p. 1-45.
203. Hamer, W.H., *Epidemic disease in England*. The Lancet, 1906. **1**: p. 733-739.
204. Ross, R., *Some a priori pathometric equations*. 1, 1915: p. 546-547.
205. Anderson, R.M., et al., *A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS*. IMA J Math Appl Med Biol, 1986. **3**(4): p. 229-63.
206. Anderson, R.M., et al., *The spread of HIV-1 in Africa: sexual contact patterns and the predicted demographic impact of AIDS*. Nature, 1991. **352**(6336): p. 581-9.
207. Anderson, R.M., et al., *Age-dependent choice of sexual partners and the transmission dynamics of HIV in Sub-Saharan Africa*. Philos Trans R Soc Lond B Biol Sci, 1992. **336**(1277): p. 135-55.
208. Jacquez, J.A., et al., *Role of the primary infection in epidemics of HIV infection in gay cohorts*. J Acquir Immune Defic Syndr, 1994. **7**(11): p. 1169-84.
209. Anderson, R.M. and G.F. Medley, *Epidemiology of HIV infection and AIDS: incubation and infectious periods, survival and vertical transmission*. Aids, 1988. **2** Suppl 1: p. S57-63.
210. Dietz, K. and K.P. Hadeler, *Epidemiological models for sexually transmitted diseases*. J Math Biol, 1988. **26**(1): p. 1-25.
211. Ghani, A.C. and G.P. Garnett, *Risks of acquiring and transmitting sexually transmitted diseases in sexual partner networks*. Sex Transm Dis, 2000. **27**(10): p. 579-87.
212. Ghani, A.C. and S.O. Aral, *Patterns of sex worker-client contacts and their implications for the persistence of sexually transmitted infections*. J Infect Dis, 2005. **191** Suppl 1: p. S34-41.

213. Gupta, S., R.M. Anderson, and R.M. May, *Networks of sexual contacts: implications for the pattern of spread of HIV*. *Aids*, 1989. **3**(12): p. 807-17.
214. Anderson, R.M., S. Gupta, and W. Ng, *The significance of sexual partner contact networks for the transmission dynamics of HIV*. *J Acquir Immune Defic Syndr*, 1990. **3**(4): p. 417-29.
215. Kretzschmar, M. and K. Dietz, *The effect of pair formation and variable infectivity on the spread of an infection without recovery*. *Math Biosci*, 1998. **148**(1): p. 83-113.
216. Ferguson, N.M. and G.P. Garnett, *More realistic models of sexually transmitted disease transmission dynamics: sexual partnership networks, pair models, and moment closure*. *Sex Transm Dis*, 2000. **27**(10): p. 600-9.
217. Abu-Raddad, L.J., P. Patnaik, and J.G. Kublin, *Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa*. *Science*, 2006. **314**(5805): p. 1603-6.
218. Currie, C.S., et al., *Tuberculosis epidemics driven by HIV: is prevention better than cure?* *Aids*, 2003. **17**(17): p. 2501-8.
219. Korenromp, E.L., et al., *Determinants of the impact of sexually transmitted infection treatment on prevention of HIV infection: a synthesis of evidence from the Mwanza, Rakai, and Masaka intervention trials*. *J Infect Dis*, 2005. **191 Suppl 1**: p. S168-78.
220. Anderson, R.M., R.M. May, and A.R. McLean, *Possible demographic consequences of AIDS in developing countries*. *Nature*, 1988. **332**(6161): p. 228-34.
221. Garnett, G.P., et al., *Antiretroviral therapy to treat and prevent HIV/AIDS in resource-poor settings*. *Nat Med*, 2002. **8**(7): p. 651-4.
222. Baggaley, R.F., G.P. Garnett, and N.M. Ferguson, *Modelling the Impact of Antiretroviral Use in Resource-Poor Settings*. *PLoS Med*, 2006. **3**(4): p. e124.
223. Blower, S.M. and A.R. McLean, *Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco*. *Science*, 1994. **265**(5177): p. 1451-4.
224. Garnett, G.P., *The basic reproductive rate of infection and the course of HIV epidemics*. *AIDS Patient Care STDS*, 1998. **12**(6): p. 435-49.
225. Nagelkerke, N.J., et al., *Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa*. *BMC Infect Dis*, 2007. **7**: p. 16.
226. Gray, R.H., et al., *The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda*. *Aids*, 2007. **21**(7): p. 845-50.
227. Clark, S.J. and J. Eaton *Population Impact of Male Circumcision to Prevent HIV Transmission, Results from Microsimulation*. in *Demography and Infectious Disease Symposium*. 2007. Stanford University, California.
228. Gregson, S., et al., *Methods to reduce social desirability bias in sex surveys in low-development settings: experience in Zimbabwe*. *Sex Transm Dis*, 2002. **29**(10): p. 568-75.

229. Anderson, R.M. and R.M. May, *Epidemiological parameters of HIV transmission*. Nature, 1988. **333**(6173): p. 514-9.
230. Morgan, D., et al., *HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries?* Aids, 2002. **16**(4): p. 597-603.
231. Boily, M.C., et al., *The impact of the transmission dynamics of the HIV/AIDS epidemic on sexual behaviour: a new hypothesis to explain recent increases in risk taking-behaviour among men who have sex with men*. Med Hypotheses, 2005. **65**(2): p. 215-26.
232. Anderson, R.M., *Transmission dynamics of sexually transmitted infections*, in *Sexually Transmitted Diseases*, S.P. Holmes KK, Mardh P-A, et al., Editor. 1999, McGraw-Hill: New York.
233. UNAIDS Reference Group on Estimates Modelling and Projections, *Evidence and causes of decline in HIV prevalence and incidence in countries with generalised epidemics. Report based on a meeting held in Harare, Zimbabwe, 15-17th November 2004*. 2005. p. http://www.epidem.org/Publications/Harare2004_report.pdf.
234. Collaborative Group on AIDS Incubation and HIV Survival, *Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe*. Lancet, 2000. **355**(9210): p. 1131-7.
235. Cote d'Ivoire: DHS, 1994 - Final Report (French). http://www.measuredhs.com/pubs/pub_details.cfm?ID=107&srchTp=advanced (accessed 14-8-07).
236. Gaillard, E.M., et al., *Understanding the reasons for decline of HIV prevalence in Haiti*. Sex Transm Infect, 2006. **82 Suppl 1**: p. i14-20.
237. Cheluget, B., et al., *Evidence for population level declines in adult HIV prevalence in Kenya*. Sex Transm Infect, 2006. **82 Suppl 1**: p. i21-6.
238. Bello, G.A., J. Chipeta, and J. Aberle-Grasse, *Assessment of trends in biological and behavioural surveillance data: is there any evidence of declining HIV prevalence or incidence in Malawi?* Sex Transm Infect, 2006. **82**(suppl_1): p. i9-13.
239. Kayirangwa, E., et al., *Current trends in Rwanda's HIV/AIDS epidemic*. Sex Transm Infect, 2006. **82**(suppl_1): p. i27-31.
240. Kirungi, W.L., et al., *Trends in antenatal HIV prevalence in urban Uganda associated with uptake of preventive sexual behaviour*. Sex Transm Infect, 2006. **82**(suppl_1): p. i36-41.
241. Hladik, W., et al., *HIV/AIDS in Ethiopia: where is the epidemic heading?* Sex Transm Infect, 2006. **82**(suppl_1): p. i32-35.
242. The MathWorks Inc., *MATLAB version 7.01.1.24704 (R14) SP1*. 2004.

243. Lewis, J.J., et al., *The population impact of HIV on fertility in sub-Saharan Africa*. Aids, 2004. **18 Suppl 2**: p. S35-43.
244. Wawer, M.J. *Declines in HIV prevalence in Uganda: not as simple as ABC*. in *Twelfth Annual Retrovirus Conference*. 2005. Boston.
245. Mundandi, C., et al., *No difference in HIV incidence and sexual behaviour between out-migrants and residents in rural Manicaland, Zimbabwe*. Trop Med Int Health, 2006. **11**(5): p. 705-11.
246. Hallett, T.B., B.A. Lopman, and S. Gregson, *Why HIV Rates Have Declined in Zimbabwe in Presentation to the UNAIDS Reference Group Steering Committee*. 2006: Harare, Zimbabwe.
247. Jaffar, S., et al., *The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review*. Bull World Health Organ, 2004. **82**(6): p. 462-9.
248. Population Services International, *New Hope with New Start*. 2002: Washington, D.C. p. available at <http://www.psi.org/resources/pubs/New-Start-august-06.pdf>.
249. Machezano, R., et al., *Impact of HIV counselling and testing on HIV seroconversion and reported STD incidence among male factory workers in Harare, Zimbabwe*. Cent Afr J Med, 1998. **44**(4): p. 98-102.
250. Sherr, L., et al., *Voluntary counselling and testing: uptake, impact on sexual behaviour, and HIV incidence in a rural Zimbabwean cohort*. Aids, 2007. **21**(7): p. 851-860.
251. Hallett, T.B., et al., *Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti*. Sex Transm Infect, 2006. **82 Suppl 1**: p. i1-i8.
252. Garcia-Calleja, J.M., E. Gouws, and P.D. Ghys, *National population based HIV prevalence surveys in sub-Saharan Africa: results and implications for HIV and AIDS estimates*. Sex Transm Infect, 2006. **82 Suppl 3**: p. iii64-70.
253. Rangsin, R., et al., *The natural history of HIV-1 infection in young Thai men after seroconversion*. J Acquir Immune Defic Syndr, 2004. **36**(1): p. 622-9.
254. Podgor, M.J. and M.C. Leske, *Estimating incidence from age-specific prevalence for irreversible diseases with differential mortality*. Stat Med, 1986. **5**(6): p. 573-8.
255. Ades, A.E., *Serial HIV seroprevalence surveys: interpretation, design, and role in HIV/AIDS prediction*. J Acquir Immune Defic Syndr Hum Retrovirol, 1995. **9**(5): p. 490-9.
256. Sakarovitch, C., et al., *Estimating incidence of HIV infection in childbearing age African women using serial prevalence data from antenatal clinics*. Stat Med, 2007. **26**(2): p. 320-35.
257. Williams, B., et al., *Estimating HIV incidence rates from age prevalence data in epidemic situations*. Stat Med, 2001. **20**(13): p. 2003-16.
258. White, R.G., et al., *HIV epidemic trend and antiretroviral treatment need in Karonga District, Malawi*. Epidemiol Infect, 2007: p. 1-11.

259. Saidel, T., et al., *Validation of a method to estimate age-specific human immunodeficiency virus (HIV) incidence rates in developing countries using population-based seroprevalence data*. Am J Epidemiol, 1996. **144**(3): p. 214-23.
260. Brisson, M., et al., *Highlights of the sexual activity of the heterosexual population in the province of Quebec*. Sex Transm Infect, 1999. **75**(5): p. 296-9.
261. Zaba, B., et al., *Age- and sex- specific mortality patterns in HIV infected individuals: a comparative analysis of six community studies in five African countries*. . Forthcoming.
262. Zaba, B., et al. *Survival following HIV infection in the pre-ART era in a rural Tanzanian cohort*. in *16th International AIDS Conference*. 2006. Toronto, Canada.
263. Lopman, B.A., et al., *Assessing adult mortality in HIV-1-afflicted Zimbabwe (1998 - 2003)*. Bull World Health Organ, 2006. **84**(3): p. 189-97.
264. Glynn, J.R., et al., *Survival from HIV-1 seroconversion in Southern Africa: a retrospective cohort study in nearly 2000 gold-miners over 10 years of follow-up*. Aids, 2007. **21**(5): p. 625-632.
265. Mulder, D.W., et al., *HIV-1 incidence and HIV-1-associated mortality in a rural Ugandan population cohort*. Aids, 1994. **8**(1): p. 87-92.
266. Boerma, J.T., et al., *Spread of HIV infection in a rural area of Tanzania*. Aids, 1999. **13**(10): p. 1233-40.
267. Lopman, B., et al., *Determinants of HIV incidence after 3 years follow-up in a cohort recruited between 1998 and 2000 in Manicaland, Zimbabwe*. In preparation.
268. Mitwa, W., et al. *Prevalence and incidence trends in rural population in Northern Tanzania during 1994-2004 (CDC0362)*. in *XVI International AIDS Conference*. 2006. Toronto, Canada.
269. Kamali, A., et al., *Seven-year trends in HIV-1 infection rates, and changes in sexual behaviour, among adults in rural Uganda*. Aids, 2000. **14**(4): p. 427-34.
270. Lopman, B.A., et al., *The role of widows in the heterosexual transmission of HIV in Manicaland, Zimbabwe, 1998/2003*. In preparation.
271. Kiwanuka, N., et al., *The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Rakai, Uganda*. Aids, 2004. **18**(2): p. 342-4.
272. Schmid, G.P., et al., *Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections*. The Lancet, 2004. **363**(9407): p. 482-488.
273. Lopman, B.A., et al., *Individual Level Injection History: A Lack of Association with HIV Incidence in Rural Zimbabwe*. PLoS Med, 2005. **2**(2): p. e37.
274. Garnett, G.P., *An introduction to mathematical models in sexually transmitted disease epidemiology*. Sex Transm Infect, 2002. **78**(1): p. 7-12.
275. Aral, S.O. and R. Roegner, *Mathematical modeling as a tool in STD prevention and control: a decade of progress, a millennium of opportunities*. Sex Transm Dis, 2000. **27**(10): p. 556-7.

276. Keeling, M.J., et al., *Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape*. Science, 2001. **294**(5543): p. 813-7.
277. Riley, S., et al., *Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions*. Science, 2003. **300**(5627): p. 1961-6.
278. Ferguson, N.M., et al., *Strategies for containing an emerging influenza pandemic in Southeast Asia*. Nature, 2005. **437**(7056): p. 209-14.
279. Garnett, G.P. and R.M. Anderson, *Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations*. IMA J Math Appl Med Biol, 1994. **11**(3): p. 161-92.
280. Duncan, M.E., et al., *First coitus before menarche and risk of sexually transmitted disease*. Lancet, 1990. **335**(8685): p. 338-40.
281. Moss, G.B., et al., *Association of cervical ectopy with heterosexual transmission of human immunodeficiency virus: results of a study of couples in Nairobi, Kenya*. J Infect Dis, 1991. **164**(3): p. 588-91.
282. Zaba, B., et al., *Age at first sex: understanding recent trends in African demographic surveys*. Sex Transm Infect, 2004. **80 Suppl 2**: p. ii28-35.
283. Glynn, J.R., et al., *Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia*. Aids, 2001. **15 Suppl 4**: p. S51-60.
284. *Action today, a foundation for tomorrow: The President's Emergency Plan for AIDS Relief. Second Annual Report to Congress*. 2006: Washington, D.C. p. (www.pepfar.gov).
285. UNAIDS and World Health Organization, *Progress on global access to HIV antiretroviral therapy. An update on "3 by 5"*. 2005.
286. Gray, R.H., et al., *Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda*. Lancet, 2001. **357**(9263): p. 1149-53.
287. UNAIDS, *UNAIDS Action plan on intensifying HIV prevention*. available at http://data.unaids.org/pub/Report/2007/jc1218_preventionactionplan_en.pdf, 2006.
288. De Cock, K.M., D. Mbori-Ngacha, and E. Marum, *Shadow on the continent: public health and HIV/AIDS in Africa in the 21st century*. Lancet, 2002. **360**(9326): p. 67-72.
289. Kippax, S., *A public health dilemma: a testing question*. AIDS Care, 2006. **18**(3): p. 230-5.
290. Technical Expert Panel Review of CDC HIV Counseling Testing and Referral Guidelines, *Revised Guidelines for HIV Counseling, Testing, and Referral*. MMWR Recomm Rep, 2001. **50**: p. 1-58.
291. Glick, P., *Scaling up HIV voluntary counseling and testing in Africa: what can evaluation studies tell us about potential prevention impacts?* Eval Rev, 2005. **29**(4): p. 331-57.

292. Padian, N.S., S.C. Shiboski, and N.P. Jewell, *Female-to-male transmission of human immunodeficiency virus*. *Jama*, 1991. **266**(12): p. 1664-7.
293. Nicolosi, A., et al., *The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Italian Study Group on HIV Heterosexual Transmission*. *Epidemiology*, 1994. **5**(6): p. 570-5.
294. *Zimbabwe: DHS, 1988 - Final Report (English)*.
http://www.measuredhs.com/pubs/pub_details.cfm?ID=324&srchTp=advanced
(accessed 10-5-07).
295. *Zimbabwe: DHS, 1994 - Final Report (English)*.
http://www.measuredhs.com/pubs/pub_details.cfm?ID=103&srchTp=advanced
(accessed 10-5-07).
296. *Zimbabwe: DHS, 1999 - Final Report (English)*.
http://www.measuredhs.com/pubs/pub_details.cfm?ID=296&srchTp=advanced
(accessed 10-5-07).
297. Terceira, N., et al., *The contribution of HIV to fertility decline in rural Zimbabwe, 1985-2000*. *Popul Stud (Camb)*, 2003. **57**(2): p. 149-64.
298. Hallett, T.B., et al., *Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti*. *Sex Transm Infect*, 2006. **82**(suppl_1): p. i1-8.
299. *Zimbabwe: DHS, 2005-6 - Preliminary Report*.
[http://harare.usembassy.gov/uploads/images/ErYMhCdkmrjnsEXXPylA/Zimbabwe Preliminary-A4_paper.pdf](http://harare.usembassy.gov/uploads/images/ErYMhCdkmrjnsEXXPylA/Zimbabwe_Preliminary-A4_paper.pdf) (accessed 10-5-07).
300. World Bank, *World development report-1991*. 1991, New York: Oxford University Press.
301. Kamenga, M., et al., *Evidence of marked sexual behavior change associated with low HIV-1 seroconversion in 149 married couples with discordant HIV-1 serostatus: experience at an HIV counselling center in Zaire*. *Aids*, 1991. **5**(1): p. 61-7.
302. Allen, S., et al., *Confidential HIV testing and condom promotion in Africa. Impact on HIV and gonorrhea rates*. *Jama*, 1992. **268**(23): p. 3338-43.
303. Allen, S., et al., *Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa*. *Bmj*, 1992. **304**(6842): p. 1605-9.
304. Jackson, D.J., et al., *Decreased incidence of sexually transmitted diseases among trucking company workers in Kenya: results of a behavioural risk-reduction programme*. *Aids*, 1997. **11**(7): p. 903-9.
305. Matovu, J., *Voluntary HIV counseling and testing acceptance, sexual risk behavior and HIV incidence in Rakai, Uganda*. *AIDS*, 2005. **19**(5): p. 503-511.
306. De Cock, K.M., E. Marum, and D. Mbori-Ngacha, *A serostatus-based approach to HIV/AIDS prevention and care in Africa*. *Lancet*, 2003. **362**(9398): p. 1847-9.

307. Mulongo, M. and F. Wasagami. *High Rate of Discordance Among Clients Receiving Antiretroviral Therapy at TASO Uganda (abstract 118)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
308. Kalamya, J., et al. *Routine HIV Counselling and Testing for Prevention of Mother-to-Child Transmission (PMTCT) of HIV in a Rural Ugandan Hospital (abstract 101)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Duran, South Africa.
309. Allen, S., et al., *Sexual behavior of HIV discordant couples after HIV counseling and testing*. *Aids*, 2003. **17**(5): p. 733-40.
310. UNAIDS, *Intensifying HIV prevention*. 2005: Geneva.
311. WHO and UNAIDS, *Guidance On Provider-Initiated HIV Testing And Counselling In Health facilities (available from <http://www.who.int/hiv/topics/vct/PITCguidelines.pdf>)*. 2007: Geneva.
312. Rojanapithayakorn, W. and R. Hanenberg, *The 100% condom program in Thailand*. *Aids*, 1996. **10**(1): p. 1-7.
313. Kumar, R., et al., *Trends in HIV-1 in young adults in south India from 2000 to 2004: a prevalence study*. *The Lancet*. **367**(9517): p. 1164-1172.
314. Stephenson, J. and J. Imrie, *Why do we need randomised controlled trials to assess behavioural interventions?* *Bmj*, 1998. **316**(7131): p. 611-3.
315. Susser, M., *Some principles in study design for preventing HIV transmission: rigor or reality*. *Am J Public Health*, 1996. **86**(12): p. 1713-6.
316. Donner, A. and N. Klar, *Design and Analysis of cluster randomization trials in health research*. 2000: A Hodder Arnold Publication.
317. Hayes, R.J. and S. Bennett, *Simple sample size calculation for cluster-randomized trials*. *Int J Epidemiol*, 1999. **28**(2): p. 319-26.
318. Localio, A.R., J.A. Berlin, and T.R. Have, *Longitudinal and repeated cross-sectional cluster-randomization designs using mixed effects regression for binary outcomes: bias and coverage of frequentist and Bayesian methods*. *Stat Med*, 2006. **25**(16): p. 2720-36.
319. Moerbeek, M., *Power and money in cluster randomized trials: when is it worth measuring a covariate?* *Stat Med*, 2006. **25**(15): p. 2607-17.
320. Eldridge, S.M., D. Ashby, and S. Kerry, *Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method*. *Int J Epidemiol*, 2006. **35**(5): p. 1292-300.
321. Campbell, M.J., A. Donner, and N. Klar, *Developments in cluster randomized trials and Statistics in Medicine*. *Stat Med*, 2007. **26**(1): p. 2-19.
322. Brookmeyer, R. and Y.Q. Chen, *Person-time analysis of paired community intervention trials when the number of communities is small*. *Stat Med*, 1998. **17**(18): p. 2121-32.
323. Martin, D.C., et al., *The effect of matching on the power of randomized community intervention studies*. *Stat Med*, 1993. **12**(3-4): p. 329-38.

324. Freedman, L.S., S.B. Green, and D.P. Byar, *Assessing the gain in efficiency due to matching in a community intervention study*. Stat Med, 1990. **9**(8): p. 943-52.
325. Edmunds, W.J., et al., *Mixing patterns and the spread of close-contact infectious diseases*. Emerg Themes Epidemiol, 2006. **3**(1): p. 10.
326. Schackman, B.R., et al., *Cost-effectiveness implications of the timing of antiretroviral therapy in HIV-infected adults*. Arch Intern Med, 2002. **162**(21): p. 2478-86.
327. Badri, M., et al., *When to initiate highly active antiretroviral therapy in sub-Saharan Africa? A South African cost-effectiveness study*. Antivir Ther, 2006. **11**(1): p. 63-72.
328. Dube, S., *Should breastfeeding in the era of HIV/AIDS still be considered?* In preparation.
329. Fraser, C., et al., *The role of antigenic stimulation and cytotoxic T cell activity in regulating the long-term immunopathogenesis of HIV: mechanisms and clinical implications*. Proc Biol Sci, 2001. **268**(1481): p. 2085-95.
330. DeGruttola, V., N. Lange, and U. Dafni, *Modeling the progression of HIV infection*. Journal of the American Statistical Association, 1991. **86**(415): p. 569-577.
331. McNeil, A.J., *Bayes estimates for immunological progression rates in HIV disease*. Stat Med, 1997. **16**(22): p. 2555-72.
332. Lepri, A.C., et al., *Is there a general tendency for CD4 lymphocyte decline to speed up during human immunodeficiency virus infection? Evidence from the Italian Seroconversion Study*. J Infect Dis, 1997. **175**(4): p. 775-80.
333. Laurent, C., et al., *No difference in clinical progression between patients infected with the predominant human immunodeficiency virus type 1 circulating recombinant form (CRF) 02_AG strain and patients not infected with CRF02_AG, in Western and West-Central Africa: a four-year prospective multicenter study*. J Infect Dis, 2002. **186**(4): p. 486-92.
334. Manasa, J., et al., *Evaluation of the Partec flow cytometer against the BD FACSCalibur system for monitoring immune responses of human immunodeficiency virus-infected patients in Zimbabwe*. Clin Vaccine Immunol, 2007. **14**(3): p. 293-8.
335. Malone, J.L., et al., *Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important*. J Acquir Immune Defic Syndr, 1990. **3**(2): p. 144-51.
336. Raboud, J.M., et al., *Quantification of the variation due to laboratory and physiologic sources in CD4 lymphocyte counts of clinically stable HIV-infected individuals*. J Acquir Immune Defic Syndr Hum Retrovirol, 1995. **10 Suppl 2**: p. S67-73.
337. Levi, F.A., et al., *Seasonal modulation of the circadian time structure of circulating T and natural killer lymphocyte subsets from healthy subjects*. J Clin Invest, 1988. **81**(2): p. 407-13.

338. Schneider, M., M. Zwahlen, and M. Egger, *Natural history and mortality in HIV-positive individuals living in resource-poor settings*. Available from www.epidem.org, 2004.
339. Central Statistical Office [Zimbabwe] and Macro International Inc., *Zimbabwe demographic and health survey 1999*. 2000, Calverton, Maryland: Central Statistical Office and Macro International Inc.
340. Adu-Sarkodie, Y., et al., *Distribution of CD4+ T-lymphocytes levels in patients with clinical symptoms of AIDS in three west African countries*. J Clin Virol, 1998. **11**(3): p. 173-81.
341. Hagopian, A. and M. Micek. *Calculating How Many Health Workers are Needed at Full Scale-up in Mozambique*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
342. Egger, M. *Outcomes of Antiretroviral Treatment in Resource Limited and Industrialized Countries*. in *14th Conference on Retroviruses and Opportunistic Infections* (http://www.retroconference.org/2007/data/files/webpage_for_CROI.htm). 2007. Los Angeles.
343. De Cock, K.M., et al., *Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice*. Jama, 2000. **283**(9): p. 1175-82.
344. Stover, J., et al., *Projecting the demographic impact of AIDS and the number of people in need of treatment: updates to the Spectrum projection package*. Sex Transm Infect, 2006. **82 Suppl 3**: p. iii45-50.
345. Marston, M., et al., *Estimating the net effect of HIV on child mortality in African populations affected by generalized HIV epidemics*. J Acquir Immune Defic Syndr, 2005. **38**(2): p. 219-27.
346. Fassinou, P., et al., *Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire*. Aids, 2004. **18**(14): p. 1905-13.
347. Weiser, S.D., et al., *Routine HIV Testing in Botswana: A Population-Based Study on Attitudes, Practices, and Human Rights Concerns*. PLoS Med, 2006. **3**(7): p. e261.
348. Bakari, M., et al., *The natural course of disease following HIV-1 infection in dar es salaam, Tanzania: a study among hotel workers relating clinical events to CD4 T-lymphocyte counts*. Scand J Infect Dis, 2004. **36**(6-7): p. 466-73.
349. Smit et al., *Comparison of ART survival outcomes in Dutch Hospitals*. In preparation.
350. Hatzold, K. and N. Taruberekera. *Effect of Perceived Treatment Availability on HIV Prevalence Among T&C Clients in Zimbabwe (abstract 155)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
351. Schilsky, A., et al. *Clinicians or counselors? Challenges to the scale-up of HIV testing and counselling in Health Facilities (abstract 487)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2007. Kigali, Rwanda.

352. Bunnell, R., et al., *Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda*. AIDS, 2006. **20**(1): p. 85-92.
353. Fiscus, S.A., et al., *Rapid, real-time detection of acute HIV infection in patients in Africa*. J Infect Dis, 2007. **195**(3): p. 416-24.
354. WHO and UNAIDS, *New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications* (available at http://data.unaids.org/pub/Report/2007/mc_recommendations_en.pdf?preview=true). 2007.
355. UNAIDS, *AIDS Epidemic Update*. (available from http://data.unaids.org/pub/EpiReport/2006/2006_EpiUpdate_en.pdf), 2006.
356. National Institute for Health and Clinical Excellence, <http://www.nice.org.uk/>, accessed 25th June, 2007.
357. BBC News, *Alzheimer's drugs court challenge*. <http://news.bbc.co.uk/1/hi/health/6230530.stm>, accessed 25th June, 2007.
358. De Cock, K. *Rolling Out Opt-Out and Other New Approaches: Updated Guidelines (G1)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2007. Kigali, Rwanda.
359. United Nations Economic and Social Council, *The Siracusa Principles on the limitations and derogation provisions in the international covenant on civil and political rights*. (available from <http://www.article23.org.hk/english/research/ICCPR.doc>). UN Doc. E/CN.4/1985/4 (1985). Annex.
360. Haigh, F., *Human rights approach to health*. Croat Med J, 2002. **43**(2): p. 166-9.
361. Pang, X., et al., *Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing, 2003*. Jama, 2003. **290**(24): p. 3215-21.
362. USA Today, *TB-infected traveler quarantined*. http://www.usatoday.com/news/health/2007-05-29-tb_N.htm, accessed 25th June, 2007.
363. BBC News, *HIV man guilty of infecting lover*. Web: www.bbc.co.uk/news/, Accessed 31/01/06.
364. The Sunday Times (South Africa), *Make HIV tests compulsory for South Africans*. <http://www.sundaytimes.co.za/PrintEdition/Article.aspx?id=481394>, accessed 25th June, 2007.
365. Garnett, G.P., et al., *Behavioural data as an adjunct to HIV surveillance data*. Sex Transm Infect, 2006. **82**(suppl_1): p. i57-62.
366. Gregson, S., et al., *HIV infection and reproductive health in teenage women orphaned and made vulnerable by AIDS in Zimbabwe*. AIDS Care, 2005. **17**(7): p. 785-94.
367. Scheer, S., et al., *Effect of highly active antiretroviral therapy on diagnoses of sexually transmitted diseases in people with AIDS*. Lancet, 2001. **357**(9254): p. 432-5.

368. Stolte, I.G., et al., *Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART*. Sex Transm Infect, 2001. **77**(3): p. 184-6.
369. Autier, P., et al., *Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children*. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. J Natl Cancer Inst, 1998. **90**(24): p. 1873-80.
370. Smith, J., et al. *Understanding the Impact of Male Circumcision as an Intervention (abstract 1673)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2007. Kigali, Rwanda.
371. Boily, M.C., C. Lowndes, and M. Alary, *The impact of HIV epidemic phases on the effectiveness of core group interventions: insights from mathematical models*. Sex Transm Infect, 2002. **78 Suppl 1**: p. i78-90.
372. Cowan, F.M., et al., *Is sexual contact with sex workers important in driving the HIV epidemic among men in rural Zimbabwe?* J Acquir Immune Defic Syndr, 2005. **40**(3): p. 371-6.
373. Were, W., et al. *Undiagnosed HIV Infection and Couple HIV Discordance Among Household Members of HIV-Infected People Receiving Antiretroviral Therapy in Uganda (abstract 134)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.
374. Mishra, V., et al. *Why Do So Many HIV-Discordant Couples in Sub-Saharan Africa Have Female Partners Infected, Not Male Partners? (abstract 1717)*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2007. Kigali, Rwanda.
375. Coffee, M.P., et al., *Patterns of movement and risk of HIV infection in rural Zimbabwe*. J Infect Dis, 2005. **191 Suppl 1**: p. S159-67.
376. *Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network)*, <http://www.lshtm.ac.uk/cps/alpha/>. London School of Hygiene & Tropical Medicine.
377. Hallett, T.B., et al., *Age at First Sex and HIV in Rural Zimbabwe – Trends and Determinants*. In press.
378. Lewis, J.J.C., et al. *Patterns of sexual behaviour and the risk of HIV infection in rural Zimbabwe*. in *XIV International AIDS Conference*. 2002. Barcelona, Spain.
379. Lewis, J.J., et al., *Evaluating the proximate determinants framework for HIV infection in rural Zimbabwe*. Sex Transm Infect, 2007.
380. Boerma, J.T., et al., *Sociodemographic context of the AIDS epidemic in a rural area in Tanzania with a focus on people's mobility and marriage*. Sex Transm Infect, 2002. **78 Suppl 1**: p. i97-105.
381. Hallett, T., et al. *Modelling the Decline in HIV Risk in Generalised Epidemics and the Potential Impact of 'ABC' Behavioural Interventions and VCT*. in *Infectious Diseases Society of America 43rd Annual Meeting*. 2005. San Francisco.
382. Aberle-Grasse, J., et al. *Potential for Advancing HIV Prevention Through Increased Pre-Marital Testing*. in *The 2006 HIV/AIDS PEPFAR Implementers' Meeting*. 2006. Durban, South Africa.

Appendix A: Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti (published manuscript)

Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti

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Objective: To determine whether observed changes in HIV prevalence in countries with generalised HIV epidemics are associated with changes in sexual risk behaviour.

Methods: A mathematical model was developed to explore the relation between prevalence recorded at antenatal clinics (ANCs) and the pattern of incidence of infection throughout the population. To create a null model a range of assumptions about sexual behaviour, natural history of infection, and sampling biases in ANC populations were explored to determine which factors maximised declines in prevalence in the absence of behaviour change. Modelled prevalence, where possible based on locally collected behavioural data, was compared with the observed prevalence data in urban Haiti, urban Kenya, urban Cote d'Ivoire, Malawi, Zimbabwe, Rwanda, Uganda, and urban Ethiopia.

Results: Recent downturns in prevalence observed in urban Kenya, Zimbabwe, and urban Haiti, like Uganda before them, could only be replicated in the model through reductions in risk associated with changes in behaviour. In contrast, prevalence trends in urban Cote d'Ivoire, Malawi, urban Ethiopia, and Rwanda show no signs of changed sexual behaviour.

Conclusions: Changes in patterns of HIV prevalence in urban Kenya, Zimbabwe, and urban Haiti are quite recent and caution is required because of doubts over the accuracy and representativeness of these estimates. Nonetheless, the observed changes are consistent with behaviour change and not the natural course of the HIV epidemic.

The prevalence of HIV among women attending antenatal clinics (ANCs), collected over time from the same sites, is fundamental to estimating the scale of the epidemic. The interpretation of trends in prevalence is important in understanding changes in population level risk but is complicated by the need to distinguish between the expected natural history of the epidemic and more pronounced changes arising from changes to individuals' sexual behaviour.¹ In the case of Uganda and Thailand this has been possible and changes in the prevalence of HIV have been accepted to be the product of widespread alterations in sexual risk behaviour.²⁻⁵ These national success stories have had profound implications for global policy on HIV control leading to the development of prevention strategies and the investment of significant resources.^{6,7} When the downturn in prevalence was first detected in Uganda the belief that behaviour change was responsible was strengthened through comparing observed prevalence trends with those generated by mathematical models with and without changes in risk behaviour.²

Mathematical models are a precise way of describing assumptions about the transmission dynamics of an infectious disease and can be used to generate predictions. It is possible to generate predictions of HIV prevalence with and without behaviour change and test which predictions are consistent with observed patterns of prevalence. Models of HIV transmission dynamics have a long history and many complexities have been explored, including the impact of variation in risk behaviour,⁸ patterns of disease and infectiousness over time,⁹ and the impact of details of the

dynamic network of sexual behaviour. However, models have also been developed to explore specific questions such as the impact of HIV on demography,¹⁰ the impact of particular interventions like hypothetical vaccines^{11,12} and the importance of particular sexual network parameters.¹³ Such models are best developed in a stepwise fashion testing the importance of each particular assumption. For simplicity the model should be parsimonious and include only as much detail as is relevant to the question in hand.¹⁴ In developing models to explore the potential changes in HIV prevalence it is important that they contain the assumptions that can impact on the results of interest.

In this supplement trends in HIV prevalence and associated evidence from sexual behaviour surveys from a number of countries have been described and interpreted. Such interpretation will be strengthened through a comparison of predicted trends under a range of assumptions in mathematical models. Because the data in ANC populations are obviously from women and include records of age, comparable model predictions should be sex and age structured. Other key elements to explore are the relation between incidence and prevalence, and the speed and variance in patterns of incidence and subsequent mortality.¹⁵ Further, while an exact description of the pattern of sexual behaviour is unnecessary, it is important to explore changes in the distribution of sexual risk behaviours resulting from

Abbreviations: AIDS, acquired immune deficiency syndrome; ANC, antenatal clinic; HIV, human immunodeficiency virus

differential AIDS associated morbidity and mortality so that they can be distinguished from "exogenous" changes brought about by interventions.¹⁶ Another factor that can alter the trends in prevalence is HIV associated sub-fertility that could introduce biases in ANC attendance that change over time.¹⁷

Here we describe the expected dynamics of a generalised HIV epidemic using a newly developed mathematical model, and compare the prevalence data from countries included in this report with model predictions. Where the model can reproduce the observed changes in prevalence with "endogenous" changes only (that is, those caused by HIV and AIDS natural dynamics) it cannot be argued from the data that the population level risks of HIV infection have been altered by the adoption of safer sexual behaviour. On the other hand, if the model cannot reproduce the observed epidemiological trends without also assuming changes in risk behaviour, this provides evidence that the proximate determinants of HIV incidence have been altered through adoption of safer sexual practices.

METHODS

We developed a deterministic mathematical model of the heterosexual transmission of HIV in a sex, age, and sexual activity (defined according to the rate of sexual partner change) stratified population, based on earlier published models.¹⁷ To focus on trends in prevalence in young women attending ANCs the model included a detailed yearly age structure of young adults allowing changes in age of sexual debut and rates of partner change in those recently entering the sexually active population. Full details of the model can be found in the supplementary material (see online at <http://sti.bmjournals.com/supplemental/>) but the key assumptions in the model are described here. HIV is assumed to be transmitted through sexual partnerships or at the time of birth from an infected mother to her child. The population is divided into five sexual activity groups with different numbers of sexual partnerships formed per year. On sexual debut most individuals enter the group with the lowest sexual activity, but a minority enter groups with much higher sexual activity. In response to differential mortality two assumptions are possible: (1) the highest sexual activity groups can be depleted if those with high risk suffer greater mortality; and (2) the relative sizes of the groups are maintained by recruiting individuals from other sexual activity groups into the higher activity groups.

An individual of a particular sex, age, and sexual activity forms a number of sexual partnerships each year, with partnerships preferentially directed between older men and younger women and with individuals of the same sexual activity class. Transmission of HIV is assumed to be prevented by consistent use of condoms with the probability of consistent use dependent on the age of both partners. To represent the long and variable incubation period and the higher transmission probability associated with initial and later stages of infection, those infected progress through three stages of asymptomatic infection prior to AIDS: a first stage lasting three months with a high transmission probability; a second stage lasting several years with the lowest transmission probability; and a third stage lasting six months with a high transmission probability.

A model scenario with no exogenous behaviour change was compared with one where behaviour change was assumed to reduce the rate of sexual partner change or the transmission probability (through increased condom use). Where behaviour data were available (using the same indicator in successive surveys) these were used to estimate the change in parameter values for an alternative run of the model. If no such data were available a stepwise change in

the transmission probability per partnership was used instead.

From each country the following data were sought for model parameterisation: median age at first sex for males and females, age specific use of condoms (at last sex/with non-regular partner), age specific mean number of sexual partners in last year, and age of spouse or last partner. These population averages fail to specify some of the details of individual behaviour required to fully parameterise the model. To overcome this lack of detail in countrywide data we used detailed sexual behaviour data from a household based population survey in rural Zimbabwe¹⁸ to specify the heterogeneity in rates of change of sexual partners and the dependency of condom use on age of both partners. For each country all values were altered to generate the observed averages. The mean age difference between sexual partners was estimated by either the mean age difference between spouses or the difference in the median age of marriage between men and women. Where no data were available default model parameters were based on rural Zimbabwe data,¹⁸ with the exception of partner acquisition rates as a function of age, which were based instead on observed patterns reported in Cote d'Ivoire for 1994. All simulations were run using common demographic background rates¹⁹ such that in the absence of infection the population would grow at approximately 4% per year with life expectancy at birth for males and females 52.1 and 54.7, respectively. The behaviour data used to parameterise the model are summarised in table 1 and the sources are identified in the supplementary material. All model parameters are listed in tables S1-S6 in the supplementary material (see online at <http://sti.bmjournals.com/supplemental/>).

A brief summary of the HIV prevalence data used follows:

- Haiti—5 urban ANC sites from 1993 to 2003²⁰
- Kenya—13 urban ANC sites from 1990 to 2003²¹
- Zimbabwe—nationwide ANC sites from 2000 to 2004 (Genscreen test)²²
- Cote d'Ivoire—10 urban sites from 1997 to 2002
- Malawi—19 nationwide sites from 1996 to 2003²³
- Rwanda—24 nationwide ANC sites in 2002 and 2003²⁴
- Uganda—5 ANC sites from 1992 to 2002 (St Mary's Hospital, Lacor, Gulu (northern Uganda), St Francis Hospital, Kampala (central Uganda), Mbarara Hospital (southwestern Uganda), Jinja Hospital (eastern Uganda) and Mbale Hospital (eastern Uganda)²⁵
- Ethiopia—urban sites from 2001 to 2003.²⁶

To avoid trends in prevalence reflecting changes in the population sampling, only data collected from the same ANCs over time were included in our analysis. Where sample sizes were available we could construct 95% confidence intervals around the prevalence estimates (data pooled by site and age if no weighting information available). If such data were not available we arbitrarily include a 3% uncertainty interval or give the range of estimates for specific sites.

The predicted growth in the prevalence of HIV from the model was roughly matched to prevalence by adjusting the transmission probability per sexual partnership and the assortativeness of mixing between the high and low sexual activity groups. Other model parameters values were chosen to maximise the natural decline in HIV prevalence and create a robust "null model" of trends without extrinsic behaviour change. These assumptions are outlined in the results. If the recorded changes in prevalence could not be reproduced without assuming changes in sexual behaviour, stepwise changes in behavioural parameters were made to reflect the trends in sexual behaviour observed in successive surveys.

Table 1 Behavioural parameters used in the model

	Haiti	Kenya	Zimbabwe	Uganda (N, C, W)*	Uganda (E)*	Ethiopia	Cote d'Ivoire	Malawi	Rwanda
Baseline settings									
Age at first sex									
Males	18	17	17†	17	17	20	18	18	17†
Females	19	17	17†	17	17	16	16	17	17†
Probability of consistent condom per partnership (male <24 with female <24)	0.09	0.29	0.06	0.42	0.42	0.11	0.27	0.32	0.32†
Mean age difference between partners (male age – female age)	6.4	5.4	7.3†	7.3†	7.3†	7.3†	8.6	5.8	7.3†
Behavioural changes (year implemented)									
Probability of HIV transmission (proportionate reduction)	N/A	N/A	50% (2000)	75% (1990)	80% (1994)	N/A	N/A	N/A	N/A
Delay in age at first sex, males (years)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Delay in age at first sex, females (years)	N/A	+1 (1999)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of sexual partnerships per year (proportionate reduction)	10% (1995)	F 30% (1999) M 26% (1999); 0.80 (2001)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Probability of consistent condom per partnership (proportionate increase)	100% (1995)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*Uganda sites were provided separately as N—north (St Mary's Hospital, Lacor, Gulu), C—central (St Francis Hospital, Nsambya, Kampala), west (Mbarara Hospital), E—eastern (Jinja Hospital and Mbale Hospital).

†The default parameter was used in place of country specific data.

Sources for behaviour data are listed in the supplementary material (see online at <http://sti.bmjournals.com/supplemental/>).
F, females; M, males; N/A, not available.

These changes were included at the time points between the surveys giving a likely match between the model and the data.

RESULTS

The aim of modelling the transmission dynamics of HIV here was to predict the course of the epidemic in the absence of behaviour change. This allows us to exclude the natural history of the epidemic in interpreting any observed reductions in prevalence. For a conservative analysis we need to adopt assumptions that maximise the predicted declines in prevalence.

As HIV spreads first among those with the highest risk of acquiring infection, incidence increases sharply, but as those high risk individuals die the risk of infection they pose to others is removed so that incidence may subsequently decline (fig 1A). A decline in prevalence 10–20 years into the epidemic could be the product of that historical reduction in incidence or a more recent reduction in incidence associated with the deliberate adoption of safer sexual behaviour. Understanding the determinants of that initial decline in incidence and how it influences later trends in prevalence is crucial in our analysis. The rapid local “saturation” of those at highest risk is a consequence of the extreme variance in sexual activity within the population^{10 27 28} with the majority forming few new sexual partnerships each year and a minority forming very many more.^{10 29 30} Soon after the infection is introduced to the population those individuals with the riskiest sexual behaviour become infected, especially if there is a high transmission probability of the virus in those recently infected (fig 1A). Subsequent infection mainly occurs in those with lower risk sexual behaviour and the number of new cases and the risk per susceptible decreases (Baggaley R, Boily MC, White RG, *et al.* Systematic review of HIV-1 transmission probabilities in absence of antiretroviral therapy. Manuscript in preparation). Whether this initial decline in incidence generates a subsequent fall in prevalence is determined by how closely incidence and prevalence are coupled—that is, the interval between infection and death.²⁷ A long interval leads prevalence to record information about

the risk experience accumulated over many years with the early reduction in incidence not manifest, but a shorter interval allows prevalence to follow the drop in incidence more closely¹⁵ (fig 1A). The relation between prevalence and incidence is easier to interpret in young people because infections will have been acquired recently as they have only recently become at risk (as they begin sexual activity). Thus, in young adults prevalence is more a reflection of the current pattern of HIV transmission and is less influenced by deaths among those infected. Changes in prevalence following the adoption of safer sexual behaviour should appear first and most clearly among young people³¹ (fig 1B).

Following the initial growth of an HIV epidemic, and as those with riskiest sexual behaviour who are infected die or reduce their sexual activity due to illness, the structure of the sexual network could begin to change; both because the high risk behaviour itself is lost, and because the opportunity for other individuals to form high risk partnerships is removed. This depends upon how an individual's risk behaviour changes as they age and the change in risk behaviour of those who remain following the deaths of those most at risk. At one extreme, if individuals remain at the same level of risk throughout their life, average sexual behaviour naturally becomes safer as those with risky behaviour die (fig 1C). For this reason, changes in average sexual behaviour should be interpreted with some caution since the safer average behaviour may not be a consequence of the deliberate adoption of safer behaviours. In the model it is also possible to assume that as the number of high risk individuals declines less risky individuals can adopt higher risk behaviour to keep constant average rate of partner acquisition. In this case, incidence remains high and may balance the surge in AIDS related mortality, maintaining a steady prevalence of infection (fig 1D).

In interpreting trends in HIV prevalence we also need to be concerned with changing biases in the ANC population as a sample of women.³² Firstly, reductions in fertility caused by the progression of HIV infection could exaggerate the decline in prevalence seen in the ANC sample relative to the general population. Recent data suggest that fertility is suppressed

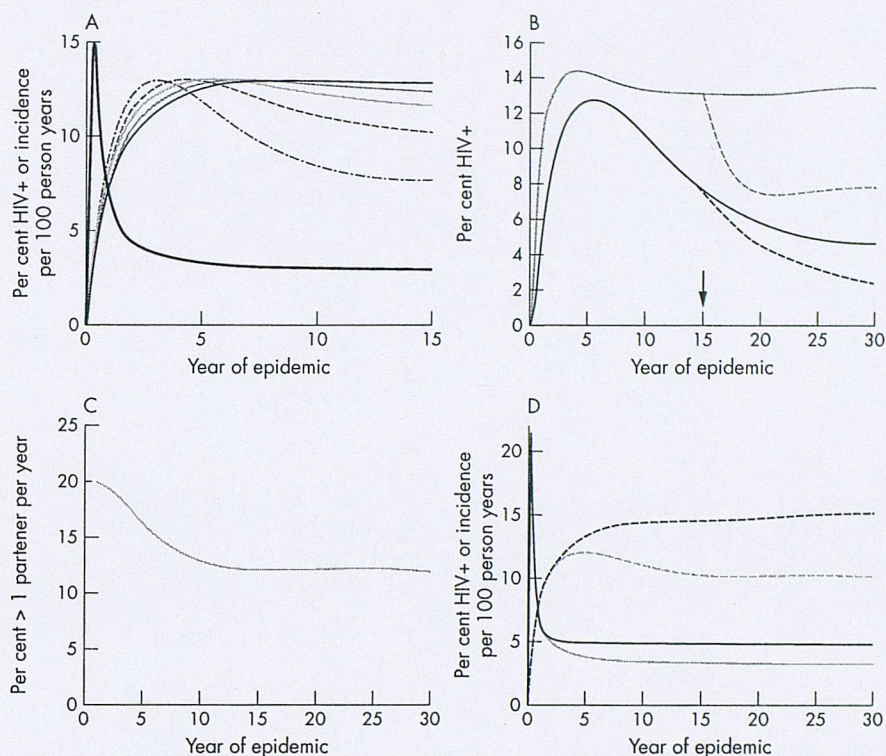


Figure 1 Natural dynamics of generalised HIV epidemic. (A) Predicted HIV incidence per 100 person years at risk (thick black line) and HIV prevalence among women for varying periods from infection to death. For 25 year olds mean interval from infection until death is 11 years (thin black line), 9 years (dark grey line), 7 years (light grey line), 5 year (dashed line), and 3 years (dotted/dashed line). (B) HIV prevalence among women aged 20–24 years (grey lines) and 30–35 years (black lines) without behaviour change (solid lines) and with the transmission probability halving at year 15 (dashed lines). (C) The proportion of men and women currently forming more than one sexual partnership per year. (D) Predicted HIV incidence per 100 person years at risk (solid lines) and HIV prevalence among women (dashed lines) with the relative size of sexual activity groups being allowed to change freely (grey lines) and being held constant with recruitment to the high activity groups from lower activity groups (black lines).

before the final stages of HIV infection.^{33 34} Simulations show that this sub-fertility and exclusion from the ANC sample of those infected will occur rapidly (fig 2A). Secondly, the ANC sample might overrepresent the women most likely to be infected with HIV, since sexual behaviour that exposes the women to the infection (for example, unprotected sex) also exposes the women to the risk of pregnancy.³² Because prevalence among high risk women rises quickly and falls steeply an ANC sample may represent the extreme changes in prevalence (fig 2B).

Our exploratory analysis found that the most extreme natural declines in prevalence arise from the greatest contrast between the initial peak and subsequent low incidence level, and from the shortest period from infection to death. Within reasonable limits we maximised the initial heterogeneity in rate of sexual partnership formation and the variation in transmission probability with stage of HIV infection. The acute peak in incidence reflects a lack of geographic space, stochastic effects, and waiting times between sexual partnership formation and HIV transmission. All of these distribute the peak in incidence over time and lessen the predicted prevalence decline (results not shown). Prevalence declines most when there is no compensatory recruitment into the high sexual activity groups in response to differential mortality and appears most extreme when assuming that the ANC over-samples high risk individuals. All model parameters are listed in tables S1–S6 in the supplementary material (see online at <http://sti.bmjournals.com/supplemental/>). In the case of Uganda, urban Kenya, Zimbabwe, and urban Haiti, under a range of realistic and extreme assumptions (not all shown), our model can only replicate

observed declines in prevalence by assuming that risk behaviour has also declined.

The data analysed from Malawi, urban Cote d'Ivoire, and Rwanda show no sign of a decrease in prevalence among all adults, or selected age groups (fig 4). There is some evidence that the proportion of men and women having had more than one or two sexual partners in the last 12 months has decreased in Malawi and Cote d'Ivoire.²³

The decline in Uganda is the earliest and most researched.^{2 3} Sites in north, central, and west Uganda have a similar epidemic curve with prevalence among both 15–49 year old and 20–24 year old women declining from approximately 30% to 10% (fig 3A, B). These declines could be generated in our model with a reduction in the transmission probability of 75% in 1992—a similar reduction to that previously estimated.^{2 3} No subsequent reduction is necessary to generate the observed trends and the assumed change in risk pre-dates observational cohort data from Rakai used to argue that incidence has not fallen.³⁵ In eastern sites (Jinja Hospital and Mbale Hospital) the decline in prevalence in women aged 15–49 years from approximately 15% to 5% (fig 3C) is only possible with behaviour change, whereas prevalence estimates for women aged 20–24 years show more fluctuations and are possible to model without risk behaviour changing (fig 3D). Such seemingly contradictory results may arise from the greater error in prevalence estimates from a more restricted age group (sample sizes were not available to estimate confidence intervals), or from shifting behavioural parameters (in particular, age at first sex), which alter the distribution of the infection with respect to age at the same time as overall prevalence is decreasing.

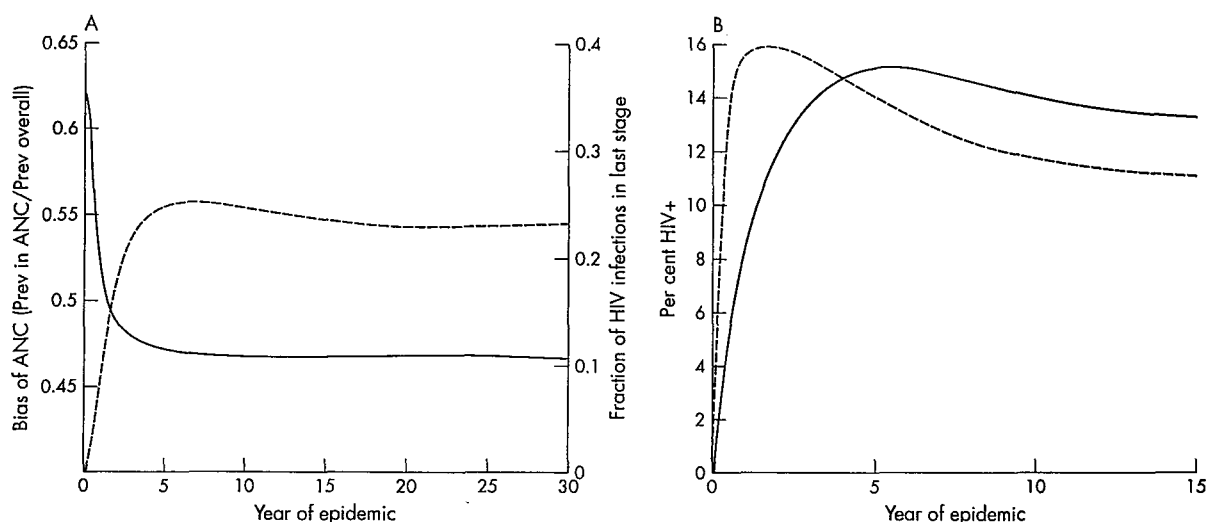


Figure 2 Biases in antenatal clinic (ANC) sample. (A) Ratio of percentage of women attending ANCs who are HIV+ and percentage of all HIV+ women, assuming that the probability of women being included in the ANC sample depends on stage of HIV (solid line) and the fraction of HIV cases in late stage of infection (tertiary stage or full-blown AIDS) (dashed line). (B) Percentage of women attending ANC who are HIV+ (dashed line) and percentage of all women HIV+ (solid line), assuming that the probability of being included in the ANC sample depends on sexual activity group.

In parts of urban Kenya HIV prevalence among women aged 15 and over fell from approximately 12% in 2001 to 9% in 2003 with a concomitant decline in those aged 20–24 years from 13% to 10%. The downturn in prevalence was particularly pronounced in four urban sites (Busia, Meru, Nakuru, and Thika) where median prevalence fell from 28% in 1999 to 9% in 2003 among 15–49 year old women and from 29% in 1998 to 9% in 2002 among 15–24 year olds (fig 3E, F). Again, to reproduce these changes requires assuming that risk behaviour has changed. Between behavioural surveys in 1993, 1998, and 2003 there were substantial reductions in the proportions of men and women having more than one sexual partner. In addition, between 1998 and 2003, median age at first sex for females increased. To represent these changes in the model, age specific reductions of the mean rate of partner change were assumed in 1998 and 2001 and an instantaneous increase in female age at first sex was included in 2001. The decrease in prevalence, though, is better matched with a reduction in the transmission probability of 70% in 1997 (dotted lines). Four other urban sites (Garissa, Kisii, Kitui, and Nyeri) also experienced a reduction in median prevalence: 14% in 2000 to 7% in 2003 among 15–49 year olds, and same behaviour changes were assumed to bring the model into agreement with the data (fig 3G). However, the trend in prevalence among 15–24 year olds is less clear and does not seem inconsistent with the null model (fig 3H).

In Zimbabwe between 2002 and 2004 a decline in prevalence from 29% to 24% is recorded among 15–44 year old women and from 25% to 20% among 15–24 year old women (fig 3I, J). In both cases, the observed changes cannot be reproduced through the natural evolution of the epidemic alone, but can be generated with if the overall probability of infection is reduced by half in 2001.

In urban Haiti, prevalence has decreased since 2000 from approximately 5.5% to 3% among 15–44 year old women—a decline that could not be generated in the absence of behaviour change (fig 3K). Among 15–24 year olds, prevalence has also declined although the uncertainty associated with these estimates does not rule out the possibility that prevalence has remained constant. In behavioural surveys there was a 20% decline in the mean number of sexual partners between 1994 and 2000 and condom use increased twofold to threefold between 2000/01 and 2003. These changes were represented in

the model by a step-change in partner change rates in 1994 and in condom use in 1999.

Adult prevalence (15–49 years) in urban Ethiopia fell from 14% in 2001 to 12% in 2003 (fig 4A) and from 15% to 13% over the same time among 20–24 year olds (fig 4B). These modest declines could be reproduced by the model without assuming any changes to sexual risk behaviour.

DISCUSSION

Our model illustrates the potential for HIV prevalence to decline without a deliberate adoption of safer sexual behaviours. However, the inability of the model to replicate the extent of the observed declines allows us to be more confident that changes in prevalence in Uganda, parts of urban Kenya, Zimbabwe, and urban Haiti are unlikely to be a product of these natural dynamics. The declines observed can be contrasted with urban Ethiopia, where the prevalence patterns could be reproduced with sexual behaviour and HIV transmission remaining unchanged, and urban Cote d'Ivoire, Malawi, and Rwanda where aggregated prevalence has not recently decreased. This does not exclude the possibility, however, that behaviour change has had a significant impact on the HIV epidemic.

The model of HIV transmission is influenced by a large number of interacting variables which, without a dramatic increase in data sources, limits our ability to statistically fit the model and estimate the most likely value of particular parameters. A statistical interpretation of our results depends upon the confidence intervals around the prevalence estimates at particular time points and whether our extreme decline in prevalence falls within them. It should be noted that some of the prevalence estimates used here did not have reported sample sizes or statistical confidence intervals. In addition to statistical error, changing biases could lead to the observed and predicted trends separating. One such bias is suggested by recent data indicating that fertility is suppressed before the final stages of HIV infection.²⁴ Sub-fertility in those with longstanding HIV infection could lead to their exclusion from the ANC sample, but our model indicates that the effects of this bias will pre-date the declines in prevalence we are now observing. Nationally, estimates of prevalence often fall as samples are recruited from progressively more remote populations or as HIV tests become more specific. To avoid

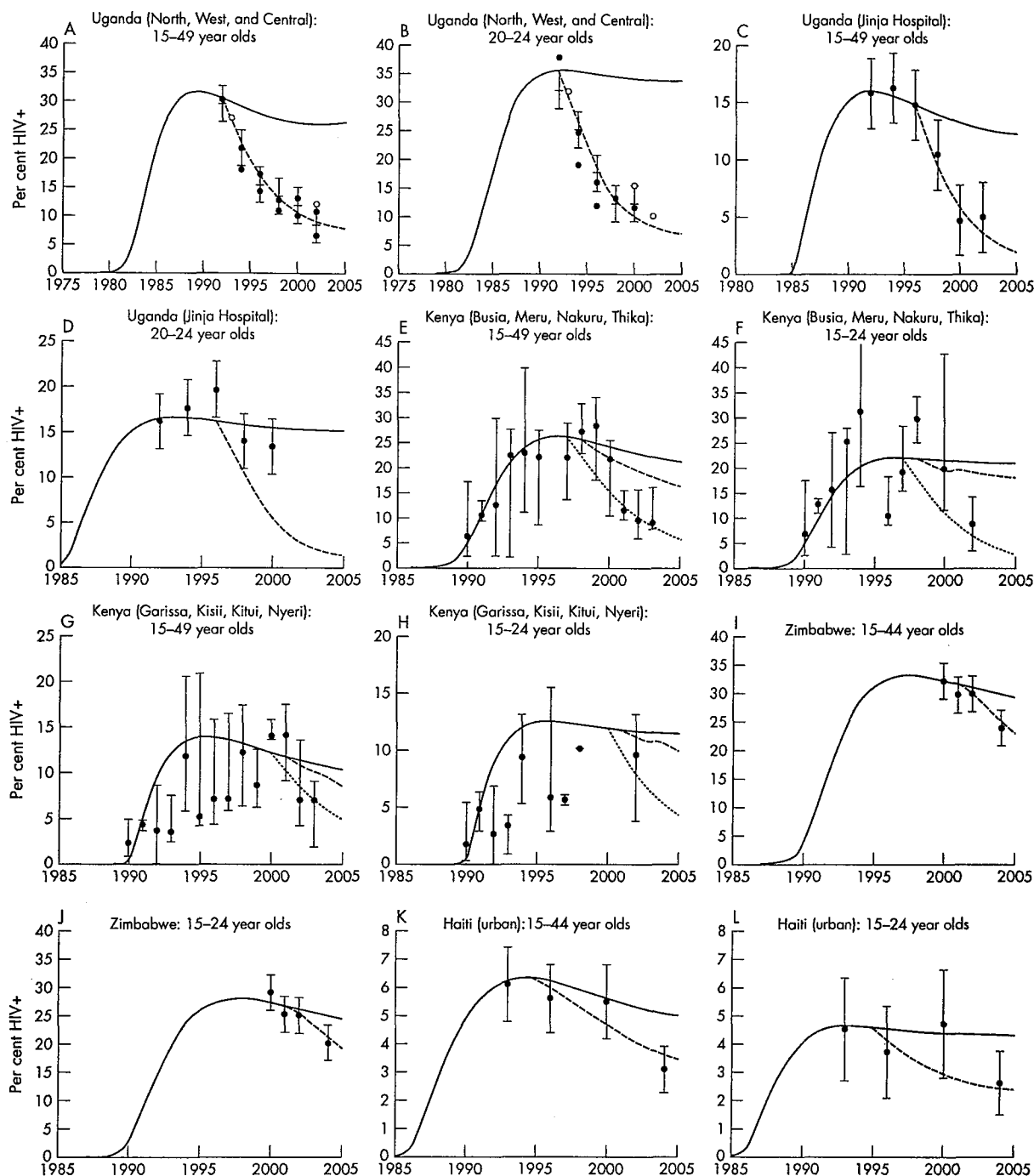


Figure 3 ANC prevalence data (dots), model output assuming no behaviour change (full lines) and model output assuming behaviour change (dashed lines). Uganda: St Mary's Hospital, Lacor, Gulu, St Francis Hospital, Nsambya, Kampala, and Mbarara Hospital (A) 15-49 years olds and (B) 20-24 year olds; Jinja Hospital (C) 15-49 year olds and (D) 20-24 year olds (error bars $\pm 3\%$). Urban Kenya: Busia, Meru, Nakuru, and Thika (E) 15-49 year olds and (F) 15-24 year olds (error bars show range); Garissa, Kisii, Kitui and Nyeri (G) 15-49 year olds and (H) 15-24 year olds (error bars show range). Zimbabwe: (I) 15-44 year olds and (J) 15-24 year olds, (error bars $\pm 3\%$). Urban Haiti: (K) 15-44 year olds and (L) 15-24 year olds (error bars $\pm 95\%$ CI).

these problems we have only presented data from clinics consistently included.

Restricting HIV prevalence data to the younger age groups often fails to help identify recent reductions in HIV incidence. In young age groups the confounding effects of mortality and sub-fertility on prevalence trends are minimised and reductions in incidence will be translated rapidly into reduced prevalence. However, the uncertainty associated with the

prevalence point estimates is often too great to detect trends. In contrast, although prevalence estimates from across all adult ages are prone to natural reductions, they may be determined more precisely and so allow trends due to the natural evolution of the epidemic and due to behaviour change to be distinguished.

One of the problems in reconstructing HIV epidemics is that current sexual behaviour already includes reductions in

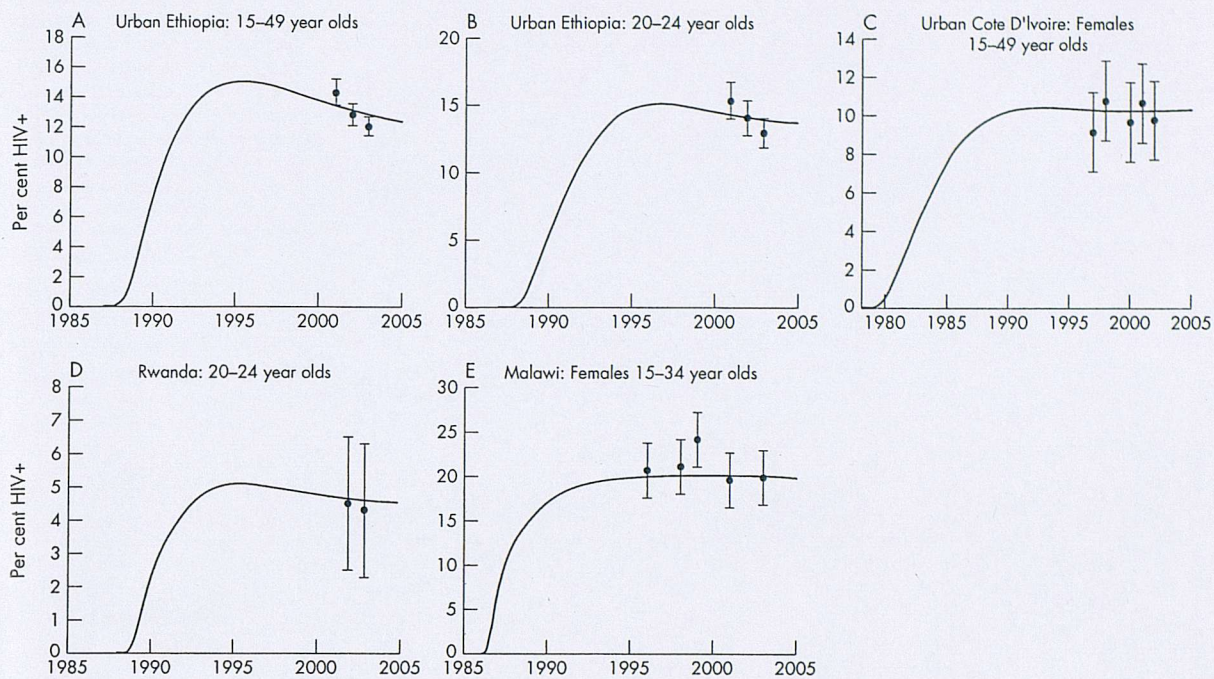


Figure 4 ANC prevalence data (dots) and model output assuming no behaviour change (full lines). Urban Ethiopia: (A) 15–49 year olds, and (B) 20–24 year olds (error bars $\pm$ 95% CI). (C) Urban Cote d'Ivoire 15–49 year olds (error bars are $\pm$ 3%). (D) Rwanda 20–24 year olds (error bars are $\pm$ 3%). (E) Malawi: 15–34 year olds (error bars are $\pm$ 3%).

risky sexual behaviour brought about by the HIV epidemic and associated mortality in those who were previously at the greatest risk of infection. We are forced to assume that the heterogeneity in sexual partner change rates was originally greater than that observed today. In addition, while we attempted a reconstruction of country specific epidemics, local patterns of risk were often not available, necessitating the adoption of standard patterns for condom use and age specific partner change rates. Fortunately, despite being important for fitting age and sex specific prevalence, these patterns have little bearing on the course of the epidemic once its magnitude is established.

In summary, our analysis supports a belief that behaviour change and decreased incidence is reducing prevalence in four countries with generalised epidemics. In all but Uganda the declines in prevalence are quite recent though the evidence of behaviour change in parts of urban Kenya is

accumulating where several sequential HIV prevalence estimates have shown a continued decline. Although a substantial prevalence decline in Zimbabwe has only been detected recently, credence is lent to this observation by the increasing evidence of behavioural change (Gregson S, Garnett GP, Nyamukapa CA, *et al.* HIV decline associated with behaviour change in eastern Zimbabwe. Submitted for publication). The observed dip in prevalence in urban Haiti, on the other hand, could turn out to be anomalous. For a long time Uganda^{2,3} and Thailand^{4,5} have been the key national level examples of success in reducing HIV incidence and the main source of evidence on HIV prevention. Perhaps it is time for Kenya and Zimbabwe to be added to the list.

AUTHORS' CONTRIBUTIONS

TBH was responsible for programming and implementing the mathematical model. The paper was written by TBH and GPG and redrafted by SG, JMG, JS, and PG. The study was jointly conceived by all of the authors and all contributed to the compilation, assessment, and analysis of the data.

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Key messages

- Twenty years into the generalised epidemics of sub-Saharan Africa, evidence is emerging from some countries that HIV prevalence is falling. Prevalence declines can result not only from individuals adopting safer sexual behaviour but also through AIDS associated mortality.
- A mathematical model has been used to assess whether the observed declines could be the result only of mortality and not of changing sexual behaviour.
- In Uganda, parts of urban Kenya, Zimbabwe, and urban Haiti, HIV prevalence has declined further than would be expected through the effects of mortality alone, suggesting that in these settings individuals have begun to adopt safer sexual behaviour.

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REFERENCES

- 1 Joint United Nations Programme on AIDS Reference Group on Estimates Modelling and Projections. *Trends in HIV incidence and prevalence: natural course of the epidemic or results of behavioural change?* Geneva: UNAIDS, 1999.
- 2 Kilian AH, Gregson S, Ndyabangi B, et al. Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda. *AIDS* 1999;13:391-8.
- 3 Stoneburner RL, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. *Science* 2004;304:714-18.
- 4 Nelson KE, Celentano DD, Eiumtrakol S, et al. Changes in sexual behavior and a decline in HIV infection among young men in Thailand. *N Engl J Med* 1996;335:297-303.
- 5 Rajanapithayakorn W, Hanenberg R. The 100% condom program in Thailand. *AIDS* 1996;10:1-7.
- 6 Joint United Nations Programme on AIDS. *2004 Report of the global AIDS epidemic*. Geneva: UNAIDS, 2004.
- 7 Office of the United States Global AIDS Coordinator. *The President's Emergency Plan for AIDS Relief, US Five-year global HIV/AIDS strategy, 2004*. Washington DC: Office of the Global AIDS Coordinator, 2004.
- 8 Anderson RM, Medley GF, May RM, et al. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA J Math Appl Med Biol* 1986;3:229-63.
- 9 Jacques JA, Koopman JS, Simon CP, et al. Role of the primary infection in epidemics of HIV infection in gay cohorts. *J Acquir Immune Defic Syndr* 1994;7:1169-84.
- 10 Anderson RM, May RM. Epidemiological parameters of HIV transmission. *Nature* 1988;333:514-19.
- 11 Blower SM, McLean AR. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. *Science* 1994;265:1451-4.
- 12 Garnett GP. The basic reproductive rate of infection and the course of HIV epidemics. *AIDS Patient Care STDs* 1998;12:435-49.
- 13 Morris M, Kretzschmar M. Concurrent partnerships and the spread of HIV. *AIDS* 1997;11:641-8.
- 14 Anderson RM, Garnett GP. Mathematical models of the transmission and control of sexually transmitted diseases. *Sex Transm Dis* 2000;27:636-43.
- 15 Gregson S, Garnett GP, Anderson RM. Is HIV-1 likely to become a leading cause of adult mortality in sub-Saharan Africa? *J Acquir Immune Defic Syndr* 1994;7:839-52.
- 16 Baily MC, Lowndes CM, Gregson S. Population-level risk factors for HIV transmission and 'the 4 Cities Study': temporal dynamics and the significance of sexual mixing patterns. *AIDS* 2002;16:2101-2.
- 17 Garnett GP, Gregson S. Monitoring the course of the HIV-1 epidemic: the influence of patterns of fertility on HIV-1 prevalence estimates. *Math Popul Stud* 2000;8:251-77.
- 18 Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet* 2002;359:1896-903.
- 19 Anderson RM, May RM, Ng TW, et al. Age-dependent choice of sexual partners and the transmission dynamics of HIV in Sub-Saharan Africa. *Philos Trans R Soc Lond B Biol Sci* 1992;336:135-55.
- 20 Gaillard EM, Boulos LM, Cayemittes MPA, et al. Understanding the reasons for decline of HIV prevalence in Haiti. *Sex Transm Infect* 2006;82(suppl 1):i14-20.
- 21 Cheluget B, Baltazar G, Oregre P, et al. Evidence for population level declines in adult HIV prevalence in Kenya. *Sex Transm Infect* 2006;82(suppl 1):i21-6.
- 22 Mahomva A, Greby S, Dube S, et al. HIV prevalence and trends from data in Zimbabwe, 1997-2004. *Sex Transm Infect* 2006;82(suppl 1):i42-7.
- 23 Bello GA, Chipeta J, Aberle-Grasse J. Assessment of trends in biological and behavioural surveillance data: is there any evidence of declining HIV prevalence or incidence in Malawi? *Sex Transm Infect* 2006;82(suppl 1):i9-13.
- 24 Kayirangwa E, Hanson J, Munyakazi L, et al. Current trends in Rwanda's HIV/AIDS epidemic. *Sex Transm Infect* 2006;82(suppl 1):i27-31.
- 25 Kirungi WL, Musinguzi J, Madraa E, et al. Trends in antenatal HIV prevalence in urban Uganda associated with uptake of preventive sexual behaviour. *Sex Transm Infect* 2006;82(suppl 1):i36-41.
- 26 Hladik W, Shabbir I, Jelaludin A, et al. HIV/AIDS in Ethiopia: where is the epidemic heading? *Sex Transm Infect* 2006;82(suppl 1):i32-35.
- 27 Anderson RM, May RM. *Infectious diseases of humans*. Oxford: Oxford University Press, 1991.
- 28 Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. *Philos Trans R Soc Lond B Biol Sci* 1993;342:137-59.
- 29 Spira A, Bajos N, and the ASCF group. *Sexual behaviour and AIDS*. Aylesbury: Aldershot, 1994.
- 30 Johnson AM, Wadsworth J, Wellings K, et al. *Sexual attitudes and lifestyles*. Oxford: Blackwell Scientific Publications, 1994.
- 31 Zaba B, Boerma T, White R. Monitoring the AIDS epidemic using HIV prevalence data among young women attending antenatal clinics: prospects and problems. *AIDS* 2000;14:1633-45.
- 32 Zaba B, Gregson S. Measuring the impact of HIV on fertility in Africa. *AIDS* 1998;12(Suppl 1):S41-50.
- 33 Lewis JJ, Ronsmans C, Ezeh A, et al. The population impact of HIV on fertility in sub-Saharan Africa. *AIDS* 2004;18(Suppl 2):S35-43.
- 34 Ross A, Van der Paal L, Lubega R, et al. HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. *AIDS* 2004;18:799-804.
- 35 Wawer MJ. Declines in HIV prevalence in Uganda: not as simple as ABC. Twelfth Annual Retrovirus Conference, Boston, MA, 2005.

***Appendix B: Behaviour change in generalised
HIV epidemics: impact of reducing cross-
generational sex and delaying age at sexual
debut (published manuscript)***

Behaviour change in generalised HIV epidemics: impact of reducing cross-generational sex and delaying age at sexual debut

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Supplementary material
available at <http://sti.bmj.com/supplemental>

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Background: Sexual behavioural change is essential to prevent HIV infections in Africa and statistical analysis of risk factors at the individual-level may be used to design interventions. The importance of reducing cross-generational sex (young women having sex with older men) and delaying age at first sex on the spread of HIV at the population-level has been presumed but not scientifically investigated and quantified.

Methods: A mathematical model of heterosexual spread of HIV was developed to predict the population-level impact of reducing cross-generational sex and delaying sexual debut.

Results: The impact of behaviour change on the spread of HIV is sensitive to the structure and reaction of the sexual network. Reducing cross-generational sex could have little impact on the risk of infection unless it is accompanied by a reduction in the number of risky sexual contacts. Even peer-to-peer sexual mixing can support high endemic levels of HIV. The benefit of delaying sexual debut is comparatively small and is reduced if males continue to prefer young partners or if young women spend more time unmarried. In Manicaland, Zimbabwe, if older men were to use condoms as frequently as young men, the reduction in risk of infection could exceed that generated by a two-year delay in first sex.

Conclusions: At the individual-level avoiding sex with older partners and delaying sexual debut can decrease the risk of infection but at the population-level these interventions may do little to limit the spread of HIV without wider-ranging behavioural changes throughout the sexual network.

The HIV pandemic continues to spread devastation globally.¹ In the generalised epidemics in sub-Saharan Africa, most of the risk is associated with heterosexual sex,²⁻⁵ and behaviour change is essential to reduce the number of new infections. Funding has been made available for interventions to promote behaviour change,^{6,7} but care must be taken to target resources at changing those aspects of sexual behaviour that are most important in the spread of HIV.

Observational studies show that usually HIV prevalence among young women far exceeds that among young men.⁸ This has prompted some to emphasise the importance of protecting young women from infection in particular.^{2,8-11} Statistical analyses of individual behaviour data show that the risk of HIV infection is lower among women who avoid older sexual partners^{12,13} and begin sexual activity later.^{12,14,15} For this reason, it has been suggested that behaviour interventions should focus on reducing cross-generational sex (young women forming sexual partnerships with older men) and delaying sexual debut.^{8,16,17} The importance of these changes at the population level has been presumed but not scientifically investigated and quantified.^{8,11,13,16-20}

Mathematical models allow an assessment of the potential effects of proposed behaviour interventions and can provide a guide to the factors most critical to their success.²¹ Increasingly, the insights gained from mathematical models are well understood and applied,²²⁻²⁴ and consulting mathematical models before implementing epidemiological interventions has become standard practice for emerging epidemiological problems.²⁵⁻²⁷ It can be argued that the same approach should be used to assess the effects of proposed behavioural change interventions on generalised HIV epidemics.

In the present study we considered two questions about proposed behavioural change interventions:

- What population-level effect could discouraging cross-generational sex and promoting delayed age at first sex have on the HIV epidemic?
- What properties of the sexual network determine the size of this impact?

To answer these questions we designed a deterministic mathematical model of the heterosexual transmission of HIV with a detailed yearly age structure of young adults so that changes in age at sexual debut, ages of sexual partners and rates of partner change in those recently entering the sexually active population could be investigated. We have parameterised the model using data collected in a cross-sectional survey in rural Zimbabwe¹² to provide a detailed and well-informed example to illustrate the qualitative results rather than provide an exhaustive description of the various generalised HIV epidemics in Africa.

METHODS

Data sources

A stratified population-based survey was carried out in the Manicaland province of eastern Zimbabwe between July 1998 and January 2000.¹² A follow-up survey was completed after three years.²⁸ A structured face-to-face interview was conducted with almost 10 000 men and women in 12 distinct communities: two forestry plantations, two tea and coffee estates, two small towns, two roadside trading centres and four subsistence farming areas. In three-quarters of interviews with literate

respondents, the answers to sensitive questions about sexual behaviour were recorded using a confidential voting method, the use of which has been associated with reporting of greater sexual activity.²⁹ Condoms were used in all reported sex acts in the last sexual partnership by 17% of males and 8% of females who reported a sexual partnership in the past month. Sex acts were self-defined in the questionnaire, but here we assume that all sex acts are insertive penile-vaginal. The distribution of age difference between sexual partners (male's age minus female's age) takes a similar form for women of all ages and can be modelled by a log-logistic function (figs S1 and S2 in the supplementary material, see <http://sti.bmj.com/supplemental>). The mean age difference is 7 years, and in approximately 25% of partnerships the age difference is 10 years or more.

Mathematical simulation model

We developed a deterministic mathematical model of the heterosexual transmission of HIV in a sex, age and activity-stratified population. The model is defined by a set of partial differential equations with respect to time and age that are solved numerically with a four-stage Runge-Kutta algorithm (time-step = 0.02 years). Full details of the model can be found in the online supplementary material (see <http://sti.bmj.com/supplemental>) but the key assumptions in the model are described here.

HIV is assumed to be transmitted through heterosexual partnerships or at the time of birth from an infected mother to her child. To represent the long and variable incubation period and stage-dependent HIV transmission probability, those infected progress through three stages of asymptomatic infection prior to AIDS: the first stage lasts three months and is associated with a high transmission probability; the second stage lasts for several years (up to a mean of 10 years, depending on age) and is associated with a low transmission probability; and the third stage lasts six months and is associated with a high transmission probability.

The population is divided into several sexual activity groups with different numbers of sexual partnerships formed in a year. To permit study of the effect of varying age at first sex and the pattern of partnership formation with respect to age, a detailed yearly age structure was incorporated. On sexual debut most individuals enter the group with the lowest sexual activity, but a few enter groups with much higher sexual activity. An individual of a particular sex, age and sexual activity forms a set number of sexual partnerships each year that are directed preferentially towards those in a similar sexual activity class and between older men and younger women. The fraction of women's partnerships that are formed with men a given number of years older is determined by the log-logistic function. This distribution allows the age difference to be moderate in most sexual partnerships but much greater in others. It can be parameterised so that the pattern of partnership formation matches that observed in Manicaland or varied to represent alternative scenarios (fig S3 in the supplementary material, see <http://sti.bmj.com/supplemental>). Two types of intervention to reduce cross-generational mixing are simulated:

- a change in the distributional form of the allocation of young women's partnerships among older men, preserving the total number of partnerships formed; and
- removal of a fraction of partnerships with a given age difference, so that there are less partnerships in total.

Both of these interventions generate the same reduction in the fraction of young women's sexual partnerships that are "cross-generational" but the former replaces those cross-generational partnerships with partnerships among peers whereas the latter does not. For consistency, the derived pattern of partnership

formation for one sex must match that of the other, and the extent to which males' demand for sexual partnerships is accommodated by the female population (or vice versa) has to be specified.

Mortality and fertility rates were chosen to represent an African population in the pre-AIDS era and the model was run for 100 years to establish a stable population structure. The infection was introduced to 0.01% of males aged 25–29 years in the highest sexual activity group.

RESULTS

Running the model with the different mixing patterns showed that with more cross-generational mixing, endemic prevalence (among those aged 15–49 years) was slightly higher (fig 1A (bars)). Female-to-male prevalence ratios for 15–24-year-olds at least equal to those observed can be created in the model without assuming any difference in susceptibility to HIV infection between men or women or over age (fig 1A (line)).

If all sexual partnerships are formed between peers the epidemic cannot become established (fig 1B). If 1% of sexual partnerships are formed with partners one year older or younger, HIV can become endemic. Simulating an intervention that reduced cross-generational mixing but preserved the total number of sexual partnership formed, showed that such a behavioural change could substantially reduce HIV prevalence among young women but prevalence among young men might rise (fig 1C (solid lines)). With this intervention, the lifetime risk of infection (the expected chance at birth that an individual will have been infected with HIV by their fifty-fifth birthday) is reduced by 10% for females and 5% for males. In contrast, if the same reduction in cross-generational mixing is simulated but without any compensatory increase in the number of partnerships among peers (dashed lines), prevalence among males can decrease and prevalence among females can decrease further. With this intervention, the lifetime risk of infection is reduced much more: by 25% for females and 22% for males.

This pattern of sexual mixing (young women forming partnerships with older men) means that the impact of young women delaying sexual debut is sensitive to the behavioural response of older men—that is, if males' would-be young sexual partners become abstinent, they may seek to replace those last partnerships with the youngest sexually active females available. Females' risk of infection in the first years of sexual activity is therefore linked to whether or not males seek to replace lost partnerships and the extent to which males control the structure of the sexual network (fig 2A). If males do seek to replace the lost partnerships, incidence is increased among women for the first years of sexual activity and this effect is greater if males are able to control the structure sexual network. The reduction in lifetime risk of infection for women is greater if males do not seek to replace lost partnerships (fig 2B). The benefit of delaying sexual debut is even greater if women become less susceptible to infection as they get older. However, in all scenarios the reduction in lifetime risk of infection associated with delaying sexual debut is relatively small.

Another issue is the relative timing of sexual debut and marriage.³⁰ The risk of infection when sexually active but not married (2% per person-year at risk during the first three years of follow-up in this population) is greater than when married (1% per person-year). This means that the benefit of delaying first sex depends on the time spent unmarried. For example, increasing the age at first sex from 18 to 21 could lead to lifetime risk of infection being reduced by 9% (if women are unmarried for 12 months less), reduced by 6% (no change in relative timing of marriage) or remain almost unchanged (if women are unmarried for an extra three years).

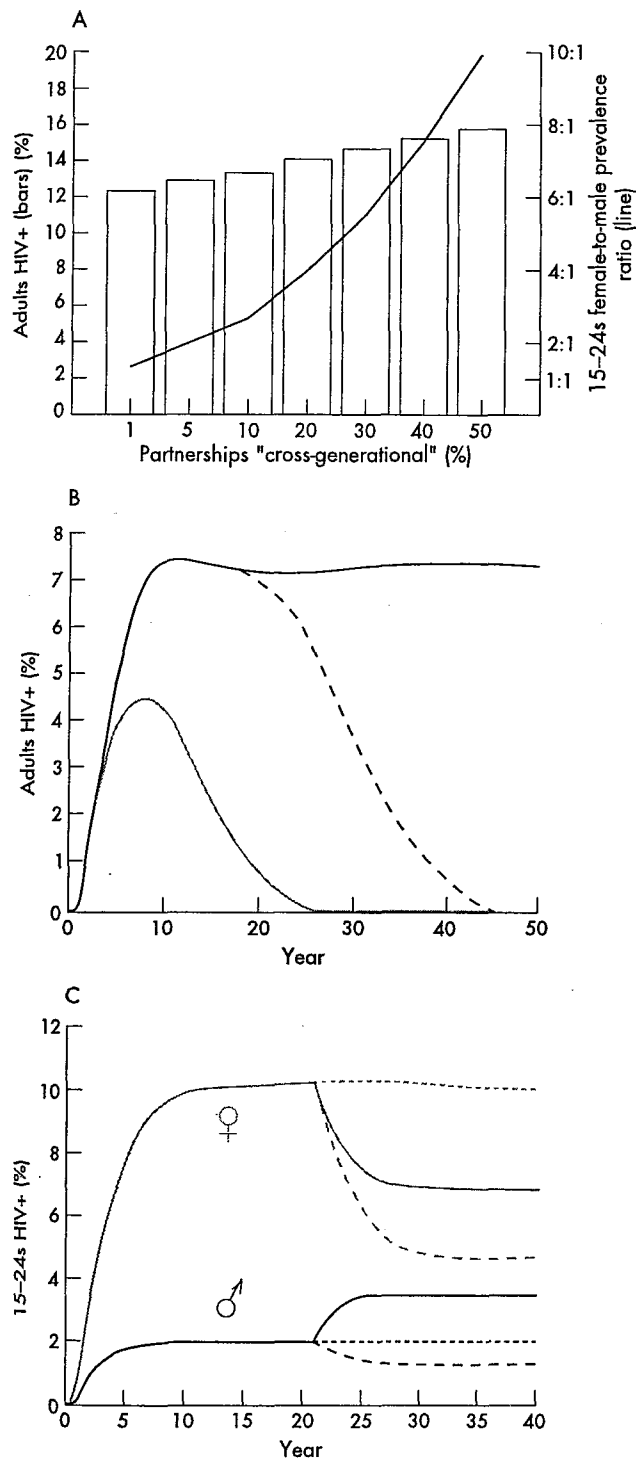


Figure 1 The impact of reducing cross-generational sex on the heterosexual spread of HIV. (A) HIV prevalence among 15-49-year-olds (bars) and female-to-male prevalence among 15-24-year-olds (line) with different levels of cross-generational mixing (percent of females' partnerships formed with males 10 or more years older), 20 years after infection introduced. (B) HIV prevalence over time if all partnerships are formed between individuals the same age (grey line) or if 1% of partnerships are formed between individuals one year older or younger (black line), or if an intervention eliminates any non-peer-to-peer partnerships at year 20 (dashed line). (C) HIV prevalence over time for 15-24-year-old males (black) and females (grey) if the proportion of cross-generational partnerships is reduced from 20% to 5% at year 20 and if there is replacement with peer-to-peer partnerships (solid lines) or if there is no replacement (dashed lines); dotted lines show "no change" scenario.

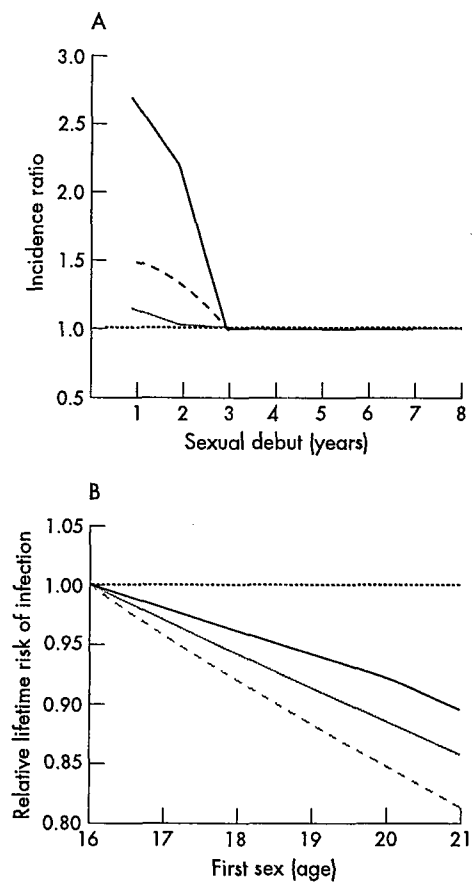


Figure 2 The impact of delaying age at first sex on the heterosexual spread of HIV. (A) HIV incidence ratio for women when age at first sex is delayed by two years for both sexes if males seek to maintain their current level of sexual activity and if mixing is determined by males (black line), females (grey line) or is an equal compromise (dashed line). (B) Relative lifetime risk of infection when age at first sex is increased from 16 years if males seek to maintain their number of sexual partnerships (black line) or if partnerships are not replaced (grey line) or if partnerships are not replaced and susceptibility to infection decreases with age (dashed line).

In rural Zimbabwe, the probability of reporting having used a condom consistently with their most recent sexual partner is particularly low for older men (25 years or older) but is higher if either the man or his partner has had many sexual partners (fig 3A). If condom use by older men is increased to the level currently reported by younger men, the lifetime risk of infection could be reduced by ~20% for both males and females. This exceeds the impact of doubling condom use in the whole population or males and females delaying sexual debut by two years under the most optimistic assumptions (fig 3B).

DISCUSSION

Sexual behaviour change is crucial to prevent HIV infections in sub-Saharan Africa.² Cross-sectional surveys of individuals' self-reported sexual behaviour show that young women who have had sex with an older man or begun sexual activity when young are more likely to have been infected with HIV.¹²⁻¹⁵ On this basis, interventions aiming to change behaviour have been proposed that focus on discouraging cross-generational sex and delaying sexual debut.^{8 16 17} Although it is clear that these changes will somewhat reduce the risk of infection to the individual it was not known what impact they could have on the spread of HIV through the population. Despite this uncertainty the importance of cross-generational sex in supporting high HIV prevalence has been presumed,¹⁷ and an increase in abstinence among young people has been partially

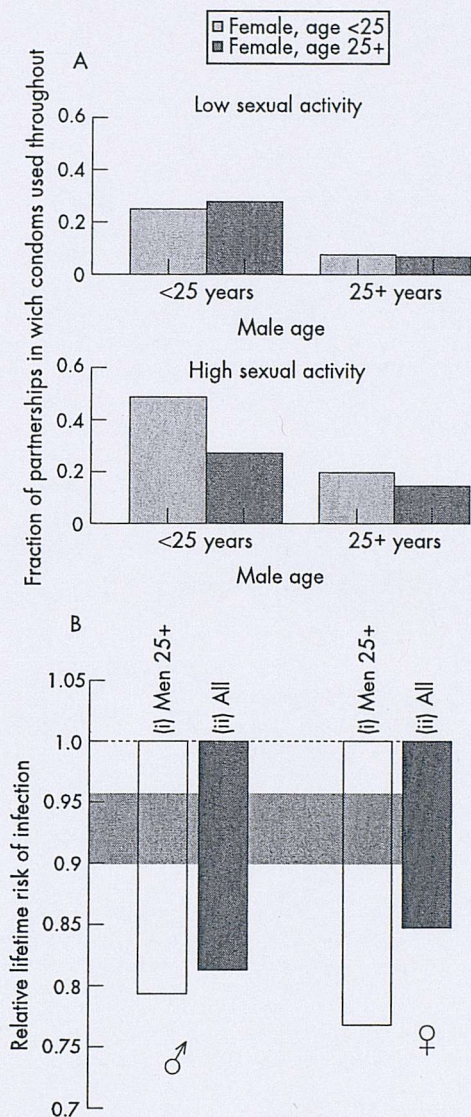


Figure 3 The impact of increasing condom use on the heterosexual spread of HIV. (A) The proportion of reported partnerships in which condoms were used in all sex acts, by the age of each partner and whether either one of the partners reported having had six or more previous sexual partners (highly sexually active). (B) Relative lifetime risk of infection for males and females if (1) condom use among males older than 25 increases to the level reported by males under 25 (open bars), (2) condom use overall is doubled (grey bars). The horizontal grey shading gives the comparable range of effects that could be expected if age at first sex for males and females is increased by two years.

credited with the decline in HIV prevalence rates in Uganda.^{31 32} In this study we used a mathematical model to quantify the reduction in the average lifetime risk of HIV infection that reducing cross-generational sex and delaying first sex could bring. The model was carefully parameterised using detailed data from a rural district in eastern Zimbabwe¹² and we expect that the qualitative insights will be generalisable to other African settings with epidemics.

Our model simulations suggest that HIV prevalence is only slightly higher with much more cross-generational mixing. Furthermore, even if 99% of sexual partnerships are formed between peers, HIV can still reach a high endemic level. This is contrary to the suggestion that without cross-generational mixing HIV could not persist endemically.¹⁷ Cross-generational sex helps increase prevalence because few of the partnerships of infected older males are with older females who are already

Key messages

- The impact of behaviour change on HIV spread is sensitive to the structure and reaction of the sexual network.
- Reducing cross-generational sex may have little effect on the risk of infection unless it is accompanied by a reduction in the number of risky sexual contacts.
- The benefit of delaying age at sexual debut is comparatively small and is reduced if males continue to prefer young partners or if young women spend more time unmarried.

infected too and more will probably be with uninfected younger females. However, the link is not strong because the infection will reach all age groups eventually under almost any mixing scenario, and then young women will be exposed instead to the high rates of sexual activity of their male peers. Sex with older men is more risky than sex with younger men partly because of the greater possibility of the former to be infected with HIV, having been exposed to the risk of infection for longer. However, the observed gradient in HIV prevalence among males by age is partly a *result* of the cross-generational mixing; prevalence among young men is suppressed by cross-generational mixing because they have only limited access to their peers and instead have sex with even younger uninfected women or not at all. A switch to peer-to-peer mixing will increase prevalence among young men making, from a female perspective, formerly “low-risk” contacts increasingly “high risk”. In this way, the benefit of peer-to-peer over cross-generational mixing to the young women is negatively frequency dependent; one young woman will put herself at less risk by choosing partners her own age over older men but as more women come to do the same the benefit of this behaviour change is reduced as HIV prevalence among young men increases.

The real impact of cross-generational sex on the population-level spread of HIV is the power imbalance in those partnerships and the implications this has for the chance that condoms will be used.^{12 19} Our results show that behaviour change interventions should aim to minimise unprotected sexual contact by young women with anyone and should not target the age difference between sexual partners per se. Nonetheless, this pattern of partnership formation between older men and younger women does seem to underlie the high female-to-male HIV prevalence ratio among young people; the model generates ratios at least as extreme as those observed without assuming any difference in susceptibility to infection by sex or age. Cross-generational mixing must be considered when examining other types of behavioural intervention; the demand for their sexual partnerships could undermine the benefit young women get from remaining abstinent for longer and the importance of transmission from older men makes the frequency with which they use condoms especially important.

Abstinence (through delaying the onset of sexual activity) removes the risk of infection for only a few years—a small fraction of one’s lifetime exposure. This period may be important because the first years of a woman’s sexual activity may carry the greatest risk of transmission for a number of biological^{33–35} and behavioural^{12 18} reasons. However, even assuming that susceptibility declines strongly with age, the lifetime benefit of delaying sex for two years is expected to be, at most, only 8%. The benefit is smaller (3%) if the “demand” for their sexual partnerships is not reduced. Although

abstinence undeniably reduces the risk of infection, its impact on the spread of HIV and the average chance of infection over a lifetime is small. It is probable, therefore, that the dramatic prevalence decline in Uganda³¹ was primarily mediated through increased condom use and fidelity rather than the two-year delay in first sex that was also reported.³²

In the coming years, ongoing and proposed behaviour interventions will be assessed and their potential effect estimated. This modelling work has highlighted the sensitivity of the efficacy of some behaviour changes to unknown properties of the sexual network (eg the response of males to female behaviour change) and projections should incorporate this uncertainty.

From an individual-level perspective it is possible to identify those elements of sexual behaviour that are associated with the highest risk of infection. However, without a dynamic description of HIV transmission it is not clear how these changes will limit the spread of HIV at the population level. The chance of infection is only partly determined by one's own sexual behaviour and interventions should not be narrowly targeted at particular at-risk groups (for example, young women) but instead should tackle risky behaviour throughout the sexual network.

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AUTHOR CONTRIBUTIONS

All authors conceived the study, assisted with model design and analysis, and drafted the manuscript.

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REFERENCES

- 1 UNAIDS/WHO. *AIDS epidemic update: December 2005*. Geneva: UNAIDS/WHO, 2005.
- 2 UNAIDS. *2004 Report of the global AIDS epidemic*. Geneva: UNAIDS, 2004.
- 3 Kiwanuka N, Gray RH, Serwadda D, et al. The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Rakai, Uganda. *AIDS* 2004;18:342-4.
- 4 Schmid GP, Buve A, Mugenyi P, et al. Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections. *Lancet* 2004;363:482-8.
- 5 Lopman BA, Garnett GP, Mason PR, et al. Individual level injection history: a lack of association with HIV incidence in rural Zimbabwe. *PLoS Med* 2005:e37.
- 6 Office of the United States Global AIDS Coordinator. *The President's Emergency Plan for AIDS Relief. US Five-year global HIV/AIDS strategy, 2004*. Washington DC: Office of the Global AIDS Coordinator, 2004.
- 7 The Global Fund to fight AIDS, tuberculosis and malaria. Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2004.

- 8 Laga M, Swartzlander B, Pisani E, et al. To stem HIV in Africa, prevent transmission to young women. *AIDS* 2001;15:931-4.
- 9 Genuis SJ, Genuis SK. Adolescent behaviour should be priority. *BMJ* 2004;328:894.
- 10 Green EC, Berman J. Liaisons fueling AIDS in Africa. *The Washington Times*. 28 December, 2003.
- 11 AIDSMark. *Cross-generational sex fueling the HIV/AIDS epidemic in sub-Saharan Africa*, International Centre for Research on Women (ICRW) and Population Services International (PSI), 2003.
- 12 Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet* 2002;359:1896-903.
- 13 Kelly RJ, Gray RH, Sewankambo NK, et al. Age differences in sexual partners and risk of HIV-1 infection in rural Uganda. *J Acquir Immune Defic Syndr* 2003;32:446-51.
- 14 Pettifor AE, Van Der Straten A, Dunbar MS, et al. Early age of first sex: a risk factor for HIV infection among women in Zimbabwe. *AIDS* 2004;18:1435-42.
- 15 Drain PK, Smith JS, Hughes JP, et al. Correlates of national HIV seroprevalence: an ecologic analysis of 122 developing countries. *J Acquir Immune Defic Syndr* 2004;35:407-20.
- 16 Population Services International. *Dangerous Liaisons*, Research Brief No. 2, Washington DC: PSI, 2003.
- 17 Cohen J. Asia and Africa: on different trajectories? *Science* 2004;304:1932-8.
- 18 Longfield K, Glick A, Waihak M, et al. Relationships between older men and younger women: implications for STIs/HIV in Kenya. *Stud Fam Plann* 2004;35:125-34.
- 19 Luke N, Kurz KM. *Cross-generational and transactional sexual relationships in Sub-Saharan Africa*. Washington DC: International Centre for Research on Women, 2002.
- 20 Buve A, Bishikwabo-Nsarhaza K, Mutangadura G. The spread and effect of HIV-1 infection in sub-Saharan Africa. *Lancet* 2002;359:2011-7.
- 21 Grassly NC, Garnett GP, Swartzlander B, et al. The effectiveness of HIV prevention and the epidemiological context. *Bull World Health Organ* 2001;79:1121-32.
- 22 Anderson RM, Garnett GP. Mathematical models of the transmission and control of sexually transmitted diseases. *Sex Transm Dis* 2000;27:636-43.
- 23 Garnett GP. An introduction to mathematical models in sexually transmitted disease epidemiology. *Sex Transm Infect* 2002;78:7-12.
- 24 Aral SO, Roegner R. Mathematical modeling as a tool in STD prevention and control: a decade of progress, a millennium of opportunities. *Sex Transm Dis* 2000;27:556-7.
- 25 Keeling MJ, Woolhouse ME, Shaw DJ, et al. Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* 2001;294:813-7.
- 26 Riley S, Fraser C, Donnelly CA, et al. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. *Science* 2003;300:1961-6.
- 27 Ferguson NM, Cummings DA, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 2005;437:209-14.
- 28 Gregson S, Garnett GP, Nyamukapa CA, et al. HIV decline associated with behavior change in eastern Zimbabwe. *Science* 2006;311:664-6.
- 29 Gregson S, Zhuwau T, Ndlovu J, et al. Methods to reduce social desirability bias in sex surveys in low-development settings: experience in Zimbabwe. *Sex Transm Dis* 2002;29:568-75.
- 30 Zaba B, Pisani E, Slaymaker E, et al. Age at first sex: understanding recent trends in African demographic surveys. *Sex Transm Infect* 2004;80(Suppl 2):ii28-35.
- 31 Stoneburner RL, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. *Science* 2004;304:714-8.
- 32 Asiimwe-Okiror G, Opio AA, Musinguzi J, et al. Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda. *AIDS* 1997;11:1757-63.
- 33 Glynn JR, Carael M, Auvert B, et al. Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia. *AIDS* 2001;15(Suppl 4):S51-60.
- 34 Moss GB, Clemenson D, D'Costa L, et al. Association of cervical ectopy with heterosexual transmission of human immunodeficiency virus: results of a study of couples in Nairobi, Kenya. *J Infect Dis* 1991;164:588-91.
- 35 Duncan ME, Tibaux G, Pelzer A, et al. First coitus before menarche and risk of sexually transmitted disease. *Lancet* 1990;335:338-40.

***Appendix C: Appropriate evaluation of HIV
prevention interventions: from experiment to
full-scale implementation (published
manuscript)***

Appropriate evaluation of HIV prevention interventions: from experiment to full-scale implementation

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Background: Preventing HIV infection is still an essential goal in tackling the HIV/AIDS pandemic. Remarkably little is known about how best to reduce HIV incidence because most trials focus on the reduction of risk behaviours and assume an effect on HIV incidence.

Objective: To discuss the evidence for the effectiveness of HIV prevention strategies, exploring the different types of evidence available: individual and community randomised controlled trials, and observational studies.

Results: Although providing a gold standard for evidence, trials have been limited in their scope and are difficult to interpret and generalise. There have been examples of national level successes in preventing HIV which have been detected in surveillance data and understood through behavioural and modelling studies. These have the advantage of being to scale and indicating effectiveness rather than efficacy.

Conclusions: Although randomised trials are important because of their scientific rigor, it is also important that evidence from observational epidemiology is not overlooked. Only if good quality, consistent data are available can the history of the HIV epidemic be appropriately analysed.

Substantial resources have been committed globally to the treatment and prevention of HIV and AIDS¹ and advances are being made in providing antiretroviral treatments in resource-poor settings.² Such advances will be unsustainable without successes in HIV prevention.³ However, remarkably little is known about the effectiveness of preventive interventions in reducing the incidence of HIV itself.⁴ In part, the "emergency" nature of the HIV epidemic has required implementation of interventions to run ahead of evidence of effectiveness. In planning a response to the global pandemic assumptions have been made about what works, using limited evidence from theory, the measurement of processes or intermediate intervention outcomes, such as behaviour change.⁵

Here we discuss how interventions have been evaluated and interpreted and the epidemiological and methodological issues that have been learned. National surveillance, with behavioural data collection as an adjunct, can provide the most powerful and relevant test of HIV interventions.

INDIVIDUAL RANDOMISED CONTROLLED TRIALS

The randomised controlled trial (RCT) provides the "gold standard" for testing the efficacy of medical interventions, providing a clear experimental design to demonstrate the presence or absence of an effect.^{6–7} This study design works well when there is a straightforward replicable intervention linked to the disease outcome.

The majority of RCTs in research on the prevention of HIV use outcome measures of risk behaviour rather than HIV incidence itself. This is appropriate for interventions aimed at HIV-positive individuals, which show decreased unprotected sex and sexually transmitted infections (STIs),⁸ and when the STIs are themselves the outcome of interest.⁹ It is less clear how useful intermediate outcomes are in other situations exploring the risks of HIV either in the individual or in the community. For example, a recent measure of an HIV intervention in a community in Uganda found that condom use increased and numbers of sex partners decreased.¹⁰ Many HIV intervention trials have now been performed and are summarised in systematic reviews, but the focus has been on how to change risk behaviour, with a concentration in the USA and on men

who have sex with men,^{11–14} and less emphasis on populations in developing countries¹⁵ or on HIV incidence as an outcome.

There are many reasons why interventions to prevent the spread of HIV are not always readily assessed in individual RCTs.

- A key problem is the low incidence of HIV in many industrialised countries where intervention trials are well resourced. The adoption of intermediate outcomes such as increased condom use, reduced numbers of sexual partners or reduced incidence of other STIs is common. Data on self-reported behaviour change may be unreliable. Even if the changes are genuine it is not clear that such changes will actually alter HIV incidence depending as they do on the epidemiological context.⁴ Changes in risk behaviour could be overwhelmed by high levels of exposure or could differentially influence lower risk contacts. Even where HIV incidence is sufficiently high to measure without prohibitively large sample sizes, the complexity and cost of measuring incident HIV infection has led to the use of proxy outcomes.
- Interventions aimed at HIV prevention are often complex, requiring skilled staff to carry out counselling and education to motivate and facilitate the adoption of safer sexual behaviours. Difficulties in ensuring that interventions are appropriately implemented create uncertainty about negative trial results and concerns about replicating the intervention outside the context of the trial.
- Other HIV interventions are not amenable to individual randomisation if the focus is the group, community or population—for example, the use of mass media advertising or educational drama can only be delivered to groups.
- Conceptually, the focus on individuals may not be appropriate because individual behaviour is greatly affected by social and cultural norms, making interventions targeted only at selected individuals largely ineffective. This is particularly the case with sexual behaviour, which must

Abbreviations: CRCT, community RCT; RCT, randomised controlled trial; STI, sexually transmitted infection

involve at least one other person. These norms vary between settings and through time within a setting, limiting the generalisability of RCT findings.

The relationship between behaviour and risk of infection is complex and dynamic. An individual's risk of acquiring an infection depends not only on their behaviour but also on their position within the dynamic network of contacts through which infection spreads.¹⁶ This is particularly important in the case of STIs and HIV, in which there is extreme heterogeneity in individual sexual behaviours and hence in the risk of acquiring and transmitting infection, with a small group of individuals dominating the spread of infection.^{17 18} At a population level, the impact of an individual changing their number or choice of sexual partners or their treatment-seeking behaviour for STI symptoms, or the course of infectiousness over time, all depend on their role in the transmission dynamics of the infection.^{4 17}

COMMUNITY RCTS

The failure of individual-level trials to determine the community-level impact of interventions has led to a number of community RCTs (CRCTs) of HIV and STI interventions.¹⁹⁻²² In these, the intervention is targeted at communities which are randomised to treatment or control arms. Randomisation is used to distribute all the differences between the communities (known and unknown) evenly to both arms of the trial. The appropriate circumstances for a CRCT have been listed by Susser²³ as requiring:

- (1) a well-defined, narrow hypothesis, so that the key to the intervention success or failure can be identified;
- (2) a measurable intervention, to be able to assess its implementation;
- (3) adequate statistical power; and
- (4) well-defined, measurable outcomes.

Unfortunately, the first three criteria are often absent in CRCTs aimed at preventing HIV. The complexity of HIV interventions and their delivery can be a problem for CRCTs just as it can for individual RCTs, but CRCTs also suffer from their scale, which presents major challenges of logistics and resources, often leading to compromises in the numbers of communities randomised. Because health promotion builds over time as knowledge increases and cultural norms and practices change, it is possible that it will take some time for the interventions to impact on incident HIV. Furthermore, the effect of changes in one group can take time to percolate to the rest of the population (Hallett *et al*, submitted for publication). The extended follow-up period thus required increases the risks of study biases caused by poor follow-up rates, migration and changes in the background epidemiological context, such as epidemic maturation or an increase in the availability of antiretroviral therapy.

The impact of STI control on HIV transmission has been a focus of CRCTs in the HIV field with conflicting results. In HIV epidemiology the question of whether the presence of another STI increased susceptibility to, or transmissibility of, HIV could not be answered using observational epidemiological studies. Other STIs and HIV have common risk factors which cannot be adequately controlled for by measuring their influence in individuals. The Mwanza trial of syndromic management of STIs, a ground-breaking study in 12 communities in Tanzania, found 40% lower HIV incidence in all six intervention communities compared with their matched control communities.¹⁹ However, subsequent trials which have included mass antibiotic administration aimed at controlling asymptomatic STIs (Rakai, Uganda²⁰), the use of syndromic management of STIs in one arm combined with information, education and

communication in a third arm (Masaka, Uganda²¹) and the use of syndromic management combined with peer-led education targeting high-risk sexual behaviours (Manicaland, Zimbabwe²²) have all shown no population-level impact on the incidence of HIV infections, despite changing patterns of risk within the intervention communities. The last provides an interesting example, where the result could be overinterpreted in determining policy on how much STI control through syndromic management should be a part of HIV prevention, because bacterial STIs were already well controlled and the main focus of the study was the behavioural intervention.

Interpreting positive CRCT results

A positive result of a CRCT conclusively demonstrates that the intervention has worked in a particular setting. However, questions remain:

- What are the necessary components of the intervention?
- What quality of intervention is required to maintain effectiveness in other settings?
- How well can the intervention be scaled up to a wider population or to a national level?

Essentially there is a problem translating the *efficacy* observed in trial conditions to *effectiveness* on a larger scale because interventions are often implemented less well when scaled-up (ie they can be less intensive, less carefully monitored and carried out in unselected populations with lower motivation). The costs of the intervention will probably be less outside the trial setting but at the same time this could compromise the effectiveness. In addition to problems of scale there is the question of whether the intervention will work in other epidemiological, social and cultural contexts. For example, the syndromic management of STIs significantly reduced HIV incidence in the Mwanza trial¹⁹ but this result has not been reproduced in the other trials of STI control targeting HIV incidence. The influence of other STIs appears to be greatest in the early stages of an HIV epidemic when infection is concentrated in high-risk parts of the population and when the curable bacterial STIs are more important than infections such as genital herpes, which cannot be cured.²⁴

Interpreting negative CRCT results

Negative CRCT results are even more difficult to interpret. They tell us that the intervention, as implemented, did not produce significant results, but there are a number of potential explanations. The study may have been inadequately powered because sample-size calculations require knowledge of the variation of incidence between the populations studied, and accurate forecasts of future patterns of incidence without interventions (Hallett *et al*, submitted for publication). Because of the dynamic nature of epidemics such future patterns may not be consistent with past incidence rates, and variation in recorded prevalence at baseline may be a misleading proxy of variation in incidence. Implementation of the intervention may not have been adequate; however, because *effectiveness* is more important than *efficacy*, and as within intervention trials the interventions are likely to be more assiduously implemented than when scaled-up, this may seem a minor problem. Nonetheless, the complex nature of many interventions means that a failure of implementation rather than efficacy can be claimed and failing interventions be continued. More reasonably, the generalisability of the negative result to other epidemiological contexts can be debated. For individual RCTs, repetition of the trial in the same and in other contexts can eliminate doubts through comparison and meta-analyses of multiple trials. Unfortunately, these are not easily achieved with long and costly CRCTs.

OBSERVATIONAL STUDIES

The urgency required in responding to the spread of a lethal infectious disease has led to many interventions being implemented before the evidence from trials has become available. In some cases where large-scale interventions have been implemented, associated observational epidemiological and behavioural studies have identified changes in HIV prevalence that can only be attributed to changes in HIV incidence and have been linked to changes in specific risk behaviours.^{25–29} Such observational studies have the advantage of assessing interventions at the regional or national scale. This immediately avoids many problems of trials, as the interventions are already to scale and measure effectiveness. However, in the hierarchy of evidence, such observational epidemiology is considered to be weak. Biases such as changes in the representativeness of antenatal clinics included in sentinel surveillance, changes in fertility due to HIV affecting data from antenatal clinics,³⁰ trends unrelated to the interventions, and the natural dynamics of the incidence of STI and HIV can lead to spurious measures of success or failure. Nonetheless, if such biases can be predicted and measured their effects can be excluded³¹ and powerful arguments of what works can be based on observational epidemiological data.

In the late 1980s and early 1990s, in response to the high prevalence of HIV, the government of Uganda implemented an HIV prevention strategy acknowledging and promoting the discussion of HIV risks and advocating a reduction in sexual risk behaviour.³² The prevalence of infection was seen to decline in young women attending antenatal clinics. Cross-sectional population-based survey data showed decreases in reported numbers of sexual partners.^{25 32} Such declines, particularly in those age groups too young to have had HIV-infected individuals removed by death or subfertility, could only be explained if HIV incidence had declined and provided a much-needed national level success story. Subsequent debate has continued over the cause of the success, with the neologism ABC—abstinence, be faithful, use condoms—being introduced, and competing claims being made over the relative importance of condom use and abstinence.^{32 33} A similar national level change in patterns of prevalence and incidence was achieved in Thailand. Here, studies that found sex work was the major focus of HIV transmission. This led to an intervention that both discouraged clients from purchasing sex and encouraged universal condom use by sex workers. Behaviour change was observed—high rates of condom use among sex workers and decreased reported visits to sex workers—and was complemented by biological outcomes: reduced incidence of sexually transmitted diseases and HIV infection in military recruits. At

the population level, this translated into reduced prevalence of HIV among women attending antenatal clinics in sentinel surveillance.^{27 28}

These two examples have had a profound influence on discussion of HIV prevention strategies, but they had not been repeated until recently. In the past years HIV prevalence has declined from very high levels in a few countries, including Zimbabwe and parts of urban Kenya.³⁴ As in the case of Uganda, the current observations are of declines in HIV prevalence, a measure reflecting cumulative risk, rather than HIV incidence, which would provide more up-to-date information. Care needs to be taken in analysing declines in prevalence because the natural pattern of incidence (ie without any behaviour change) in an epidemic is to increase until the at-risk population is saturated and then to decline to a new lower level matching the supply of new susceptible individuals (fig 1).³⁵ Prevalence can then fall if HIV mortality associated with the earlier higher incidence exceeds the acquisition of new infections. Such a decline could be expected approximately a decade after the period of most rapid HIV spread. These natural dynamics need to be excluded as an explanation of decreases in HIV prevalence if we are to detect success in HIV control. The trends in prevalence observed in Zimbabwe and parts of urban Kenya were not reproduced by a “null model” of these natural dynamics.³⁴ Observational studies exploring national reductions in HIV prevalence require mathematical models of the transmission dynamics of HIV to create a null model describing the trajectories of incidence and prevalence in the absence of the intervention. It is then possible to compare the observed data with this null model to estimate the impact of the intervention.^{24 26 32 34} Such analyses can give striking insights—for example, it was estimated that the decline in prevalence in Uganda was mediated by a reduction in incidence roughly equivalent to an 80% efficacious vaccine given to everyone in the population.³²

The analyses of HIV trends in Zimbabwe and Kenya were restricted to those antenatal clinics sampled continuously over time. This will have limited the extent to which the country's population is represented as such clinics are mostly located in urban centres. However, it avoids the artificial declines in prevalence that could be expected from the expansion of clinics to include those serving more rural populations over recent years. The requirement for settings with consistently sampled clinics will limit the number of places where prevalence trends can be explored. Another way of dealing with problem of sampling biases that change over time is to explicitly explore them. The comparison of random sample population-based surveys with sentinel surveillance data allows the identification

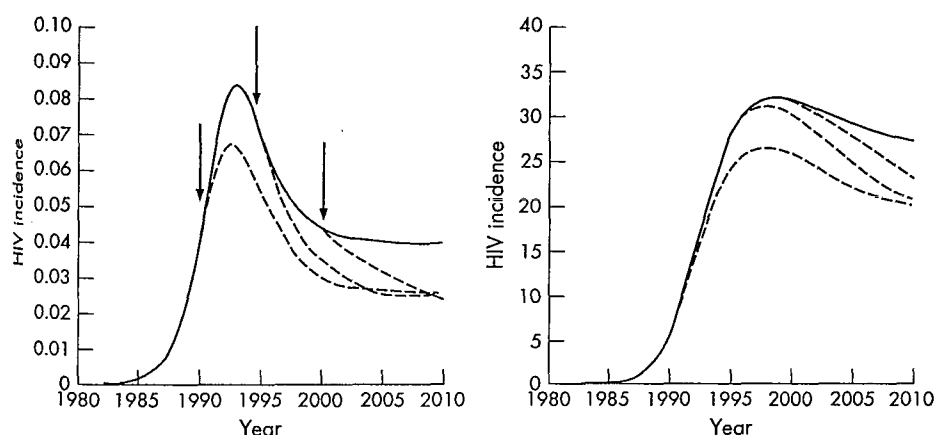


Figure 1 Modelled HIV prevalence and incidence in a generalised epidemic assuming no behaviour change (solid line) and behaviour change amounting to a 50% reduction in the risk of infection. The timing of this behaviour change occurs in year 1990, 1995 or 2000 (arrows).

of biases, which can then be included in mathematical models. For example, there is a concern that HIV-associated subfertility will increase over the course of an infection, thereby decreasing the proportion of HIV-infected women becoming pregnant as an epidemic ages. In mathematical models this effect is counteracted by the decreasing bias caused subfertility due to bacterial STIs, which becomes less important after HIV has spread beyond those most likely to have STIs and as HIV-related mortality selectively removes such individuals from the population.^{31 34}

Once we are confident that declines in HIV prevalence exceed those expected from the natural dynamics the obvious question is what has caused the declines. Questions of attribution are important as we need to know which risks are amenable to change and how they might be changed. There are two causal levels of interest: first, what change in the distribution of risk explains the reduction in HIV incidence, and second, can these changes in risk be attributed to particular interventions? Unfortunately, in Uganda there has been much scope for speculation and appropriation of the success story to support *a priori* beliefs because of the lack of representative, contemporaneous and detailed risk-behavioural data. However, despite the lack of behavioural data it is possible to draw some conclusions from the observed pattern of prevalence decline. Fitting a model to the decline in Kampala shows that the reduction in aggregate risk must have begun during the late 1980s (fig 2), which indicates it probably was not driven by the increased use of socially marketed condoms that happened later.^{32 33} On the other hand, it seems that the dramatic turnaround would not have been possible without all three types of behaviour change across the population—that is, delaying commencing sexual activity by two years, lowering partner change rates and increasing condom use^{25 26 32} (fig 2).

In Zimbabwe the situation is clearer because the observed national-level decline in HIV prevalence³⁷ coincided with population-based surveys of sexual behaviour in the rural eastern highlands²⁹ and observed reductions in incidence among postnatal women and male factory workers in the urban population.³⁸ The former suggested that in these rural communities declines in numbers of sexual partners and an increase in age of sexual debut were associated with the changing incidence, but the latter observed that an increase in

condom use was associated with changes in risk in Harare. Behavioural data can be used to identify the components leading to HIV declines when the observed behaviour changes can have a direct influence on the risk of acquisition and transmission of HIV and other similar risk behaviours have not changed. Only if the proximate determinants of HIV infection change can interventions alter the course of the HIV epidemic. The proximate determinants of HIV incidence are those factors influencing³⁹:

- exposure of uninfected individuals to HIV-positive individuals;
- transmission probability of the virus when such exposure occurs; and
- duration of infectiousness of HIV-positive individuals.

Social, demographic, economic, and other, factors that affect HIV incidence ultimately act through their effect on these proximate determinants.

Beyond attributing reduced HIV incidence to particular behaviour changes, relating those behaviour changes to particular interventions requires data measuring exposure to the interventions, perceived responses to those interventions, and plausible mechanisms linking the interventions and the observed changes. Such attribution will always be weak if there are multiple interventions and societal changes. A failure to change risk over the long term may be indicative of unsuccessful interventions, but behaviour change that is consistent with an intervention's goals suggests that the intervention has worked and that the replication and expansion of the approaches taken might be warranted. Too often such evidence is ignored because it does not meet the requirements of "rigorous" evaluation. Although observed trends in risks within populations do not provide definitive evidence of the failure or success of an intervention generally, the same is true for CRTs where results from trials of interventions designed to target specific groups or behaviours cannot be generalised.

Use of national-level surveillance data is not suitable for all epidemiological questions. It would not be possible to resolve the difference between the natural, intrinsic course of the epidemic from an epidemic where extrinsic changes alter the course of a growing epidemic (ie when incidence has not already reached a peak) because patterns of risk cannot be adequately assessed in order to predict the peak prevalence. If behaviour changes before the incidence saturates, then the epidemic will settle to a lower level than it would have otherwise but the decline in prevalence will look like the natural dynamics only, leading to the erroneous conclusion that behaviour has not changed (fig 1).

Another problem is the ability of surveys of risk behaviour to capture the details of sexual behaviour necessary to accurately assess the potential for epidemic spread. The distribution of numbers of sexual partners, the pattern of sexual partner choice, the overlap between sexual partners, and the number and type of sex acts within partnerships, all influence the acquisition and transmission of HIV and many advances in study design have improved our ability to measure such detail. However, some uncertainty is inevitable. Details about the sexual contacts of one's sexual contacts cannot be measured in ordinary population-based surveys. In addition, as the highest-risk individuals are typically a small proportion of the population—and may be under-represented in household surveys (eg sex workers, injecting drug users)—it is difficult to obtain reliable estimates of their behaviour although they contribute disproportionately to the transmission. This matters if declines in HIV incidence are not explained in surveys or if observed changes are insufficient to explain the magnitude of declines. However, it is unlikely that less-obvious changes in

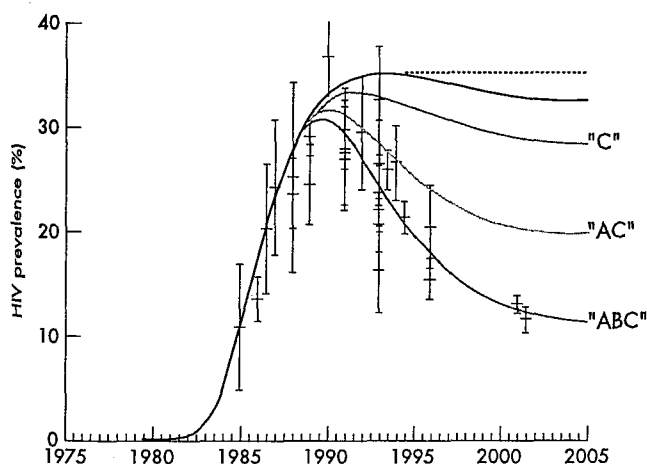


Figure 2 The epidemic in Kampala, Uganda, and the effect of "ABC" interventions. HIV epidemic model fitted (line "ABC") to antenatal clinic HIV prevalence estimates (black bars with 95% CI). (Source: US Census Bureau.³⁶) Also shown are epidemic projections assuming no behavioural change (—line), increases in condom use (line "C"), and increase in condom use and two-year average delay in first sex (line "AC"), parameterised according to observed behaviour change.²⁵ The horizontal dashed line shows peak prevalence and is for ease of reading.

Key messages

- Demonstrating that an intervention is successful at changing individual sexual behaviour does not necessarily mean it is effective at reducing the transmission of sexually transmitted infections.
- Community randomised controlled trials are the best standard of evidence of the effectiveness of an intervention but questions remain about impact on a larger scale, and how strongly study design influences whether there is a significant beneficial outcome.
- High-quality sentinel surveillance data in conjunction with behavioural and modelling studies can be used to assess the effectiveness of scaled-up interventions.

behaviour will explain dramatic decreases in HIV incidence, especially as surveys are well designed, with reasonably large sample sizes.

The expansion in funding for HIV prevention activities associated with the creation of the Global Fund for AIDS, Tuberculosis and Malaria⁴⁰ and the (US) President's Emergency Plan for AIDS Relief (PEPFAR)⁴¹ and associated increases in representative HIV surveillance and behaviour data from sentinel sites and from Demographic and Health Surveys with HIV serological surveys (DHS+) has increased both the imperative and the opportunities for testing the large-scale success of interventions. Large-scale interventions must be associated with the collection of sufficiently detailed data to allow their evaluation using mathematical models to determine the magnitude of their impact and for its attribution to different components of the intervention. DHS+ and second-generation surveillance data⁴² should be explored to determine whether it is possible to link behaviour change to particular interventions. The above-described methods using observational studies in conjunction with mathematical models have the advantage of exploring the actual implementation of interventions at the scale of interest, and, if performed rigorously, provide a set of tools for epidemiology and the development of health policy.

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AUTHOR CONTRIBUTIONS

All the authors developed and contributed to the ideas in the manuscript. TBH programmed and analysed the model advised by GPG and PJW. All authors contributed to drafting the manuscript.

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REFERENCES

- 1 Stover J, Bertozzi S, Gutierrez JP, *et al.* The global impact of scaling up HIV/AIDS prevention programs in low- and middle-income countries. *Science* 2006;**311**:1474–6.
- 2 Boerma JT, Stanek KA, Newell ML, *et al.* Monitoring the scale-up of antiretroviral therapy programmes: methods to estimate coverage. *Bull World Health Organ* 2006;**84**:145–50.
- 3 Salomon JA, Hogan DR, Stover J, *et al.* Integrating HIV prevention and treatment: from slogans to impact. *PLoS Med* 2005;**2**:e16.
- 4 Grassly NC, Garnett GP, Schwartz B, *et al.* The effectiveness of HIV prevention and the epidemiological context. *Bull World Health Organ* 2001;**79**:1121–32.
- 5 UNAIDS. 2006 Report on the global AIDS epidemic. Geneva: UNAIDS, 2006, (http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp).
- 6 Stephenson JM, Cowan FM. Evaluating interventions for HIV prevention in Africa. *Lancet* 2003;**361**:633–4.
- 7 Aral SO, Peterman TA. Do we know the effectiveness of behavioural interventions? *Lancet* 1998;**351**(Suppl 3):33–6.
- 8 Crepaz N, Lyles CM, Wolitski RJ, *et al.* Do prevention interventions reduce HIV risk behaviours among people living with HIV? A meta-analytic review of controlled trials. *AIDS* 2006;**20**:143–57.
- 9 Manhart LE, Holmes KK. Randomized controlled trials of individual-level, population-level, and multilevel interventions for preventing sexually transmitted infections: what has worked? *J Infect Dis* 2005;**191**(Suppl 1):S7–24.
- 10 Kajubi P, Kanya MR, Kanya S, *et al.* Increasing condom use without reducing HIV risk: results of a controlled community trial in Uganda. *J Acquir Immune Defic Syndr* 2005;**40**:77–82.
- 11 Johnson WD, Holtgrave DR, McClellan WM, *et al.* HIV intervention research for men who have sex with men: a 7-year update. *AIDS Educ Prev* 2005;**17**:568–89.
- 12 Herbst JH, Sherba RT, Crepaz N, *et al.* A meta-analytic review of HIV behavioral interventions for reducing sexual risk behavior of men who have sex with men. *J Acquir Immune Defic Syndr* 2005;**39**:228–41.
- 13 Elwy AR, Hart GJ, Hawkes S, *et al.* Effectiveness of interventions to prevent sexually transmitted infections and human immunodeficiency virus in heterosexual men: a systematic review. *Arch Intern Med* 2002;**162**:1818–30.
- 14 Semaan S, Kay L, Strouse D, *et al.* A profile of U.S.-based trials of behavioral and social interventions for HIV risk reduction. *J Acquir Immune Defic Syndr* 2002;**30**(Suppl 1):S30–50.
- 15 Siegfried N, Clarke M, Volmink J. Randomised controlled trials in Africa of HIV and AIDS: descriptive study and spatial distribution. *BMJ* 2005;**331**:742.
- 16 Eames KT, Keeling MJ. Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. *Proc Natl Acad Sci U S A* 2002;**99**:13330–5.
- 17 Garnett GP, Anderson RM. Sexually transmitted diseases and sexual behavior: insights from mathematical models. *J Infect Dis* 1996;**174**(Suppl 2):S150–61.
- 18 Ghani AC, Garnett GP. Risks of acquiring and transmitting sexually transmitted diseases in sexual partner networks. *Sex Transm Dis* 2000;**27**:579–87.
- 19 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.
- 20 Wawer MJ, Sewankambo NK, Serwadda D, *et al.* Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. *Lancet* 1999;**353**:525–35.
- 21 Kamali A, Quigley M, Nakiyingi J, *et al.* Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003;**361**:645–52.
- 22 Gregson S, Adamson S, Papaya S, *et al.* Impact and process evaluation of integrated community and clinic-based HIV-1 control: a cluster-randomised trial in eastern Zimbabwe. *PLoS Med* 2007;**4**:e102.
- 23 Susser M. Some principles in study design for preventing HIV transmission: rigor or reality. *Am J Public Health* 1996;**86**:1713–6.
- 24 White RG, Orroth KK, Korenromp EL, *et al.* Can population differences explain the contrasting results of the Mwanza, Rakai, and Masaka HIV/Sexually transmitted disease intervention trials? : a modeling study. *J Acquir Immune Defic Syndr* 2004;**37**:1500–13.
- 25 Asiimwe-Okiror G, Opio AA, Musinguzi J, *et al.* Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda. *AIDS* 1997;**11**:1757–63.
- 26 Kilian AH, Gregson S, Nyanabangi B, *et al.* Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda. *AIDS* 1999;**13**:391–8.
- 27 Nelson KE, Celentano DD, Eiumtrakol S, *et al.* Changes in sexual behavior and a decline in HIV infection among young men in Thailand. *N Engl J Med* 1996;**335**:297–303.
- 28 Rojanapithayakorn W, Hanenberg R. The 100% condom program in Thailand. *AIDS* 1996;**10**:1–7.
- 29 Gregson S, Garnett GP, Nyamukapa CA, *et al.* HIV decline associated with behavior change in eastern Zimbabwe. *Science* 2006;**311**:664–6.
- 30 Lewis JJ, Ronsmans C, Ezeh A, *et al.* The population impact of HIV on fertility in sub-Saharan Africa. *AIDS* 2004;**18**(Suppl 2):S35–43.
- 31 Garnett GP, Gregson S. Monitoring the course of the HIV-1 epidemic: the influence of patterns of fertility on HIV-1 prevalence estimates. *Math Popul Stud* 2000;**8**:251–77.
- 32 Stoneburner RL, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. *Science* 2004;**304**:714–8.
- 33 Hogle AJ. *What happened in Uganda? Declining HIV prevalence, behavior change and the national response.* Washington, DC: US Agency for International Development, 2002.
- 34 Hallett TB, Aberle-Grasse J, Bello G, *et al.* Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti. *Sex Transm Infect* 2006;**82**:i1–8.

- 35 **Garnett GP**, Gregson S, Stanecki KA. Criteria for detecting and understanding changes in the risk of HIV infection at a national level in generalised epidemics. *Sex Transm Infect* 2006;**82**:i48–51.
- 36 **US Census Bureau**. *HIV/AIDS surveillance data base*, Washington, DC. Available at <http://www.census.gov/ipc/www/hivaidsd.html>, 2004.
- 37 **Mahomva A**, Greby S, Dube S, *et al*. HIV prevalence and trends from data in Zimbabwe, 1997–2004. *Sex Transm Infect* 2006;**82**(Suppl 1):i42–7.
- 38 **UNAIDS**. Evidence for HIV decline in Zimbabwe: a comprehensive review of the epidemiological data, 2005. www.epidem.org.
- 39 **Boerma JT**, Weir SS. Integrating demographic and epidemiological approaches to research on HIV/AIDS: the proximate-determinants framework. *J Infect Dis* 2005;**191**(Suppl 1):S61–7.
- 40 **The Global Fund to fight AIDS, tuberculosis and malaria**. Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2004.
- 41 **Office of the United States Global AIDS Coordinator**. *The President's Emergency Plan for AIDS Relief. US Five-year global HIV/AIDS strategy, 2004*. Washington DC: Office of the Global AIDS Coordinator, 2004.
- 42 **World Health Organization/United Nations Joint Programme on AIDS**. *Second generation surveillance for HIV: the next decade*. Geneva: UNAIDS/WHO, 2000.

***Appendix D: Age at first sex and HIV infection in
rural Zimbabwe (published manuscript)***

Age at First Sex and HIV Infection in Rural Zimbabwe

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Beginning sexual activity introduces an individual to the risk of acquiring sexually transmitted infections. In this study, cross-sectional behavioral data linked to HIV-status from 4,138 men and 4,948 women interviewed in rural Zimbabwe are analyzed to investigate the distribution and consequences of early first sex. We find that age at first sex (at a median age of 19 years for males and 18 years for females) has declined among males over the past 30 years but increased recently among females. Those in unskilled employment, those not associated with a church, and women without a primary education begin to have sex earlier than others. Early sexual debut before marriage precedes a lifetime of greater sexual activity but with more consistent condom use. Women who begin to have sex earlier than others of their age are more likely to be infected with HIV. This finding can be explained by their having a greater lifetime number of sexual partners than those whose first sexual experience occurs later. (STUDIES IN FAMILY PLANNING 2007; 38[1]: 1–10)

The age at which individuals become sexually active has been associated with a number of important demographic and sociological outcomes. For example, age at first sex has been shown to be a primary determinant of fertility (Bongaarts and Potter 1983). An increasing average age at first sex may indicate higher female status and autonomy (Dyson and Moore 1983), whereas beginning sexual activity early is associated with dropping out of school prematurely, early marriage and pregnancy, and a resulting reduction in future life opportunities (Blanc 2000). The timing of sexual debut also has consequences for risk of infection with HIV and other sexually transmitted infections (STIs). One reason early onset of sexual activity is a risk factor for acquiring an STI is that the pe-

riod of potential exposure to infection is longer. Additionally, for young women, physiological and immunological immaturity of the female genital tract may increase susceptibility (Duncan et al. 1990; Moss et al. 1991; Royce et al. 1997; Glynn et al. 2001; Drain et al. 2004; Pettifor et al. 2004; Kaestle et al. 2005). Furthermore, young girls who have sex with older men are unlikely to be able to insist on the use of condoms (Gregson et al. 2002a; Luke and Kurz 2002; Longfield et al. 2004). For these reasons, encouraging young people to delay the onset of sexual activity has been an objective of the United Nations since 1994 (as expressed in the Programme of Action recommended at the United Nations International Conference on Population and Development [ICPD] held in Cairo) and has been made a key objective of the (United States) President's Emergency Plan for AIDS Relief (PEPFAR) (Laga et al. 2001; Office of the United States Global AIDS Coordinator 2004; UNAIDS 2004).

Developing an appropriate psychosocial program aimed at persuading individuals to delay first sex requires a detailed understanding of the influences and motivations for beginning sexual activity. Identifying the characteristics of young people who are likely to start having sex early could help to improve the targeting of such a program. In developed countries, many socioeconomic variables have been shown to be associated with the timing of sexual debut (Johnson et al. 1994; Laumann et al. 1994; Spira et al. 1994). In many parts of Africa, young women commonly exchange sex with older men ("sugar daddies") for goods (Gregson et al. 2002a; Luke and Kurz 2002); an obvious root cause of this behavior

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is poverty (Longfield et al. 2004). In sub-Saharan Africa, men and women who are more educated tend to delay sexual initiation longer than others (Gupta and Mahy 2003), and the most educated individuals are considered to be more likely than others to change their behavior in response to the HIV/AIDS pandemic (Gregson et al. 2001). Knowledge of the risk of acquiring HIV/AIDS may also deter individuals from initiating sexual activity. Reproductive practices have also been linked to exposure to family planning messages presented through the mass media (Adamchak and Mbizvo 1991).

Although delaying sexual debut would reduce an individual's risk of becoming infected if no other aspect of her or his sexual behavior changed, studies based on the application of mathematical models (Hallett et al. 2007) suggest that the impact on the spread of HIV of delaying first sex may be small unless delaying sex also translates into reduced sexual activity later in life. In this study, we examine the trends in and determinants of age at first sex in Zimbabwe, where fertility has declined steadily since the mid-1980s (CSO and Macro International 2000) following the socioeconomic development associated with achieving independence in 1980, Zimbabweans' concomitant increased access to secondary education (UNDP 2000), and the relentless spread of the HIV pandemic (UNAIDS 2005; UNAIDS/WHO 2005). We address four questions about the age of sexual debut in Zimbabwe: (1) Has the average age of sexual debut changed recently? (2) Which groups of young people are likely to begin to have sex earlier than others? (3) Do individuals who begin to have sex early go on to be more sexually active than others? (4) Are individuals who become sexually active at an early age more likely than others to become infected with HIV?

Methods

Analyzing trends in sexual debut, including the association between age at first sex and personal characteristics, and the relationships between age at first sex and (a) subsequent sexual behavior and (b) the risk of acquiring HIV infection requires gathering sensitive information about sexual behavior, linked HIV-test results, and other potentially correlated social, economic, and geographic variables. Such detailed data were collected in a stratified population-based survey carried out in the Manicaland province of rural Zimbabwe between July 1998 and January 2000. The population strata comprised 12 distinct communities: two forestry plantations, two tea and coffee estates, four subsistence farming areas, two small towns, and two roadside trading centers. A preliminary household census enumerated 8,233 (98 percent) of 8,386

known households in the study areas. One man or woman from each married couple in a household was invited to participate in the survey. In total, 4,331 men aged 17–54 and 5,149 women aged 15–44 agreed to participate (77 percent of those eligible).

Structured interviews were conducted face to face by trained social science graduates familiar with the local culture but from outside the study area. The question about the age at which the subject first had sex came midway through the interview and after an informal discussion designed to build rapport between the interviewer and the subject. Responses to sensitive questions about sexual behavior were recorded using an informal confidential voting interview (ICVI) method in 75 percent of the interviews with literate respondents (selected at random) (Gregson et al. 2002b). By this method, the participant writes his or her responses to certain questions on a card so that the interviewer cannot read them and deposits them in a locked box. Interviews using this method have been shown to elicit from respondents reports of having more sexual partners than are reported in interviews conducted using other methods, suggesting that data collected in this way may be subject to less social-desirability bias.

Written informed consent was sought as a condition of enrollment, and free voluntary HIV counseling and testing and free STI treatment were made available in each study area. Prior ethical approval for the study was obtained from the Research Council of Zimbabwe and from the Applied and Qualitative Research Ethics Committee in Oxford, UK. Custom-made forms in SPSS-PC version 5.0 software were used for data entry and validation, and STATA version 8.0 software was used for data analysis.

Trends in Age at First Sex

Quartiles of reported age at first sex are reported by respondents' age category, and Mantel-Haenszel estimates of the rate ratio of having first sex are calculated with reference to the oldest age group (40–44 for females and 45–54 for males). Because older cohorts were at risk of experiencing sex before younger cohorts, this method can be used to estimate the trend in the "hazard" of first sex over the past 30 years. The hazard is the chance that an individual has experienced first sex at age A , given that he or she had not had sex before their A^{th} birthday. The ratio of hazard between cohorts is assumed to be constant.

Personal Characteristics Associated with Timing of First Sex

We treat age at first sex as time-to-event data to allow for first sex being censored (that is, the event—first sex—

may not have occurred by the time of the survey). In the model, individuals are born as virgins and “survive” until they first have sex. The eventual age at first sex of individuals who were not sexually experienced at the time of the survey is said to be “censored.” Because individuals were recruited for the study before anything was known of their sexual history, censoring is independent with respect to the outcome of interest. The analysis of the personal characteristics associated with age at sexual debut is restricted to those younger than 25 because the responses of older individuals may not be representative of their characteristics at the time of sexual debut (for example, the respondent’s current level of wealth may not correspond to his or her wealth at the time of first sex). We expected that the factors associated with first sex for males and for females would differ (Paul et al. 2000; Gupta and Mahy 2003). Therefore, we analyzed data for males and females separately throughout. Individuals whose reported age, date of birth, and/or age at first sex were inconsistent were excluded.

Mantel-Cox Hazard Ratios were used in the preliminary univariate analyses. Mantel-Cox χ^2 tests (log-rank tests) were performed for each comparison. Multivariate analyses used the Cox Proportional-Hazards Model, and the Breslow method was used for ties. A multivariate model was found by means of backward stepwise elimination using the likelihood-ratio test ($p \geq 0.05$) for exclusion. The scaled Schoenfeld Residuals from the multivariate model were tested for trend with age, and those variables that did not conform to the proportional-hazard assumption were broken down so that effect of “exposure X” was replaced with “exposure X for individuals aged 0– yr_1 ,” and “exposure X for individuals aged yr_1 –24.” The cutoff point (yr_1) was chosen after examination of the hazard profile.

Age at First Sex and Sexual Behavior

To explore how age at first sex is related to subsequent sexual behavior, logistic and linear regression models were constructed for which the outcome variable was sexual behavior and the explanatory variables were young-age-at-first-sex (younger than 18 years) and age (continuous variable). The sexual behavior variables were as follows: number of lifetime partners, number of current sexual relationships, number of sexual partners in the past month, number of sex acts in the past two weeks (all continuous variables), consistent condom use in the past two weeks (dichotomous variable, recorded as positive if the respondent reported that a condom was used in each sexual encounter), and ever divorced (dichotomous variable). The analysis was stratified by whether the first

sexual experience occurred within the first marriage (or long-term cohabiting relationship).

Age at First Sex and HIV Status

Logistic regression was used to assess the association between HIV serostatus (outcome variable) and age at first sex for those who had experienced sexual activity (explanatory variable). Adjustment was made for the length of time an individual had been sexually active and his or her lifetime number of sexual partners. All explanatory variables were divided into quartiles.

Results

Respondents were asked at what age they first had sex (they were given the option of responding that they had not yet had sex). Forty-nine males (1 percent) and 20 females (0.4 percent) did not answer this question. Of those who responded, 142 males (3 percent) and 180 females (4 percent) were excluded because information they gave about their age and their age at first sex were inconsistent. In total, data from 4,138 males and 4,948 females were analyzed, of whom 83 percent of males and 81 percent of females reported that they had begun sexual activity. For 7 percent of men and 71 percent of women, age at first sex coincided with their age when they first entered a long-term or cohabiting relationship or married.

Overall, females began sexual activity before males; median age at first sex was 18 years for females and 19 years for males (see Table 1 and Figure 1) (the log-rank test for equality of survivorship functions: $\chi^2 = 32.32$, 1 df, $p < 0.0001$). Over the past 30 years, males have been earlier in starting to have sex (the log-rank test for trend: $\chi^2 = 64.11$, 1 df, $p < 0.0001$). Although average age at first sex for females has not changed over the past 20 years, it may have increased in recent years (log-rank test for trend for all ages: $\chi^2 = 5.53$, 1 df, $p < 0.019$).

Determinants of Age at First Sex

Of those aged 24 or younger at the time of the interview, 2,113 males and 2,164 females gave consistent responses to questions about age at first sex. Sixty-nine percent of men and 58 percent of women reported having begun sexual activity.

Males

As shown in Table 2, univariate tests suggest that the hazard of having experienced first sex was significantly higher for males who live on agricultural estates, in towns, and in roadside trading centers, for those who watch tele-

Table 1 Percentage distribution of respondents surveyed, age at first sex by quartile, and Mantel-Haenszel estimate of rate ratio of having experienced first sex, by age group and sex, rural Manicaland province, Zimbabwe, 1998–2000

Age	Year when mean age of respondents was 20	Percent	(N)	Age by which respondents experienced first sex			Rate ratio of first sex
				25 percent	50 percent	75 percent	
Males							
17–19	2000	23	(953)	16	18	— ^a	1.65***
20–24	1998	26	(1,060)	16	18	20	1.89***
25–29	1991	18	(755)	17	19	21	1.53***
30–34	1986	10	(432)	17	19	21	1.51***
35–39	1981	9	(354)	17	19	21	1.52***
40–44	1976	6	(249)	18	19	22	1.25*
45–54 (r)	1969	8	(337)	18	20	23	1.00
Total	—	100	(4,140)	17	19	21	—
Females							
15–19	2001	24	(1,177)	17	— ^a	— ^a	0.77**
20–24	1996	20	(987)	17	18	20	1.08
25–29	1991	17	(836)	17	19	20	1.02
30–34	1986	13	(642)	17	18	20	0.93
35–39	1981	13	(646)	16	18	20	1.20*
40–44 (r)	1976	13	(661)	17	19	20	1.00
Total	—	100	(4,949)	17	18	20	—

*Significant at $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. (r) = Reference category. — = Not applicable.

^aFor age groups in which fewer than 75 percent or 50 percent of respondents have become sexually active, no value is given.

vision every week, who belong to a traditional church or no church, and for those who belong to a minority tribe or have relocated from a rural area. The hazard of having experienced first sex was lower for males who have completed primary education, who were students or were unemployed, and for those who possess above-average knowledge of HIV/AIDS. Only “church,” “tribe,” and “employment status” were retained by the multivariate model selection process. Those respondents belonging to traditional churches or to one of the minority “other” tribes had a significantly greater hazard of having had first sex, whereas students and the unemployed had a significantly lower hazard of having had first sex. The

multivariate model conforms to the proportional-hazards assumption (the test for trend in scaled Schoenfeld residuals: $\chi^2 = 12.32$, 14 df, $p = 0.5805$).

Females

As shown in Table 3, univariate tests suggest that the hazard of having experienced first sex was higher for females who live in towns, who belong to a traditional church or no church, or one of the “other” smaller churches, who belong to the Zezuru tribe or to one of the minority tribes, or who have relocated from either an urban or a rural area. The hazard of having experienced first sex was lower for females who are literate, who have completed primary education, who are professionals or skilled workers, who are unemployed or are students, who have above-average knowledge of HIV/AIDS, who read the news at least once a week, who watch television every week, who listen to the radio every day, or who live in a household that has a radio or in a dwelling with a cement floor. Five variables remained after the multivariate model selection process: “completion of primary education,” “employment status,” “listening to radio every day,” “tribe,” and “relocation.” The hazard ratio of the variable “completed primary education” was not constant over age, so it was calculated separately for females aged 15–19 and 20–24. Having completed primary education was significantly associated with a lower hazard of having experienced first sex only for females in the younger age group. Skilled or professional females, students, and those who listen to the radio every day had a lower hazard of having had first sex. Members of the minority tribes, those who

Figure 1 Kaplan-Meier estimates of survival until first sex for females and males, rural Manicaland province, Zimbabwe, 1998–2000

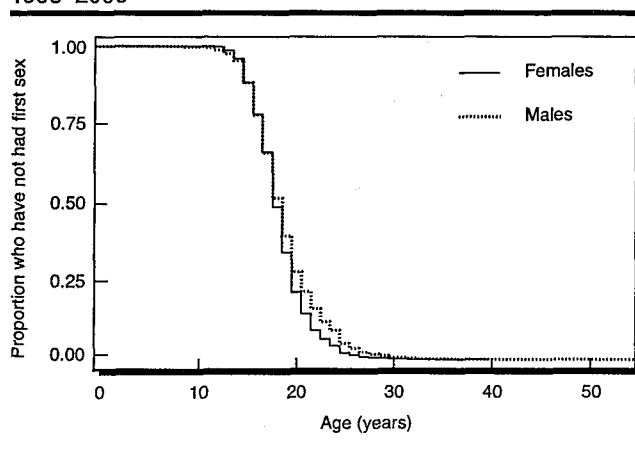


Table 2 Percentage distribution, median age at, and hazard ratio for first sex for males, by selected explanatory variables, rural Manicaland province, Zimbabwe, 1998–2000

Variable	Per-cent	(N)	Median age at first sex	Mantel-Cox hazard ratio (univariate test)	Adjusted hazard ratio (multivariate test)
Residence					
Agricultural estate	37	(746)	18	1.24***	—
Subsistence farm (r)	32	(635)	19	1.00	—
Town	16	(320)	18	1.44***	—
Roadside	15	(312)	18	1.26*	—
Total	100	(2,013)	18	—	—
Literate					
No (r)	3	(63)	18	1.00	—
Yes	97	(1,937)	18	0.75	—
Total	100	(2,000)	18	—	—
Completed primary education					
No (r)	19	(379)	18	1.00	—
Yes	81	(1,634)	18	0.84*	—
Total	100	(2,013)	18	—	—
Employment status					
Professional or skilled	7	(146)	18	0.91	0.93
Manual (r)	49	(966)	18	1.00	—
Unemployed	27	(528)	18	0.79**	0.86*
Student	17	(336)	20	0.54***	0.61***
Total	100	(1,976)	18	—	—
AIDS knowledge					
Below average (r)	42	(821)	18	1.00	—
Above average	58	(1,144)	18	0.86*	—
Total	100	(1,965)	18	—	—
Reads news once a week					
No (r)	61	(1,207)	18	1.00	—
Yes	39	(757)	18	1.06	—
Total	100	(1,964)	18	—	—
Watches television every week					
No (r)	69	(1,377)	18	1.00	—
Yes	31	(629)	18	1.16*	—
Total	100	(2,006)	18	—	—
Listens to radio every day					
No (r)	37	(742)	18	1.00	—
Yes	63	(1,267)	18	1.04	—
Total	100	(2,009)	18	—	—
Church					
Traditional	11	(229)	18	1.58***	1.39**
Methodist	7	(131)	19	0.94	0.96
Anglican (r)	25	(497)	18	1.00	—
Roman Catholic	16	(322)	18	1.07	1.03
Apostolic	2	(43)	19	1.07	0.99
None	10	(201)	18	1.30*	1.21
Other	29	(590)	18	0.98	0.97
Total	100	(2,013)	18	—	—
Tribe					
Karanga	5	(105)	18	1.00	0.95
Manyika (r)	57	(1,137)	18	1.00	—
Maungwe	16	(329)	18	1.02	1.08
Ndau	8	(160)	18	0.92	0.87
Zezuru	5	(101)	18	1.29	1.23
Other	9	(173)	17	1.46**	1.25*
Total	100	(2,005)	18	—	—
Household has radio					
No (r)	41	(793)	18	1.00	—
Yes	59	(1,154)	18	1.03	—
Total	100	(1,947)	18	—	—

(continued)

Table 2 (continued)

Variable	Per-cent	(N)	Median age at first sex	Mantel-Cox hazard ratio (univariate test)	Adjusted hazard ratio (multivariate test)
House has cement floor					
No (r)	17	(338)	18	1.00	—
Yes	83	(1,601)	18	1.00	—
Total	100	(1,939)	18	—	—
Residence history					
In survey location since birth (r)	49	(977)	18	1.00	—
Previously in urban area	11	(219)	18	1.23	—
Previously in rural area	40	(796)	18	1.20**	—
Total	100	(1,992)	18	—	—

*Significant at $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. (r) = Reference category.
— = Not applicable.

Note: Hazard ratios greater than one convey that the age at first sex is younger than the age at first sex for the reference category.

do not belong to a church, and those who have relocated from urban and from rural areas had a higher hazard of having experienced first sex. The multivariate model conformed to the proportional-hazards assumption (the test for trend in scaled Schoenfeld residuals: $\chi^2 = 22.26$, 13 df, $p = 0.0515$).

Association between Age at First Sex and Sexual Behavior

Males who began to have sex outside of marriage before they were 18 tended to have more lifetime sexual partners, to have more sexual partners in the past month, to engage in more acts of sexual intercourse in the past two weeks, and to be involved in more sexual relationships at the time of the interview (as shown in Table 4). Males who began to have sex just as early but did so within their first marriage did not go on to engage in riskier sexual behavior than males who started to have sex when they were older. Females who began to have sex early tended to be more sexually active than those who started to have sex later, and this association was stronger for females engaging in premarital sex. Males and females who had first sex early and outside of marriage, however, were more likely to use condoms consistently thereafter.

Age at First Sex and HIV Infection

According to a univariate analysis for which results were adjusted for years of sexual activity, females who began to have sex when they were 12 to 16 were more likely to be infected with HIV than those who began at age 21 or later. When number of lifetime sexual partners was taken

Table 3 Percentage distribution, median age at, and hazard ratio for first sex for females, by selected explanatory variables, rural Manicaland province, Zimbabwe, 1998–2000

Variable	Per- cent	(N)	Median age at first sex	Mantel-Cox hazard ratio (univariate test)	Adjusted hazard ratio (multivariate test)
Residence					
Agricultural estate	28	(611)	18	1.18	—
Subsistence farm (r)	37	(808)	19	1.00	—
Town	16	(343)	18	1.28*	—
Roadside	19	(402)	19	0.92	—
Total	100	(2,164)	19	—	—
Literate					
No (r)	2	(52)	18	1.00	—
Yes	98	(2,097)	19	0.50***	—
Total	100	(2,149)	19	—	—
Completed primary education					
No (r)	26	(557)	17	1.00	—
Yes	74	(1,607)	19	0.41***	—
15–19 years ^a	— ^a	— ^a	— ^a	—	0.70***
20–24 years ^a	— ^a	— ^a	— ^a	—	1.10
Total	100	(2,164)	19	—	—
Employment status					
Professional or skilled	2	(39)	20	0.34***	0.50**
Manual (r)	33	(694)	18	1.00	1.00
Unemployed	43	(919)	18	0.85*	0.90
Student	22	(475)	— ^a	0.11***	0.20***
Total	100	(2,127)	18	—	—
AIDS knowledge					
Below average (r)	44	(918)	18	1.00	—
Above average	56	(1,175)	19	0.80**	—
Total	100	(2,093)	18	—	—
Reads news once a week					
No (r)	76	(1,617)	18	1.00	—
Yes	24	(514)	19	0.62***	—
Total	100	(2,131)	19	—	—
Watches television every week					
No (r)	87	(1,875)	18	1.00	—
Yes	13	(288)	19	0.64***	—
Total	100	(2,163)	19	—	—
Listens to radio every day					
No (r)	59	(1,275)	18	1.00	—
Yes	41	(881)	19	0.70***	0.80**
Total	100	(2,156)	19	—	—
Church					
Traditional	3	(57)	17	2.56***	—
Methodist	10	(212)	19	0.96	—
Anglican (r)	28	(602)	19	1.00	—
Roman Catholic	17	(375)	19	1.07	—
Apostolic	2	(36)	18	1.50	—
None	4	(89)	18	2.30***	—
Other	37	(793)	18	1.35**	—
Total	100	(2,164)	19	—	—
Tribe					
Karanga	4	(97)	19	1.32	1.10
Manyika (r)	55	(1,187)	19	1.00	—
Maungwe	19	(418)	19	1.07	1.10
Ndau	3	(74)	18	1.14	0.90
Zezuru	8	(181)	18	1.43**	1.10
Other	9	(200)	18	2.16***	1.50***
Total	100	(2,157)	18	—	—
Household has radio					
No (r)	45	(937)	17	1.00	—
Yes	55	(1,160)	17	0.72***	—
Total	100	(2,097)	17	—	—

(continued)

Table 3 (continued)

Variable	Per- cent	(N)	Median age at first sex	Mantel-Cox hazard ratio (univariate test)	Adjusted hazard ratio (multivariate test)
House had cement floor					
No (r)	16	(339)	16	1.00	—
Yes	84	(1,760)	17	0.62***	—
Total	100	(2,099)	17	—	—
Residence history					
In survey location since birth (r)	46	(979)	18	1.00	—
Previously urban area	17	(359)	17	1.56***	1.30**
Previously rural area	38	(805)	16	2.00***	1.40***
Total	100	(2,143)	17	—	—

*Significant at $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. (r) = Reference category.

— = Not applicable.

^aFor age groups in which fewer than 75 percent or 50 percent of respondents have become sexually active, no value is given.

Note: Hazard ratios greater than one convey that the age at first sex is younger than the age at first sex for the reference category.

Table 4 Coefficients from regressions of early first sex on the association between various sexual-behavior outcomes, rural Manicaland province, Zimbabwe, 1998–2000

Variable	Regression coefficient: first sex prior to age 18 ^a
Males whose first sex was within marriage^b (population: 7 percent of sexually experienced males)	
Lifetime partners ^c	2.50**
Lifetime partners adjusted for years of sexual activity ^c	1.00
Number of partners in past month ^c	–0.03
Number of sex acts in past two weeks ^c	–0.46
Number of current sexual relationships ^c	0.02
Consistent condom use past two weeks ^d	–0.27
Divorced ^d	0.93
Males whose first sex was before marriage^b (population: 93 percent of sexually experienced males)	
Lifetime partners ^c	4.04***
Lifetime partners adjusted for years of sexual activity ^c	2.32***
Number of partners in past month ^c	0.20***
Number of sex acts in past two weeks ^c	0.64***
Number of current sexual relationships ^c	0.28***
Consistent condom use past two weeks ^d	0.43**
Divorced ^d	0.11
Females whose first sex was within marriage^b (population: 67 percent of sexually experienced females)	
Lifetime partners ^c	0.47***
Lifetime partners adjusted for years of sexual activity ^c	0.38**
Number of partners in past month ^c	0.00
Number of sex acts in past two weeks ^c	0.39*
Number of current sexual relationships ^c	0.04*
Consistent condom use past two weeks ^d	0.31
Divorced ^d	0.28*
Females whose first sex was before marriage^b (population: 33 percent of sexually experienced females)	
Lifetime partners ^c	1.47***
Lifetime partners adjusted for years of sexual activity ^c	1.01**
Number of partners in past month ^c	0.14***
Number of sex acts in past two weeks ^c	0.67**
Number of current sexual relationships ^c	0.18**
Consistent condom use past two weeks ^d	0.56*
Divorced ^d	0.29

*Significant at $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

^a"First sex at younger age than 18" is the explanatory variable used in the regression model; it is adjusted for age category. A positive value implies that early first sex is associated with a higher value of the sexual-behavioral outcome variable or is affirmative for a dichotomous variable. ^bThe term "marriage," as used here, includes long-term cohabiting relationships. ^cA linear model is used for this continuous variable. ^dA logistic model is used for this dichotomous variable.

Table 5 Odds ratios of having acquired HIV infection, by age at first sex for males and females, rural Manicaland province, Zimbabwe, 1998–2000

Age at first sex	Percent of sample	Multivariate test					
		Univariate test		Odds ratio adjusted for years of sexual activity	p-value	Odds ratio adjusted for number of lifetime partners	p-value
		Odds ratio	p-value				
Males							
12–16	27	0.75	0.02	0.79	0.07	0.59	0.07
17–18	30	0.96	0.71	1.11	0.38	0.82	0.10
19–20	22	1.18	0.17	1.30	0.17	1.07	0.13
21+ (r)	20	1.00	—	1.00	—	1.00	—
Females							
12–16	27	1.49	0.00	1.60	0.00	1.14	0.23
17–18	30	1.07	0.55	1.11	0.32	0.94	0.55
19–20	22	1.18	0.12	1.23	0.06	1.11	0.37
21+ (r)	20	1.00	—	1.00	—	1.00	—

(r) = Reference category. — = Not applicable.

into account, however, no statistically significant association was found (see Table 5). Males who began to have sex when they were young were less likely than others to be infected with HIV.

Discussion

In rural Zimbabwe, we found a median age of sexual debut of 18 years for women and 19 years for men, medians that lie in the middle of international estimates (Singh et al. 2000) but are relatively high for African countries (Zaba et al. 2004). Thus, the magnitude of the HIV epidemic in this rural population—the prevalence at the time of the survey was 19 percent among males aged 17–54 and 26 percent among females aged 15–44—does not appear to be explained by early sexual debut. The lower age of debut for women compared with men may be explained in part by the number of older men who seek out young sexual partners, behavior that also could contribute to the scale of the HIV spread in Zimbabwe (Gregson et al. 2002a).

In contrast to survey results from industrialized countries (for France see Spira et al. 1994; for Great Britain see Johnson et al. 1994; and for North America see Laumann et al. 1994), we found few associations between socioeconomic and geographic variables and age at first sex. Although in a cross-sectional survey such as this the sequence of events is unclear, these data do not suggest that early sexual debut leads to a spiral of decline and riskier sexual behavior. Rather, they point toward other influences linking early sexual debut and subsequent higher risk. The Zimbabwean Demographic and Health Survey (DHS) suggests that the most educated and the wealthiest men and women experience sexual debut later than their less educated and poorer counterparts (CSO

and Macro International 2000). This finding suggests that a primary motive for young women to begin sexual activity may be to obtain money and gifts from an older partner (Gregson et al. 2002a).

In common with other settings (Johnson et al. 1994; Laumann et al. 1994; Spira et al. 1994; Gupta and Mahy 2003), young women in Manicaland who completed primary education and young men and women who are students were at less risk of starting to have sex. Whether being in school or university reduces the risk of experiencing first sex or whether young women who have become sexually active (and perhaps become pregnant) are more likely to drop out of school or university is unclear. The preference among young women to form partnerships with employed men (Gregson et al. 2002a) may also help explain the relatively early sexual debut of manual laborers and the later debut of male students. The lack of an effect of primary education among 20–24-year-old women could indicate that early education becomes a less important determinant of behavior as women age or may be the result of random or differential recall bias.

The effect of primary education on age at first sex has increased over time; the univariate rate ratio of first sex for primary education was 0.85 among 40–44-year-old women having a mean age of 20 years in 1969, compared with 0.42 for 20–24-year-old women having a mean age 20 years in 1996 (not shown). That educated women lead the trend in delaying first sex is consistent with the recently reported downturn in HIV prevalence among more educated groups (Gregson et al. 2006). This finding echoes the pattern of behavioral change observed when medical facilities and methods of family planning became widely available (Rogers 1983; Gregson et al. 2001). No such pattern for females was detected in the data collected for the Zimbabwe DHS between 1994 and 1999, although the proportion of the most-educated 15–24-year-old men re-

porting having had sex declined ($OR = 0.7; p \leq 0.001$) (not shown). Further analysis based on education beyond the primary level (such as highest level of education attained) was not possible because we did not know what the eventual educational level would be for respondents currently attending school, nor their educational status when they first had sex. Another limitation of this cross-sectional data is the absence of information on the socioeconomic status of the individual at the time of first sex. Although the average interval between experience of first sex and the interview was only three to four years, 23 percent of males and 19 percent of females relocated during this time, increasing the likelihood that their circumstances could have changed substantially.

Individuals' reports of their sexual behavior are susceptible to social desirability bias (Catania et al. 1990). In the survey upon which this study's analyses are based, measures were taken when asking sensitive questions to encourage honest reporting. These measures tend to be associated with reports of less socially desirable outcomes (Gregson et al. 2002b), giving us greater confidence in the accuracy of these self-reports of sexual behavior.

A young age at sexual debut has been associated with greater subsequent sexual activity (Greenberg et al. 1992; Drain et al. 2004; Pettifor et al. 2004; Kaestle et al. 2005), and our findings support this association. A key modifying factor, however, is whether early first sex occurs within early marriage; if it does, the association with greater risk is markedly reduced. We also found a greater tendency to use condoms among those who began sex early than among others, which is consistent with the finding that those reporting the riskiest sexual behavior also report the greatest use of condoms (Mbizvo et al. 1994; Mnyika et al. 1996; Gregson et al. 2002a), possibly because they are more aware than others of the risks they face. For females, however, the protective benefits of higher rates of condom use did not appear to outweigh the increased risk of HIV infection associated with having more sexual partners.

Whether early sex is causally related to subsequent high levels of sexual activity—through pathways such as pregnancy, leaving school, and engaging in commercial sex—or is correlated through psychological, social, or economic factors is unclear. The association between early first sex and HIV infection in this rural population can be explained, however, by subsequent behavioral differences. This explanation does not support delaying age at first sex specifically to prevent transmission of HIV; rather, it suggests that decreasing casual sex is likely to have a greater effect in reducing the spread of infection. Although delaying sexual debut would reduce the lifetime risk of HIV infection at the individual level, at the

population level it would have a limited effect, because those who begin sexual activity early tend to have more partners, engage more frequently in sexual activity, and have a higher concurrency of sexual partnerships than others. The casual nature of their sexual activity rather than their early sexual debut appears to be what leads to their infection. Among young women in urban Zimbabwe, by contrast, the association between age at first sex and HIV infection has been found to be statistically significant even when subsequent sexual behavior is taken into account (Pettifor et al. 2004).

With other factors being equal, we would expect that males who begin to have sex early would be more likely than others to be HIV positive. The observation from our findings that males who began sex early were less likely to have been infected might indicate that their higher-than-average condom use is sufficient to offset their greater exposure to HIV. This result, however, could also arise from unreliable reports of age at first sex (for example, males with the fewest sexual partners or latest sexual debut may have reported that they were younger when they first had sex than, in fact, they were).

An encouraging finding is that in recent years young women have begun sexual activity later than in the past. The long-term trend among men for lower age at first sex is a cause for concern, however, especially if this trend is exacerbated by messages aimed at reducing the age difference between partners in order to limit young women's risk of acquiring infection from older men (Gregson et al. 2002a; Hallett et al. 2007). Alternatively, the trend could be generated by recall bias or by the selective effects of mortality; men in older cohorts who began to have sex early may have died of AIDS, so that only those who began to have sex later could be surveyed. In fact, the DHS data indicate that between 1994 and 1999, a slight decrease was found in the proportion of 15–24-year-olds who had begun to have sex.

A current focus of many HIV interventions is delaying first sex, often by emphasizing abstinence as part of the ABC plan that also endorses being faithful to one partner and using condoms (Office of the United States Global AIDS Coordinator 2004). Our results show that such programs could benefit from focusing on the employed rather than students and the unemployed. Members of traditional churches and those who report no religious affiliation should also be targeted. The shorter period that elapsed between first sex and marriage for males than for females among traditional church members suggests that faithfulness within marriage may be a more appropriate message to promote for this group. That the small group of women (4 percent) who were not associated with a church reported younger age at sexual debut and a long-

er period before marriage suggests that this group may be an appropriate focus for abstinence programs.

Young women who have relocated should also be targeted for interventions. Relocation can be a source of intense anxiety and can lead to feelings of low self-worth and poor social integration (Paul et al. 2000; Pedersen et al. 2003). Young women in this position may be more vulnerable to demands for sex, particularly from older men (Gregson et al. 2002a; Longfield et al. 2004). The association between younger age at sexual debut and having relocated could also arise, however, as a result of this society's tradition of patrilocal marriage, whereby a newly married woman moves to her husband's place of residence. More women who had relocated were married at the time of the interview (68 percent) than were those who had stayed in the same location since birth (34 percent), and slightly more women who had begun having sex early (before they were 18) reported moving because of a partner's work than their counterparts who began sexual activity later (12 percent versus 9 percent).

Men who had regular access to the mass media (including radio, television, and newspapers) tended to begin sexual activity earlier than women who had similar access. This pattern is echoed in other sub-Saharan countries (Gupta and Mahy 2003) and may reflect a greater receptivity among women to the safe-sex messages that are broadcast in the media and may reflect women's use of this information to negotiate for safe sexual behavior with their partners. Additional research is needed to investigate how mass-media campaigns could have a greater impact on young men's behavior.

Cross-sectional data, such as those analyzed here, are not amenable to analysis in terms of the sequence of events; we cannot, for example, distinguish which happened first: beginning to have sex early or leaving school without a primary education. Furthermore, a survey cannot hope to untangle fully the complex interactions between all the social, cultural, demographic, behavioral, and epidemiological variables. Nonetheless, a local picture for this area of rural Zimbabwe emerges: sexual debut occurs at a late median age but early sexual debut precedes greater sexual activity, which leads to a greater risk for HIV infection among women but not among men in this area of high HIV prevalence. The lower risk for men may exist because men who have early and frequent sex tend to use condoms more often than others.

References

Adamchak, Donald J. and Michael T. Mbizvo. 1991. "Family planning information sources and media exposure among Zimbabwean men." *Studies in Family Planning* 22(5): 326-331.

Blanc, Ann. 2000. "The relationship between sexual behaviour and level of education in developing countries." Report prepared for UNAIDS. Geneva: UNAIDS.

Bongaarts, John and Robert G. Potter. 1983. *Fertility, Biology and Behaviour. An Analysis of the Proximate Determinants*. San Diego: Academic Press.

Catania, J.A., D.R. Gibson, D.D. Chitwood, and T.J. Coates. 1990. "Methodological problems in AIDS behavioral research: Influences on measurement error and participation bias in studies of sexual behavior." *Psychological Bulletin* 108(3): 339-362.

Central Statistical Office (CSO) (Zimbabwe) and Macro International. 2000. *Zimbabwe Demographic and Health Survey 1999*. Calverton, MD: CSO and Macro International.

Drain, P.K., J.S. Smith, J.P. Hughes, D.T. Halperin, and K.K. Holmes. 2004. "Correlates of national HIV seroprevalence: An ecologic analysis of 122 developing countries." *Journal of Acquired Immune Deficiency Syndromes* 35(4): 407-420.

Duncan, M.E., G. Tibaux, A. Pelzer, K. Reimann, J.F. Peutherer, P. Simmonds, H. Young, Y. Jamil, and S. Daroughar. 1990. "First coitus before menarche and risk of sexually transmitted disease." *Lancet* 335(8,685): 338-340.

Dyson, Tim and Mick Moore. 1983. "On kinship structure, female autonomy, and demographic behavior in India." *Population and Development Review* 9(1): 35-60.

Glynn, J.R., M. Caraël, B. Auvert, M. Kahindo, J. Chege, R. Musonda, F. Kaona, and A. Buvé. 2001. "Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya and Ndola, Zambia." *AIDS* 15(Supplement 4): S51-S60.

Greenberg, J., L. Magder, and S. Aral. 1992. "Age at first coitus. A marker for risky sexual behavior in women." *Sexually Transmitted Diseases* 19(6): 331-334.

Gregson, S., G.P. Garnett, C.A. Nyamukapa, T.B. Hallett, J.J. Lewis, P.R. Mason, S.K. Chandiwana, and R.M. Anderson. 2006. "HIV decline associated with behavior change in eastern Zimbabwe." *Science* 311(5,761): 664-666.

Gregson, S., C.A. Nyamukapa, G.P. Garnett, P.R. Mason, T. Zhuwau, M. Caraël, S.K. Chandiwana, and R.M. Anderson. 2002a. "Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe." *Lancet* 359 (9,321): 1,896-1,903.

Gregson, S., H. Waddell, and S. Chandiwana. 2001. "School education and HIV control in sub-Saharan Africa: From discord to harmony?" *Journal of International Development* 13: 467-485.

Gregson, S., T. Zhuwau, J. Ndlovu, and C.A. Nyamukapa. 2002b. "Methods to reduce social desirability bias in sex surveys in low-development settings: Experience in Zimbabwe." *Sexually Transmitted Diseases* 29(10): 568-575.

Gupta, N. and M. Mahy. 2003. "Sexual initiation among adolescent girls and boys: Trends and differentials in sub-Saharan Africa." *Archives of Sexual Behavior* 32(1): 41-53.

Hallett, T.B., S. Gregson, J.J.C. Lewis, B.A. Lopman, and G.P. Garnett. 2007. "Behaviour change in generalised HIV epidemics: The impact of reducing cross-generational sex and delaying age of sexual debut." Forthcoming.

Johnson, A.M., J. Wadsworth, K. Wellings, and J. Field. 1994. *Sexual Attitudes and Lifestyles*. Oxford: Blackwell Scientific Publications.

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- Kaestle, C.E., C.T., Halpern, W.C. Miller, and C.A. Ford. 2005. "Young age at first sexual intercourse and sexually transmitted infections in adolescents and young adults." *American Journal of Epidemiology* 161(8): 774–780.
- Laga, M., B. Schwartlander, E. Pisani, P.S. Sow, and M. Caraël. 2001. "To stem HIV in Africa, prevent transmission to young women." *AIDS* 15(7): 931–944.
- Laumann, Edward O., John H. Gagnon, Robert T. Michael, and Stuart Michaels. 1994. *The Social Organization of Sexuality: Sexual Practices in the United States*. Chicago: University of Chicago Press.
- Longfield, Kim, Anne Glick, Margaret Waithaka, and John Berman. 2004. "Relationships between older men and younger women: Implications for STIs/HIV in Kenya." *Studies in Family Planning* 35(2): 125–134.
- Luke, N. and K.M. Kurz. 2002. "Cross-generational and transactional sexual relationships in sub-Saharan Africa." Washington, DC: International Center for Research on Women.
- Mbizvo, M.T., S. Ray, M. Bassett, W. McFarland, R. Machekano, and D. Katzenstein. 1994. "Condom use and the risk of HIV infection: Who is being protected?" *The Central African Journal of Medicine* 40(11): 294–299.
- Mnyika, K.S., K.I. Klepp, G. Kvale, and N. Ole-King'ori. 1996. "Risk factors for HIV-1 infection among women in the Arusha region of Tanzania." *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 11(5): 484–491.
- Moss, G.B., D. Clemetson, L. D'costa, F.A. Plummer, J.O. Ndinya-Achola, et al. 1991. "Association of cervical ectopy with heterosexual transmission of human immunodeficiency virus: Results of a study of couples in Nairobi, Kenya." *Journal of Infectious Diseases* 164(3): 588–591.
- Office of the United States Global AIDS Coordinator. 2004. "The President's Emergency Plan for AIDS Relief." US Five-year Global HIV/AIDS Strategy. Washington, DC: US Department of State.
- Paul, C., J. Fitzjohn, P. Herbison, and N. Dickson. 2000. "The determinants of sexual intercourse before age 16." *Journal of Adolescent Health* 27(2): 136–147.
- Pedersen, W., S.O. Samuelsen, and L. Wichstrom. 2003. "Intercourse debut age: Poor resources, problem behavior, or romantic appeal? A population-based longitudinal study." *Journal of Sex Research* 40(4): 333–345.
- Pettifor, A.E., A. Van Der Straten, M.S. Dunbar, S.C. Shiboski, and N.S. Padian. 2004. "Early age of first sex: A risk factor for HIV infection among women in Zimbabwe." *AIDS* 18(10): 1,435–1,442.
- Rogers, E. 1983. *Diffusion of Innovations*. New York: The Free Press.
- Royce, R.A., A. Sena, W. Cates, Jr., and M.S. Cohen. 1997. "Sexual transmission of HIV." *New England Journal of Medicine* 337(11): 1,072–1,078.
- Singh, Susheela, Dierdre Wulf, Renee Samara, and Yvette P. Cuca. 2000. "Gender differences in the timing of first Intercourse: Data from 14 countries." *International Family Planning Perspectives* 26(1): 21–28, 43.
- Spira, Alfred, Nathalie Bajos, and the ACSF Group. 1994. *Sexual Behaviour and AIDS*. Aldershot, UK: Avebury.
- Terceira, N., S. Gregson, B. Zaba, and P. Mason. 2003. "The contribution of HIV to fertility decline in rural Zimbabwe, 1985–2000." *Population Studies* 57(2): 149–164.
- UNAIDS (Joint United Nations Programme on HIV/AIDS). 2004. *2004 Report of the Global AIDS Epidemic*. Geneva: UNAIDS.
- . 2005. *Evidence for HIV decline in Zimbabwe: A Comprehensive Review of the Epidemiological Data*. Geneva: UNAIDS.
- UNAIDS and World Health Organization (WHO). 2005. *AIDS Epidemic Update: December 2005*. Geneva: UNAIDS and WHO.
- United Nations Development Programme (UNDP). 2000. *Human Development Report*. New York: UNDP.
- Zaba, B., E. Pisani, E. Slaymaker, and J.T. Boerma. 2004. "Age at first sex: Understanding recent trends in African demographic surveys." *Sexually Transmitted Infections* 80(Supplement 2): ii28–ii35.

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