

Mathematical Modelling for assessing HIV Epidemics and the impact of interventions in Latin America

Candidate: Juan Fernando Vesga

Department of Infectious Disease Epidemiology

School of Public Health

Imperial College London

Thesis submitted in examination for the degree of Doctor of Philosophy

September 2014

Declaration of Originality: I declare that all of the work presented in this thesis is my own, and is referenced or acknowledged otherwise. The thesis comprises original work I conducted between October 4, 2010 and September 25, 2014 during my Full-time PhD programme at Imperial College London.

I acknowledge the supervision by Dr Timothy Hallett and Dr Marie-Claude Boily.

I acknowledge the assistance of Dr. Francisco Inacio Bastos at Instituto Oswaldo Cruz, Rio de Janeiro, Brazil during elaboration of chapter 3. Roberta Pati Pascom and Dr Fabio Mesquita at *Departamento de DST, Aids e Hepatites Virais* in Brasilia, Brazil, provided data from Brazil's Ministry of Health.

I also acknowledge the assistance of Anne Cori (Imperial College) and Ard van Sighem (Stichting institute, Amsterdam) for work related to the contents in Chapter 4.

The work presented in Chapter 4: "Estimating HIV Incidence from Case-report Data: Method and an Application in Colombia", has been published and is attached to this thesis. Reproduction of its contents is authorized and does not breach copyright rules according to the publisher, Wolters Kluwer Health | Lippincott Williams & Wilkins.

Vesga JF, Cori A, van Sighem A, Hallett TB. Estimating HIV incidence from case-report data: method and an application in Colombia. AIDS. 2014 Nov;28 Suppl 4:S489-96

Copyright Declaration: *The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.*

ABSTRACT

Latin America is a region of diversity, inequality, poverty and an outstanding capacity to remain stable despite these challenges. The HIV epidemic in the region resembles these same characteristics, with a wide range of risk behaviours, a disproportionate burden in vulnerable groups and yet perhaps a highly effective response.

Brazil and Colombia have extensively deployed prevention strategies and delivered antiretroviral treatment and there are still further expansions in sight. However, the likely impact of these HIV programmes on the epidemic has never been evaluated. This thesis addresses these gaps by retrospectively evaluating the impact of antiretroviral treatment and prevention campaigns on new HIV infections. This is done by means of mathematical models that represent HIV transmission in these settings and which creates a counterfactual projection for the trajectory the epidemic might otherwise have taken. These estimations are interpreted in the context of ambitious plans to scale treatment further, along with a growing realisation of the long-term costs that these programmes imply.

Tracking the epidemic is essential for the evaluation of programmes in the next phase of the response. To support this, a new method for incidence estimation is proposed. This method relies exclusively on case-report data, which is robust in these settings, and a flexible model specification that should be suitable for a wide range of epidemic scenarios. The parameters for the model are estimated in Bayesian framework and applied to the case study of Colombia. These resulting estimates of the historic course of the epidemic in Colombia are strikingly different to that which has previously been estimated and casts new light on the nature of epidemics in this region and the response to it that is now required.

Overall, these results stand as the first analysis of this kind in the region and present useful results and methods that should support a continued effective response to HIV epidemic in this region.

ACKNOWLEDGEMENTS

To Sophia, for her love and constant support that has made this years of hard work incredible enjoyable. To my Mother, my Father and my sisters for their trust, support and for always being there.

I would like to thank my supervisors Tim Hallett and Marie-Claude Boily, for believing in my ideas, guiding me and being infinitely patient whenever I needed their advice. To Tim, for supporting my work and “squeezing” the best out my many modelling projects. Marie-Claude, for listening patiently and engaging with my work and my many doubts to which always found clever solutions.

I am especially grateful with Francisco “Chico” Bastos at FIOCRUZ in Rio de Janeiro for his constant availability and immense help in the colossal task of trying to simulate HIV in Brazil. People at DST AIDS e *Hepatitis viraes* for providing data and advice related to surveillance systems in Brazil.

I am also very grateful with Ard van-Sighem, in Amsterdam, for facilitating useful code and his experience in the project of HIV incidence estimation from case-report data.

People at UNAIDS in both Geneva and RST LA Panama for giving me the opportunity to work with Modes of Transmission, from which I gained invaluable experience.

Special thanks to Dr Carlos Alvarez at Hospital San Ignacio in Bogota, for his support and mentorship during decisive years, and for encouraging my interest in infectious diseases.

With immense gratitude to my friends and colleagues from DIDE for their constant support and their feedback. To Anne Cori for patiently spending hours of her busy days to introduce me into the depths of the Bayesian methods. Thibaut, Sharmistha, Annick, Minttu for cheering, proofreading and helping through the writing up. Jack, Nick, Hugo, Patrick, Michael and others that have spent time with me, listening and providing great companion.

To my funder, Colciencias and people at Laspau for making all this possible.

To my friends in Bogotá, London and Munich.

TABLE OF CONTENTS

Declaration of own work	2
Abstract	3
Acknowledgements	4
List of Figures	8
List of Tables	10
Acronyms	11
Chapter 1: Introduction	12
1. Background	13
2. HIV a success of biology a catastrophe of public health	14
2.1. The origins	14
2.2. The epidemic expansion	17
3. HIV in Latin America	20
3.1. Background	20
3.2. Men who have sex with Men (MSM)	21
3.3. Female Sex Workers (FSW)	24
3.4. People Who Inject Drugs (PWID)	25
3.5. The HIV epidemic in Colombia	26
3.5.1. Social and cultural context	26
3.5.2. Epidemiology of HIV in Colombia	29
3.5.3. Response to HIV epidemic	30
3.6. AIDS and treatment in Brazil	31
4. HIV prevention: focus on treatment	34
4.1. Treatment as prevention	34
4.2. Challenges of TasP	35
5. Evaluation of prevention programmes	37
5.1. Randomised controlled trials	41
5.2. Observational studies of serodiscordant couples	43
5.3. Ecological studies and observational cohorts for the population effect of ART	47
5.4. Mathematical modelling in HIV programme evaluation	48
5.4.1. Models for estimating the impact of ART at the population level	50
5.5. The importance of HIV incidence estimation for assessing the impact of interventions.	52
6. Rational and thesis layout	52
7. References	56
Chapter 2: Estimating the Impact of Antiretroviral Treatment in the HIV epidemic of Bogota, Colombia	63
1. Introduction	64
2. Methods	66
2.1. Model Structure	66
2.2. Model Equations	70

2.2.1. Ordinary differential equations	70
2.2.2. Force of Infection	72
2.2.3. Mixing matrix and contact patterns in the model	74
2.2.4. Initial conditions and numerical solution	76
2.3. Data and parameterization	77
2.3.1. Behavior change: condom use in the model	77
2.3.2. Modelling ART	79
2.4. Model calibration	83
2.4.1. Parameter sampling	83
2.4.2. Fitting to outcomes data	84
2.4.3. Goodness of fit	87
2.5. Plan of analysis	88
2.5.1. Characterization of HIV epidemic in Bogota	88
2.5.2. Estimation of retrospective impact of interventions	89
3. Results	91
3.1. Calibration results	91
3.2. HIV Epidemic Characterization	93
3.2.1. HIV infections by risk group	93
3.2.2. Sources of transmission	94
3.2.3. Drivers of HIV epidemic	96
3.2.4. Estimation of retrospective impact of interventions	97
4. Discussion	100
5. References	105
Chapter 3: Estimating the retrospective impact of Antiretroviral Treatment scale-up in Brazil	109
1. Introduction	110
2. Methods	113
2.1. Model structure	114
2.2. Population Structure and risk heterogeneity	115
2.3. Model Equations	117
2.3.1. Ordinary Differential Equations	117
2.3.2. Force of Infection	120
2.4. Initial conditions	122
2.5. Condom use in the model	122
2.6. Antiretroviral therapy in the model	124
2.7. Data and sources of information	126
2.8. Parameter sampling	126
2.9. Model calibration	126
2.9.1. Prior Limits on output	130
2.9.2. Likelihood Estimation	134
2.9.3. Posterior weight and Model selection	136

2.10.	Analysis plan	136
2.10.1.	Post-calibration	136
2.10.2.	Estimating the impact of ART	137
3.	Results	138
3.1.	Calibration results	138
3.2.	Estimated impact of ART for reducing HIV incidence in Brazil	146
4.	Discussion	152
5.	References	156
Chapter 4: Estimating HIV Incidence from Case-report Data: Method and an Application in Colombia		161
1.	Introduction	162
2.	Methods	163
2.1.	Mathematical model	165
2.2.	Model parameterization	165
2.2.1.	HIV infection rate	165
2.2.2.	IV detection rates	167
2.3.	Model validation and calibration procedures	168
2.4.	Assessment of Model Performance Using Synthetic Data	170
2.5.	Application of the Model to Colombia	170
3.	Results	171
3.1.	Assessment of Model Performance Using Synthetic Data	171
3.2.	Estimating HIV Incidence in Colombia	172
4.	Discussion	174
5.	References	176
Chapter 5: Discussion		179
1.	Summary of main findings	181
2.	The role of model assumptions in the impact of interventions	183
2.1.	The impact of ART in the presence of behaviour changes	183
2.2.	Different approaches to modelling ART in key populations	184
2.3.	HIV Prevention effect in concentrated epidemics	185
2.4.	HIV prevention effect and the stage of infection	186
3.	More and better data for better estimations	187
4.	Insights from the methodological approach	190
5.	The scope of research and a health policy perspective	192
6.	Future Work	194
7.	References	195
Appendix to Chapter 2		197
Appendix to Chapter 4		201

LIST OF FIGURES

Chapter 1: Introduction

Figure 1 World distribution of HIV-1 subtypes distribution	16
Figure 2 Number of people living with HIV and AIDS and population size in Latin America	21
Figure 3 HIV Prevalence in MSM in selected countries of Latin America in 2009-2010	22
Figure 4 HIV Prevalence in FSW from selected countries of the Caribbean and Latin America	25
Figure 5 Map of Colombia in the north of South America	27
Figure 7 HIV Prevalence in Colombia: from seven national surveys carried out among pregnant women	29
Figure 7 Reported AIDS cases and AIDS deaths in Brazil 1981-2010	32
Figure 8 Forest plot of observational cohorts of ART in serodiscordant couples	44

Chapter 2: Estimating the Impact of Antiretroviral Treatment in the HIV epidemic of Bogota, Colombia

Figure 1 Distribution of reported HIV/AIDS cases by CD4 cell count at time of detection	66
Figure 2 Model structure for the sexual transmission of HIV	68
Figure 3 Population stratification according to sexual behaviour and gender	69
Figure 4 Number of new patients receiving ART in Bogota, 1997-2011	80
Figure 5 Median times between HIV diagnosis and ART initiation in Bogota, by time period	81
Figure 6 Calibration results to reported mortality by AIDS data	92
Figure 7 Modelled HIV incidence and prevalence in Bogota, 1975-2014	93
Figure 8: Distribution of cumulative HIV infections by risk group in Bogota, 1975-2015	94
Figure 9 Source of HIV transmission by clinical stage of infection	95
Figure 10: Source of HIV transmission by risk category	96
Figure 11 Box Plot for the total number of cumulative HIV infections averted from 1997 to 2013	97
Figure 11 Modelling results of effect of interventions over HIV epidemic in Bogota	99

Chapter 3: Estimating the retrospective impact of Antiretroviral Treatment scale-up in Brazil

Figure 1 Population distribution of Brazil	112
Figure 2 Model structure	116
Figure 3 Sexual mixing in the model	116
Figure 4 Modelled proportions of acts protected by condom by risk group and region	124
Figure 5 Model comparison to data in Northern region	141
Figure 6 Model comparison to data in North East region	142
Figure 7 Model comparison to data in South East region	143
Figure 8 Model comparison to data in South region	144
Figure 9 Model comparison to data in Central West	145
Figure 10 Model projections of HIV incidence rate	146
Figure 10 Cumulative absolute and relative HIV incidence reductions from modelling results	147
Figure 11 Modelled HIV incidence rate in five regions of Brazil under two scenarios of ART	148

availability

Figure 12 Modelled HIV prevalence in five regions of Brazil under two scenarios of ART availability 149

Figure 13 Cumulative absolute and relative HIV incidence reductions from modelling results by risk group and region in Brazil 150

Figure 14 Posterior distribution of ART effectiveness on transmission parameter 151

Chapter 4: Estimating HIV Incidence from Case-report Data: Method and an Application in Colombia

Figure 1 Model of HIV infection and progression: 164

Figure 2 Incidence estimation with four configurations of the spline function 172

Figure 3 Model fit to data in Colombia 173

Figure 4 Estimated number of new HIV infections in Colombia 174

LIST OF TABLES

Chapter 1: Introduction

Table 1 Penalization of homosexuality and any male to male intercourse in the Caribbean and Latin America	23
Table 2 Summary of Primary outcome evolution in ART trials	39
Table 3 Summary of main characteristics of on-going C-RCTs of combined prevention	44

Chapter 2: Estimating the Impact of Antiretroviral Treatment in the HIV epidemic of Bogota, Colombia

Table 1 Parameters and calibration information	77
Table 2 HIV prevalence studies among MSM in Bogota	84
Table 3 HIV prevalence studies among FSW in Bogota	84
Table 4 HIV prevalence studies among pregnant women in Bogota	85
Table 5 Reported mortality due to AIDS and people receiving ART in Bogota	86
Table 6 Population Attributable Fraction of cumulative HIV incidence by risk group	96

Chapter 3: Estimating the retrospective impact of Antiretroviral Treatment scale-up in Brazil

Table 1 HIV prevalence studies among FSW and MSM in Brazil	128
Table 2 Number of reported AIDS deaths by region, Brazil 1995-2011	129
Table 3 Number of people receiving ART by region, Brazil 2008-2012	130
Table 4 Parameters table	131
Table 5 Prior and posterior parameter ranges and PRCC analysis for cumulative HIV incidence reduction (1997-2014) due to ART	140

Chapter 4: Estimating HIV Incidence from Case-report Data: Method and an Application in Colombia

Table 1 Model parameters	169
--------------------------	-----

Chapter 5: Discussion

Table 1 Summary table of modelling results of the impact of ART on HIV Incidence	182
--	-----

ACRONYMS

AIDS Acquired Immunodeficiency Syndrome

ANC Antenatal clinic

FSW Female sex worker(s)

GP General Population

HIV Human immunodeficiency virus

MSM Men who have sex with men

NRTI Nucleoside Reverse Transcriptase Inhibitors

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitors

PAF Population attributable fraction

PWID Persons who inject drugs

RCT Randomised controlled trial

RDS Respondent driven sampling

SIV Simian Immunodeficiency Virus

SSA Sub-Saharan Africa

STD Sexually transmitted disease

TP Total population

Chapter 1: Introduction

1 BACKGROUND

Since the first documented case in 1981, the number of people estimated to be living with HIV/AIDS in 2012 was 32 to 38 million. Of those, at least 2.3 million were incident infections happening in the same year [1]. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2010 report, the global trend of HIV prevalence now seems to be declining after having peaked in 1999. This is most likely due to the extended provision of antiretroviral treatment (ART) and other preventive strategies which have resulted in a 19% reduction in AIDS mortality between 2004 and 2009 [2].

In the absence of a feasible form of intervention that could completely eradicate HIV in the population, it is imminent to draw upon the available primary prevention tools in order to explore new ways of containing the spread of infection. Those tools have existed for many years in the form of condoms, antiretroviral therapy (ART) and needle exchange programmes, shaping the epidemic as we know it.

This study intends to shed light on the interaction between some of these preventive interventions when applied to the specific context of concentrated epidemics. It will do so by retrospectively evaluating the impact of combined HIV prevention in South America. It also explores a method to estimate incidence of HIV, capitalising on the strength of local surveillance systems in the region.

This chapter is an introduction to the epidemic, reviewing concepts of infection transmission, HIV prevention, the epidemiology of HIV, and a historical background of the pandemic, with a focus in South America – the theoretical framework of this thesis.

2 HIV: A SUCCESS OF BIOLOGY, A CATASTROPHE OF PUBLIC HEALTH

2.1 The origins

Several decades have passed since HIV made its initial jump from African primates to its first human host. It then went on to become the most widespread and deadly epidemics of the late 20th and 21st centuries.

The zoonotic origin of the HIV epidemic is widely accepted and has been largely reported and investigated [3]. An exhaustive and unprecedented hunt for the origins of HIV has taken place all over the world since HIV's first public appearance in 1981.

After the isolation of HIV-1 virus and its –mostly- undisputed role as the causing agent of the acquired immunodeficiency syndrome [4], much research has been carried out to explain the origin of the pandemic not only from an evolutionary point of view but as an epidemiological phenomenon.

HIV-1 and HIV-2, both from similar origin, are the only two members of the Lentivirus family of retroviruses known to infect humans and cause the clinical syndrome commonly known as AIDS. Though they are part of the same family, the origin of these two viruses is different. Both however can be traced back to simian ancestors in different geographical locations in Africa. The Simian Immunodeficiency Virus (SIV) is the simian counterpart of HIV in humans and it is its ancestral source. The SIV virus circulates naturally in primates in different African locations and contrary to its name, it does not cause immunodeficiency among its natural hosts. However, it is known to cause an aggressive form of illness when transmitted inter-species. It acquired its scientific name, SIV, when different species of primates like the rhesus macaques and other Asian species fell-ill after being infected with

SIV in laboratories all over the United States of America (USA). It turned out that these animals had been kept in long-term captivity together with other species now recognized as being the natural African hosts of SIV [5].

SIV has infected several species of non-human primates, and each infecting virus corresponds to a specific phylogenetic lineage. SIVsm was named after its natural host, the sooty mangabey (*Cercocebus atys*) monkey of western Africa. SIVsm is the closest related virus to HIV-2. Its prevalence finds its highest levels among the sooty mangabey monkeys in Guinea-Bissau, Senegal and Côte d'Ivoire, which also holds the highest prevalence of HIV-2 in adults [6].

In West African countries HIV-2 has been the cause of a more silent epidemic than HIV-1 has been in the rest of the continent. Causing milder symptoms and having a characteristically longer incubation period, HIV-2 can remain unnoticed during the life-span of infected individuals [5]. Cases of HIV-2 infection outside West Africa are rare, with some clusters of transmission occurring in Mediterranean countries and Portugal among others, most likely due to intense migration during the years of the independence conflict (mid 1970s) in the former Portuguese-Guinea, now Guinea-Bissau [5].

SIVcpz is the simian origin of HIV-1, and was named after its host *Pan troglodytes* or chimpanzee. This lineage of SIV is the common ancestor for all the known groups in HIV-1, namely M, N, O and P, and each one of these groups is thought to correspond to a specific simian-to-human transmission event [3]. M stands for “major”, N for “non-M”, and O for “outlier”. P is the newest one, only discovered in 2009, and its letter is meant to be after “pending further identification” since only one human case has been reported [7]. Group M is the one encompassing the greatest majority of HIV-1 strains found among infected individuals today. Groups N, O and P are outliers contrasted to the epidemic spread of group

M, and are almost restricted to the western part of central Africa, namely Cameroon, Gabon and Congo [3]. For the purpose of this thesis HIV-1 group M, will be referred to as HIV.

On the other hand, group M comprises several subtypes or “clades”, designated with capital letters from A to K. It is interesting to notice the geographical relation of these subtypes: A and C are the most common mainly because they caused the epidemics in South Africa, central Europe and Southeast Asia. Subtype B was the one spreading through the Americas, Australia and Europe, and is the main subtype in the epidemic among MSM around the world. However, it is more common now to see different subtypes and recombinants (CRF) in places not originally related to that clade [8] (**Figure 1**).

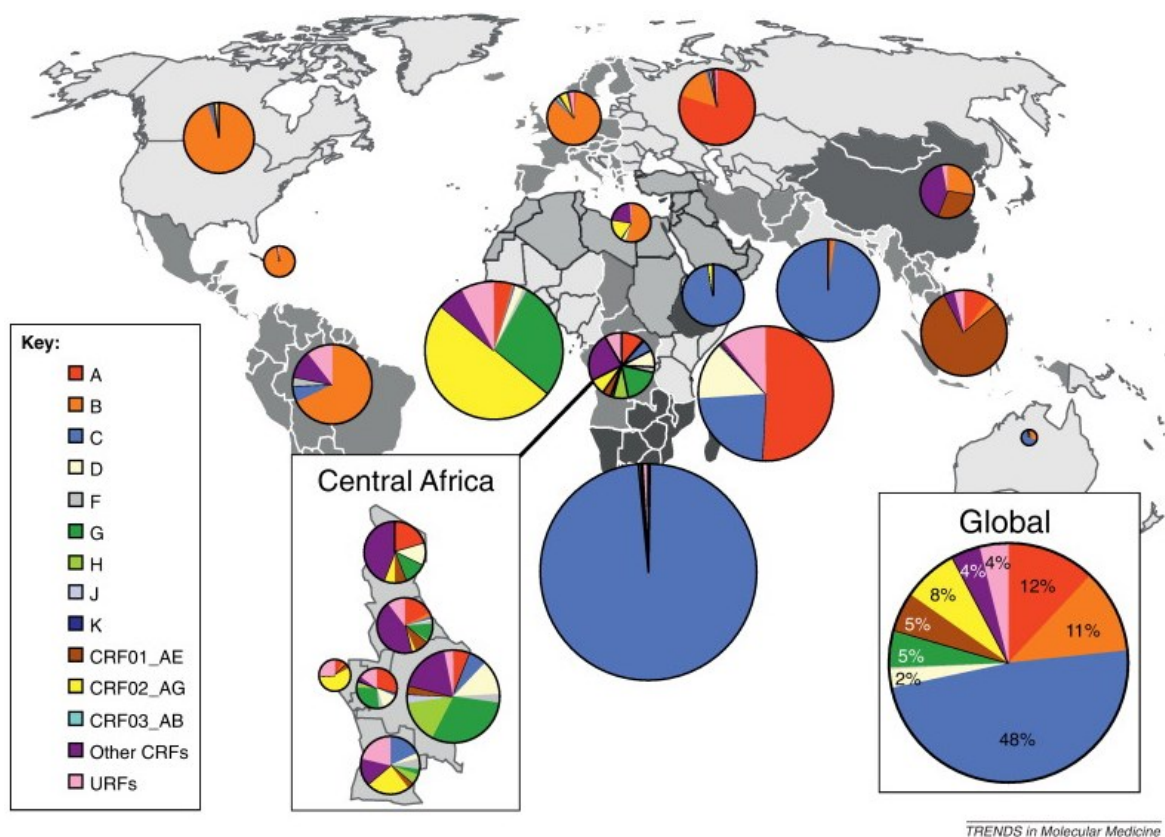


Figure 1 World distribution of HIV-1 subtypes distribution. Source: Hemelaar 2012[9].

The means by which SIV jumped from primates to become HIV is disputed, but the most feasible sequence of events involves the very ancient tradition of hunting and consuming bush-meat in Central Africa. A close and repeated contact with simian blood and fluids might have offered a good-enough chance for SIV to pass into humans. However, more intricate explanations have been proposed, like one involving the trials of the attenuated Polio virus vaccine in the former Belgian Congo in the 1950s [3]. This hypothesis suggests that chimpanzee-kidney cells carrying SIVcpz were used to cultivate the virus which posteriorly gave birth to the world expansion of HIV-1 group M epidemic. However the fact is that the animals used in such experiments were actually bonobos rather than chimpanzees, contradicting all the evidence currently known about the virus origins [3].

When exactly did those first transmission events happen is uncertain, but with help of phylogenetic techniques and molecular clock procedures it has been estimated that it could have been around 1930 with an uncertainty range of 20 years [10].

2.2 The epidemic expansion

After that colossal sequence of events that ended up with HIV successfully transmitting from human-to-human, a confluence of factors were necessary for HIV to achieve its epidemic expansion. Cultural and behavioural factors might have contributed to the initial burst of transmission. It is difficult to pin-point a single factor behind the epidemic spread in Africa, and today it is more accepted that behaviour heterogeneities, together with other biological conditions, had a synergistic effect on the initial epidemic growth. The non-uniformity observed in HIV prevalence across different parts of central, eastern and southern Africa has revealed the reason of these uneven patterns. Sexual behaviour, mainly the number of sexual partners and concomitant partnerships, has been reported as an explanation, but this alone

does not sufficiently explain the fast rate at which HIV has spread in African countries [11]. Biological factors affecting HIV transmission have inevitably been involved, such as co-infections with other sexually transmitted disease (STD) (herpes simplex virus-2 , syphilis)[11, 12], and different levels of circumcision in the male population in some areas[13]. Other causal factors include the socio-economic background of the most affected communities as well as the role of women in the community and patterns of transactional sex [14]. The widespread use of non-sterile syringes during mass vaccination campaigns carried out by European and American missions in Africa has also been hypothesised as a possible cause behind the initial epidemic expansion [5], but the evidence is mostly anecdotic.

The transatlantic journey of HIV is likely to have happened several decades after the approximated initial inter-species transmission events. HIV-1 has been found with polymerase chain reaction (PCR) analysis in pathological specimens and blood samples collected from patients suffering from syndromes similar to AIDS, dating as far back as the 1960s in the USA and 1959 in Europe [5]. As it was mentioned before, HIV-1 subtype B was the one that spread all over the Americas and parts of Western Europe. But its first port of arrival is now known to have been Haiti. Haiti has the oldest HIV-1 epidemic outside of Africa, and is almost exclusively caused by HIV-1 subtype B. All strains that sparked subsequent epidemics in North, Central and South America (known as the subtype B epidemic clade) have a common ancestor in Haiti's subtype B. This first strain was estimated to have been introduced in Haiti around 1969 [15], possibly by Haitian migrant workers in the Democratic Republic of Congo who then returned to their country [5]. This may partly explain the early observations of AIDS cases being more frequently reported among Haitian immigrants living in the USA.

The first syndromic report of AIDS dates back to 1981. However, retrospective analyses of blood samples carried out in the 1980s in New York and San Francisco, showed a 5%

seroprevalence of HIV-1 among MSM in 1978 [16, 17], suggesting that the virus had already spread silently for a while.

Some important epidemiological insights can be drawn from the previous description of HIV and its origins. The first one is that HIV was circulating in the general population in Central Africa for several decades before making its way to America. Even outside Africa, as reported above, silent transmission was occurring maybe as early as the late 1950s. The introduction of HIV from Haiti to the USA might have influenced the trends that were observed in the following years. Haiti, despite having a heterosexual epidemic was known for being a hub for homosexual and bisexual tourism, particularly among North American men [18]. Other factors related to the changing perceptions of sexuality, particularly among MSM, the “sexual liberation” era, the appearance of places for gay socialisation and sexual exchange (like saunas, bars and clubs) could have been of central importance in the spread of the virus in the USA and Europe [19, 20].

This suggests that behavioural, cultural and historical factors were shaping -since the early 1960s- different types of epidemics around the world. These differences in the pattern and extent of transmission across contexts motivated the classification of epidemics.

Aimed at standardizing the categorization and further response to HIV, UNAIDS developed a classification based on the prevalence levels among different groups. This numerical surrogate of the dynamics of infection divided epidemics as low-level, concentrated and generalized. Low-level epidemics were those where HIV prevalence had not exceeded 5% in any sub-group or key population. Concentrated epidemics were those with prevalence greater than 5% in at least one sub-population but less than 1% in the general population (pregnant women). Finally, generalized epidemics were those where HIV prevalence was consistently greater than 1% in the general population [21]. This categorization appeared to be very broad

to understand and encompass other types of epidemics described all over the world, like mixed epidemics, falling in between concentrated and generalized, where sub-populations sustain higher than usual levels of HIV prevalence but are consistently lower than 5%. For this reason, more recent attempts to assess epidemic types have focused on describing and disentangling the drivers of transmission and focusing on the prevention effect of interventions for controlling HIV transmission at the population level [22-24].

3 HIV IN LATIN AMERICA

3.1 Background

The great diversity of cultures, ethnic groups and traditions encompassing Latin America, makes it impossible to talk about one “Latin American culture”. Similarly, it is equally hard to attribute the same epidemic patterns to HIV transmission to the whole region.

HIV and AIDS have had a different impact in Latin American countries however similar structural factors have helped to the propagation of the epidemic in this region: health inequalities, sexual discrimination, stigma and homophobia.

In 2012 an estimated 1.4 million (1.1 to 1.7) people living with HIV and AIDS (PLHA) lived in Latin America, which is approximately 200,000 more people than in 2001 [25, 26](**Figure 2**).

Between 2011 and 2012, around 83,000 people acquired the HIV infection in the region. For the same period 53,000 deaths resulted in relation to HIV and AIDS [25, 26].

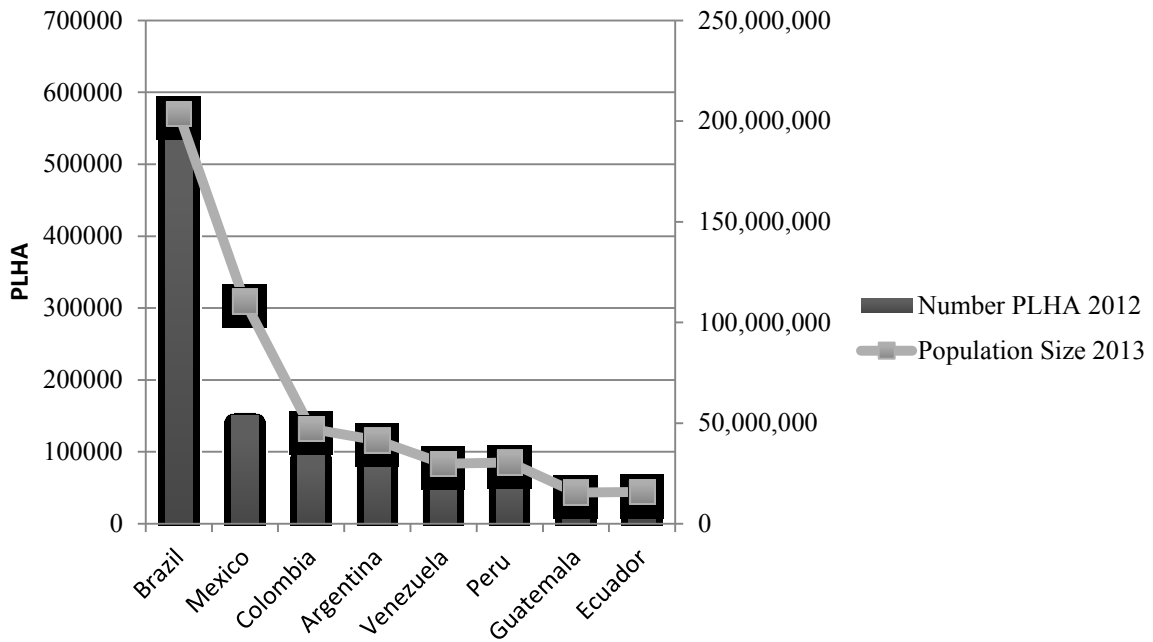


Figure 2 Number of people living with HIV and AIDS and population size in Latin America: Nine countries with the greatest number of PLHA according to UNAIDS estimation, contrasted to population size. Source: [25, 26].

As can be seen in **Figure 2**, the size of the major epidemics in Latin America, according to estimations from the latest UNAIDS Global Report [25, 27] is a reflection of the overall size of the total population.

3.2 Men who have sex with men (MSM)

Since the epidemic in the region has been characteristically concentrated among a key population, MSM, it is necessary to look into this population group to understand the epidemiological nuances within the region.

The MSM population has high HIV prevalence in the entire Latin American & Caribbean region but is particularly high in Central and South America. Jamaica stands above these countries with the highest prevalence in the whole region. **Figure 3** shows the highest estimations of HIV prevalence for selected countries in the region [25, 27].

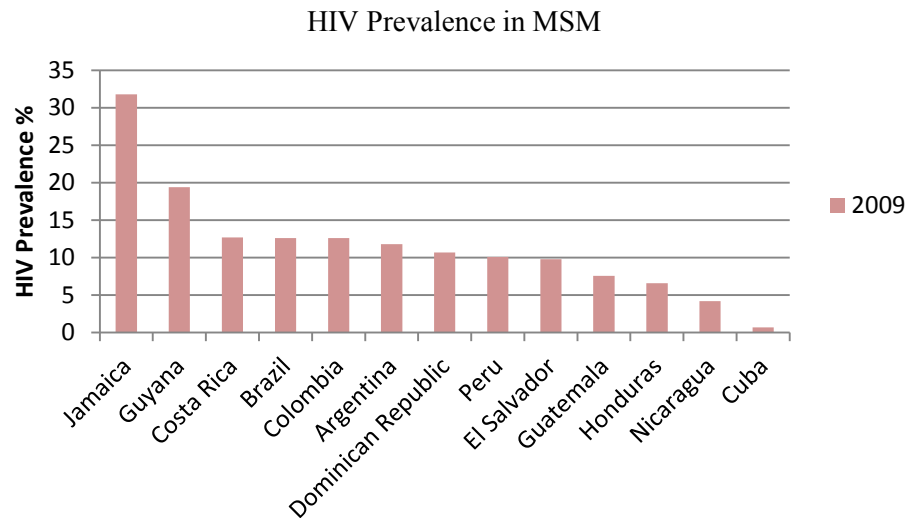


Figure 3 HIV Prevalence in MSM in selected countries of Latin America in 2009-2010. Source: UNAIDS Global Report 2013 [25, 27].

MSM contribute with over 50% of the new HIV infections in Latin America [2, 28-31]. This disproportionate concentration of risk is perpetuated by high levels of stigma, marginalization and even penalization, which strengthens segregation and hampers MSM population's access to prevention campaigns and health services [2, 28, 32-34]. Ultimately, it forces gay and bisexual men to surreptitious unprotected activity.

Nine countries in Latin America and the Caribbean still consider male-to-male intercourse as a criminal act with penalties ranging from hard labour to life imprisonment (**Table 1**).

Legal frameworks that embody homophobic legislation can thus greatly disadvantage efforts to eradicate HIV and AIDS. In the words of the UNAIDS Executive Director Michel Sidibé *“In most of the countries in the Caribbean that don't have repressive laws, HIV prevalence is between 1% and 8% among men who have sex with men. This contrasts sharply with a range of between 20% and 32% in countries which outlaw sex between men”* [35] .

Penalization might also discourage the disclosure of sexual preferences between partners, leading to a frequent phenomenon of concealed bisexuality [2, 36]. Although the use of this term is not straight-forward, it could be used in this context since most of the men engaging in bisexual activity seek to maintain their role in society as heterosexuals and therefore do not identify themselves as bisexual or homosexual. In a survey on sexual behaviour carried out in Bogota, Colombia, 20% out of 533 men reported sexual contact with other men during their lives, and only 11% considered themselves as homosexual or bisexual [37].

Table 1 Penalization of homosexuality and any male to male intercourse in the Caribbean and Latin America.

Country	Legal Condition	Penalization
Antigua	Illegal	Imprisonment from 15 years to life under the charge of “Buggery”
Barbados	Illegal	Imprisonment from 15 years to life under the charge of “Buggery”
Costa Rica	Illegal	Imprisonment from 10 year under the charge of “Unnatural Crime”
Dominica	Illegal	Imprisonment from 10 year under the charge of “Buggery”
Grenada	Illegal	Imprisonment from 10 year under the charge of “Unnatural Connection”
Guyana	Illegal	Imprisonment for life under the charge of “Buggery”
Jamaica	Illegal	Imprisonment for 10 years and hard labour under the charge of “Unnatural Crime”
Saint Kitts/Nevis	Illegal	Imprisonment for 10 years and hard labour under the charge of “Buggery”
Saint Vincent and Grenadines	Illegal	Imprisonment for 10 years and hard labour under the charge of “Buggery”

Source : ILGA, International lesbian, gay, bisexual, trans and intersex association [38].

In MSM concentrated epidemics, bisexual activity becomes an epidemiological bridge between high transmissibility networks and a lower risk heterosexual groups, where women are the most affected, as is especially the case in the Caribbean epidemic. For that region, women outnumber the cases reported in males but the epidemic shows high levels of concentration among MSM [2]. This reflects not only the disjointment between prevalence estimations and current transmission but also, and more importantly, the limited access to health services and the systematic discouragement of HIV testing among the MSM population group.

3.3 Female Sex Workers (FSW)

FSW workers are the second group most affected in the region with countries like Guyana and Haiti displaying prevalence greater than 5%. This epidemic has been of particular importance in most Caribbean countries. The Population Attributable fraction (PAF) of HIV infections to FSW has been estimated to be 7% (3.9% to 9.9%) in Latin America and 9% (7.6% to 11.6%) in the Caribbean [39].

Figure 4 shows a selection of countries in the region with the highest estimates of prevalence [25]. In these countries, low levels of condom use has been reported, signalling the important role of transmission in this group [26].

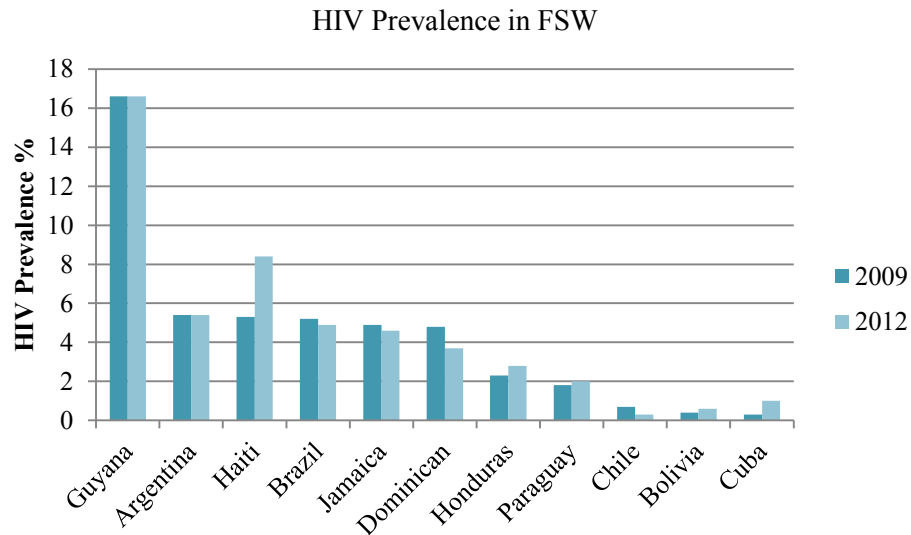


Figure 4 HIV Prevalence in FSW from selected countries of the Caribbean and Latin America.
Source: UNAIDS Global report 2013 [25]

Concentration of risk in this group is a complex issue, since there are great geographical variations even within countries, where some port cities, touristic places and work camp sites (for oil exploration, mining) can mobilize a great number of sex workers, making the regional assessment more difficult [40-42].

3.4 *People who Injects Drugs (PWID)*

PWID in Latin America have been associated with the biggest cities and mostly in the southern cone of South America, with Brazil and Argentina reporting the highest incidences. Around 50% of PWID in Argentina live with HIV and 48% in Brazil for the same population. In Brazil only 25% of these receive ART [43].

As will be described below, the epidemic among PWID was of major relevance in the southern and southeastern parts of Brazil, reaching HIV prevalence as high as 60% in Rio de Janeiro in 1992 [44]. This trend seemed to have changed in Brazil, with the trends in drug use leading to a reduction in the total number of people using injected drugs [45]. In Colombia, during all the 1990s and most of the 2000s, injecting behaviour was not regarded as a main

contributor to the epidemic. However, the use of heroin has increased in more recent years [45].

The presence of HIV-1 subtype C in the southern cone of the continent, contrary to the large dominance of subtype B in the northern countries is thought to be related to HIV transmission networks of PWID. At least in Argentina, Paraguay, Uruguay and Brazil, subtype C has been reported, as well as many recombination variants from the co-existence with subtype B [46, 47]. Subtype B though is the dominant HIV-1 subtype in these countries. The presence of subtype C in the same areas where drug injecting behaviour is more important suggests that this clade could be attached to a network of transmission. However, different studies have failed to demonstrate this consistently [8, 48].

3.5 The HIV epidemic in Colombia

3.5.1 Social and cultural context

Transmission seems to be occurring more intensely in the MSM population group in Colombia. Conversely, the role of other vulnerable groups like FSW and their clients, and PWID have been less explored and the cross sectional studies carried out do not suggest a significant concentration in these groups.

Colombia is the host of heterogeneous patterns of transmission with characteristics of the Caribbean epidemic in the northern coast and an influence of the Andean countries in the southern half (**Figure 5**).

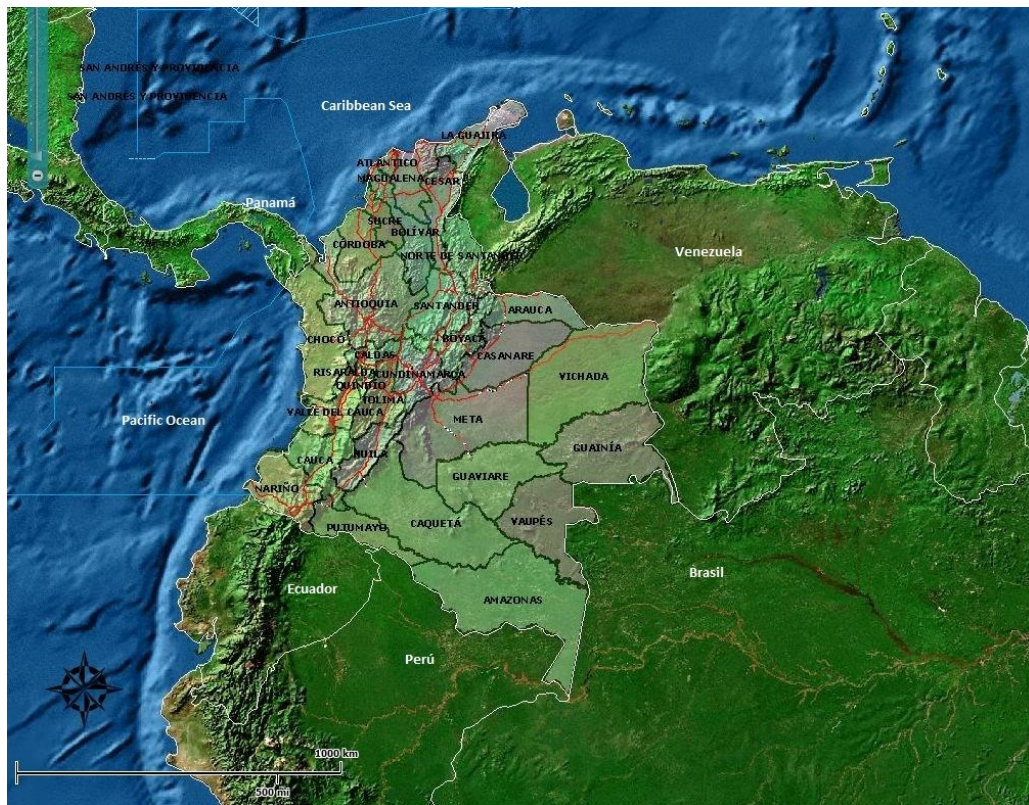


Figure 5 Map of Colombia in the north of South America. Source [49].

A growing number of female cases of HIV in the recent years suggest that the influence of this Caribbean pattern of transmission is becoming stronger in the country.

Caribbean countries have the largest epidemic among women and female sex workers in the region in Latin America [39]. This condition is fuelled by the bisexual activity of MSM as well as male sex work. It is not a coincidence that cities like Cartagena, Santa Marta and Medellín in the Caribbean coast and north of Colombia have been recognized as the main centres of sex tourism in the country [50]. Homophobia and gender inequalities, so commonly seen all over Latin America, complete the picture for transmission of HIV [51, 52].

Caribbean and Andean cultures are at the centre of the country's behavioural diversity grounded in the historical and geographical conditions of these regions. Historically, the Caribbean coast have had strongly defined gender roles with women traditionally acting as

family keepers, confined to their homes to a great extent. Men, as economic providers might become itinerant supporters, frequently engaging in simultaneous polygyny (*i.e.* concurrency) as part of their role. This role is not only accepted but encouraged by society, feeding the stereotype of “manhood” and hyper-sexuality with which Caribbean men are frequently identified [51, 53].

Widespread gender inequalities are also found in the centre and south of the country, but attitudes towards sex are a very different story. In these areas sexual behaviour is experienced in a less explicit way. Sex is a less commented subject, possibly due to a deeply rooted Roman Catholic tradition influencing morality in these communities [50].

Social and political factors have also played their part in providing a backdrop of displacement and vulnerability which have facilitated HIV transmission in Colombia. An armed conflict has taken place for over 60 years in Colombia and the ongoing struggle between the army, the guerrillas and the paramilitaries to exert control in rural areas, has forced a large part of the rural population to move from the countryside to the cities. According to the Internal Displacement Monitoring Centre (IDMC), Colombia has the largest internally-displaced population in the world, with a total of between 4.9 and 5.5 million [54]. Forced to leave their homes, the only solution for this population is moving to slums around the cities putting themselves in critical situations of vulnerability: out of reach from the health system, at the mercy of transactional sex for survival, drug use and sexual violence [55].

3.5.2 *Epidemiology of HIV in Colombia*

The first case of AIDS was reported in 1983 and since then around 80,000 cases have been reported. The male ratio in reported cases was 12:1 in 1983, and over the years the impact among women has taken more importance, with an estimated ratio by 2010 of 2:1 [27].

The age pattern of all reported cases shows a greater impact in the youngest groups, with 1 out of three new cases occurring within the age range of 25 to 34 years [56].

HIV prevalence has been estimated in the overall population of Colombia through seven cross-sectional studies, mostly among pregnant women, and generally remaining below 0.5%, finding a peak at around 0.6% in 2003 and declining from there to the more recent estimation of 0.2% in 2009 [27](**Figure 6**).

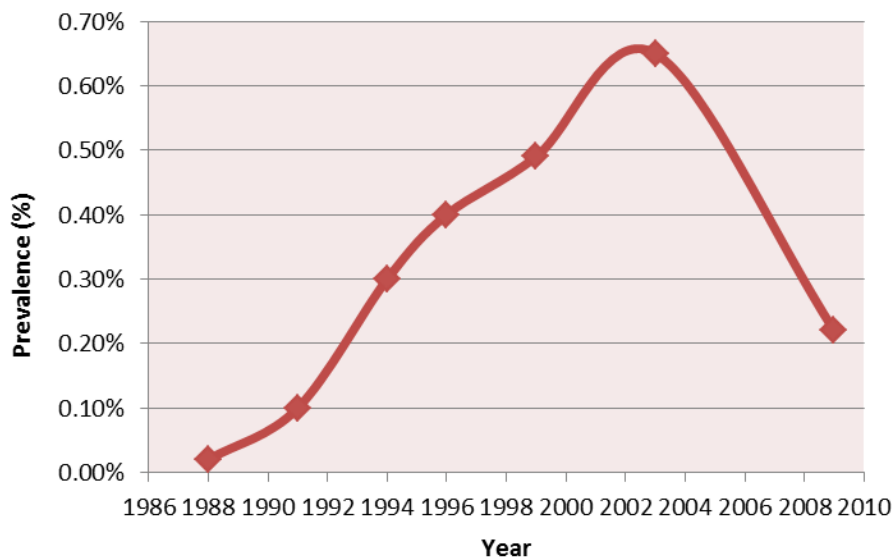


Figure 7 HIV Prevalence in Colombia: from seven national surveys carried out among pregnant women (1988, 1991, 2000, 2003, and 2009) and adults (1994, 1997).

MSM have been the most affected group as demonstrated by several surveys. Two cross sectional studies in 2000 and 2004 found an HIV prevalence of 19% and 25% respectively [50, 57]. In 2010 a behavioural and seroprevalence survey among MSM was carried out in seven cities in the country, finding HIV prevalence between 5% and 24%. When stratified by

age, the prevalence among those older than 25 doubled and even tripled in some cases the values for the group < 25 years, showing an important ageing pattern of HIV epidemic in MSM in Colombia [58].

On the other hand, female sex workers in Colombia have been estimated to have HIV prevalence between 0.8% and 1.4%, according to different studies [27, 42]. PWID have been largely overlooked over the years in part because it was thought that injecting behaviour did not have a major role in the drug consumption spectrum of the country. A survey in 2003 showed a prevalence of 1% in current PWID and 1.6% among ex-PWID [50]. The most recent survey from 2011 in the cities of Medellin and Pereira showed a HIV prevalence of 3.8% (CI 95%: 0.8%-7.1%) and 2%(CI95% 0.5% - 3.7%) respectively [59] .

3.5.3 *Response to HIV epidemic*

The beginning of the Highly Active Antiretroviral Therapy (HAART) era in 1996 caught Colombia in the middle of a complete makeover of its health system. For many decades Colombians accessed health services through the social insurance scheme for civil servants or private insurers. The great majority, with neither the money nor the civil servant's employment, had no option but to queue for the meagre welfare attention provided by hospitals and health centres. The health reform came to life in 1996 with the intention of bringing access to health services to every Colombian regardless of their financial position. In a couple of years the results were stunning, increasing the coverage of health services from 25% in 1986 to 75% in 2005, and around 90% in 2010[60]. The new social system now consists of two schemes: the Contribution Regime (CS) and the Subsidised Regime (SR). The CS encompasses all the population in the formal labour force and their families. The SR, financed by the CS, covers the rest of the population and is designed to reach those in the poorest conditions [61].

HIV patients that previously had to pay for their own treatment -in the era of monotherapy and at the beginning of HAART- from 1997 had complete access to free treatment and attention. HIV testing and treatment was included in the system but the number of available drugs was limited.

ART has been offered in Colombia since 2012 to HIV+ individuals with symptomatic disease or a CD4+ count $< 500 \text{ cell/mm}^3$. This recommendation changed from the previous guidelines in which treatment was delayed among the HIV+ until CD4+ $< 250 \text{ cell/mm}^3$ or between 250 and 350 cell/mm^3 with a viral load greater than 100.000 copies of RNA HIV-1/mL.

The preferred first line ART scheme is based on two nucleoside reverse transcriptase inhibitor (NRTI) (abacavir/lamivudine, tenofovir/emtricitabine) plus one nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz) or a boosted protease inhibitor (atazanir/ritonavir, darunavir/ritonavir) or an integrase inhibitor like raltegravir [62].

3.6 AIDS and treatment in Brazil

Brazil reported its first case of AIDS in 1982. From there, the country experienced the biggest epidemic expansion seen in Latin America reaching 10,000 cases detected by 1990 [63], in what is now referred to as the first epidemic expansion in Brazil. This initial growth was largely due to transmission among MSM, most of them living in the big cities of the South East (*i.e.* Sao Paulo and Rio de Janerio). By 1985 the male-to-female ratio was 24:1 in the reported cases, reflecting the burden of homosexual transmission at the time.

A second wave took place from 1990 to 1992, affecting mostly PWID in the South, and raising the count of cases to 76,000 by 1993 [44, 64]. The third expansion started in 1993

after a consistent spread among gay and bisexual men in urban areas which gave way to a new trend of *heterosexualization* of the epidemic in the early 1990s. By 1994 the rate of infection (by cases reported) was higher among heterosexuals than in MSM [65] and the outlook of HIV in Brazil by 1995 was that of an epidemic at the brink of generalization. With at least two risk groups displaying HIV prevalence greater than 25% in different parts of the country (63% in PWID from Rio [44] and 35% in MSM from Santos [66]) and the death toll reaching its peak (**Figure 7**), the Brazilian government made an unprecedented move by introducing universal free access to ART for every person with AIDS in Brazil. The process was not as straight forward, and more details about the Brazilian struggle are provided in Chapter 3, but the consequence was remarkable: By 2006 12% of all the patients receiving treatment in middle and low income countries lived in Brazil [64].

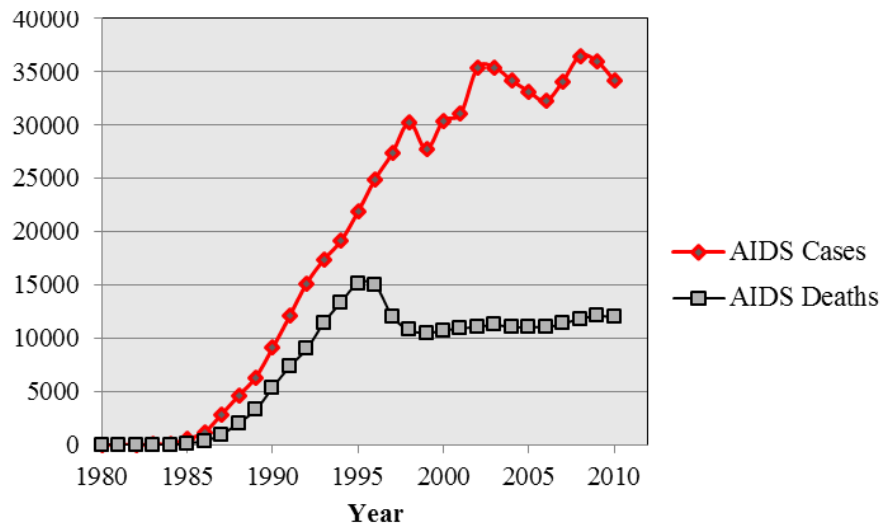


Figure 7 Reported AIDS cases and AIDS deaths in Brazil 1981-2010. Source: Departamento de DST, Aids e Hepatites Virais

Although ART played a major role in controlling Brazil's epidemic, other preventive strategies were also set in place for tackling HIV transmission, like the expanded distribution of condoms with subsidised prices, and needle exchange programmes [67].

The current picture has changed considerably. The epidemic among PWID has slowly faded out partly because of a change in urban consumption patterns, with most of the PWID now consuming crack cocaine, and also due to a very high mortality rate among this group [44, 68]. The latest UNAIDS estimation of HIV prevalence in the general population was 0.55% in 2013 [69], and a large survey in MSM from 10 cities in 2010 found a prevalence of 10.5% [70].

The current coverage of ART (as the number of people treated over the estimated PLHA) estimated by UNAIDS is 46% [69], and the total number of people in ART up to 2013 was 313,175 with an average annual increase of 30,000 new people starting ART since 2002 [71].

The story of Brazil's treatment campaign does not stop there. The government of Brazil announced in 2013 its intention to further expand its already colossal HIV programme, so as to implement Treatment as Prevention (TasP) at national scale, and offering ART to every person who is HIV+ irrespective of the infection's clinical stage. The programme is planned to provide treatment to 100,000 new patients by the end of 2014, at a cost of approximately US\$ 100 million [72]. The World's eyes are on Brazil, eager to see how this new venture develops and what solutions it will offer to all the challenges and concerns raised by the scientific community about implementing TasP as the main treatment strategy.

4 HIV PREVENTION: FOCUS ON TREATMENT

4.1 *Treatment as Prevention*

An observation that became a fact and is believed to be at the core of what we now know as TasP is as follows: **when HIV+ people taking ART reach undetectable levels of viral load the risk of transmission to their serodiscordant couples is drastically reduced. If we bring this to a population scale, the result is consistent reduction of HIV incidence.**

This is not a new idea, and the concept has been around for over 20 years. Garnett and Anderson [73] explored the idea of the population effect of treatment relying on the fact that antiretrovirals reduced viral load. However, it was too early in the HAART era to predict the real potential of combined therapy for steadily suppressing viral load. In 1996, combined therapy was just starting to take over as the mandatory prescription for patients with AIDS. The evidence at the moment was mainly coming from individuals on dual and monotherapy, showing consistently that after initiation of treatment it was a matter of weeks to months before observing a rapid re-emergence of viral loads to pre-treatment levels [74]. Biological mechanisms, like a high rate of viral replication and mutation made viral load very difficult to control with the early antiretroviral schemes.

More arguments to this debate came from the impressive effect of antiretrovirals (ARVs) for preventing mother to child transmission (PMTCT) with almost 50% risk reduction against placebo [75].

A few years later, evidence about the relationship of viral load and transmission was made available from HIV trials in Rakai, Uganda [76]. This triggered others to envision the use of treatment as a form of prevention in real life settings [77-80]. Further observational studies in

serodiscordant couples confirmed the initial observations [81, 82], and the HPTN 052 trial gave the final blow to any doubts still standing [83].

4.2 Challenges of TasP

With all this said the big question needs to be answered: how to implement TasP in real life conditions and reach the desirable benefits?

This type of question is a “modelling question” and has indeed been addressed with mathematical simulations, specifically Universal Test and Treat (UTT) (i.e. active and universal HIV testing) which also poses a challenge since HIV tests could be as scarce as ART in many contexts (49). Mathematical models have explored UTT with different levels of impact, even suggesting by Granich et al. reductions in HIV incidence below 1% by the year 2016, and that HIV eradication was a feasible goal [84]. Strong assumptions about the dynamics of the epidemic and the feasibility of the strategy were made in order to reach these conclusions. The first and most important assumption is that all the HIV+ could be reached by universal voluntary testing. This overlooks the many factors that influence individuals to take HIV tests and accept the treatment with full compliance [85, 86]. Furthermore the lack of understanding about the role of the epidemiological setting in the overall effectiveness of ART might be an another barrier to the effectiveness of TasP or at least to the extrapolation of trial and modelling results [87].

Will the effectiveness of ART be diminished by a lack of coverage of hard-to-reach populations? How can we enrol, and keep track of patients on ART whose risk comes from illegal activities? How much will their HIV testing cost? Some of these questions have been partially answered. Modelling exercises in high risk groups have already remarked the

exceptional role of ART for reducing HIV incidence in concentrated epidemics. Such are the cases of Australia and San Francisco where HIV transmission is still highly concentrated among MSM [88, 89]. However, these models dealt with the distribution and uptake of ART rather than the challenges of targeted screening.

How much it costs and how it is going to be funded are questions that remain unanswered by the proponents of TasP. Implementation of UTT has proven to be costly and to be far beyond the available budget for the most affected countries. In the previously mentioned work by Granich et al., they projected that the short-run cost could be between USD\$ 2.3 and 5.3 billion per year, which is nearly three times the cost of the standard strategy for screening and treatment in South Africa, and is almost 50% of the Global Fund's total budget to fight AIDS, TB and malaria for the next three years.¹ That model also showed that after 2015 the cost of the theoretical strategy began to fall while the cost of the usual delayed-treatment strategy climbed due to the increasing number of people needing therapy [84]. However, more recent evidence remarks the cost-effectiveness of expanded criteria for ART initiation, finding it highly cost-effective in South Africa among other contexts [90].

Here lies one of the obstacles that need to be hurdled and that some are already boldly addressing, like the mentioned case of Brazil: what will be the returns of that immense initial investment to a country's economy in the mid and long-term when HIV incidence actually starts to fall? The answer to this question will emerge over time through our close observation of Brazil

A different concern around ART as prevention is related to the frequently unrecognized coexistence of ART with other behavioural and biomedical interventions, resulting in an overestimation of treatment effects, which could eventually lead to both decreased rates of

¹ Global Fund to fight AIDS, malaria and tuberculosis announced a three year budget of US\$ 11.7 Billion. See <http://www.theglobalfund.org/en/> [accessed 27/10/2010].

utilization of preventive measures and to increased risky behaviour [91]. Besides, viral resistance, adverse reactions as well as social acceptability, fuel the debate about prioritizing the public health benefits of TasP over the individual costs [92].

If treatment is prevention, it will be subject to the same difficulties as other preventive measures, such as “prevention fatigue”, meaning that the long term exposure to TasP might lead to a loss of impact (lost adherence, treatment drop-out) and the consequential re-emergence of infectiousness [34, 93, 94]. This has been demonstrated in contexts of highly concentrated HIV epidemics like San Francisco, showing an increase in unprotected anal sex despite the abundance of preventive efforts on safe sex; similar findings come from France [34, 93].

It could be said that we are living a historical moment in the fight against HIV and that TasP is meant to be a central part of the future response to AIDS.

5 EVALUATION OF HIV PREVENTION PROGRAMMES

As challenging as is implementation of preventive interventions is the evaluation of impact. Prevention programs are carried out in the hope of tangible benefits (e.g. Cost-Savings, life-years saved, infections averted), and its assessment is of central importance in the design of interventions.

Programmes can be evaluated through different methods that will be described in this section, namely Randomised Control Trials, observational cohort studies, ecological studies, and finally mathematical modelling.

Before describing these forms of evaluation, it is important to mention a few concepts of epidemiological studies that may guide our understanding about health programme assessments.

To start with, a measure of the effect of an intervention is commonly defined as an estimator to measure disease occurrence and make comparisons between population groups. It also often seen as an attribute of a specific epidemiological design [95]. This is how, for example, incidence is the best way of measuring the occurrence of events in prospective studies (RCTs, observational cohorts). Other measures as prevalence are more useful for different designs like surveys and cross-sectional studies, and not too informative about the rate of appearance of specific events.

Furthermore, not only the measure of the event requires a thoughtful selection, but the event itself. Some diseases, and also interventions, have specific characteristics that drive the researcher to choose one or other endpoint/outcome (i.e. the event to be observed). Infections with a very long incubation period might require too long follow-up time until symptomatic disease is observable, thus choosing a symptom to measure incidence in this case might be costly in every sense. Also, our growing knowledge about a specific disease might evolve with the time and affects our choice of both outcome and measure of effect.

For the specific case of HIV/AIDS, different endpoints in the natural history of disease can be identified and measured. The job of the HIV researcher is to define which one of these outcomes is the most pertinent to assess the impact of an intervention. HIV offers an interesting example of how knowledge has influenced the way we measure and choose outcomes.

Antiretroviral drugs were introduced in 1984 and the complexity of its combinations changed with the years, from AZT (zidovudine) monotherapy [96], dual therapy [97], and

HAART [98]. Monotherapy and dual therapy were first assessed in terms of its immediate impact in the clinical condition of AIDS patients: mortality, CD4+ cell count, weight-loss and the appearance opportunistic infections [96] [97]. A triple combination of drugs proved to be highly potent for reducing morbidity and mortality, and combined therapy started to be offered to patients in earlier stages of their disease. At this point progression to AIDS was the primary endpoint of interest together with changes in CD4+ count [98, 99]. Evidence was reported about the relationship between viral-replication control and immunological restoration [100], and also the importance of suppressing viral load for containing viral re-emergence from latent reservoirs [101, 102]. This shifted the scope of primary endpoint from the clinical syndrome to viral load. Currently, viral load suppression is the endpoint of election in almost every trial for ART [103-105]. More recent findings, discussed above in this chapter, gave a whole new dimension to the study of ART in HIV+ positive patients, by turning treatment into prevention. Then the endpoint had to be re-assessed in order to put ART in the preventive toolbox together with other prevention strategies (i.e. condoms, circumcision, microbicides) that measure HIV incidence as their primary outcome of interest [106, 107].

A summary of the evolution of primary outcomes in ART trials can be seen in **Table 1**.

Table 2 Summary of Primary outcome evolution in ART trials

Timeline	Form of Delivery	Primary outcome	HIV Research Milestone	Reference
1987-1988	Monotherapy	Death	ARVs reduce mortality and incidence of opportunistic infections in AIDS patients	[96]
1988-1996	Dual therapy	Death		[97]
1996-2000	HAART (triple combination therapy)	CD4+ count Progression to AIDS	Combination of three drugs restores immune system and extends survival	[98]
2000-	HAART	Viral load suppression (HIV-1 RNA < 50 copies /mL)	Viral suppression prevents viral re-emergence and is related to immune restoration	[101-103]
2011-	ART* (combination therapy)	HIV Incidence	ART reduces the risk of acquiring HIV in HIV-partners in serodiscordant couples	[83]

*ART is the current name given to all forms of combined therapy (at least three drugs).

Primary prevention programmes, as opposed to other forms of therapeutic interventions (secondary prevention), are intended to have an effect before the event of infection actually occurs, thus the most direct assessment of HIV prevention would be the rate of appearance of new HIV infections (i.e. incidence).

As explained above, outcomes might change as we move upstream in the causal pathway of prevention, as an example, measuring uptake of a vaccination programme might be informative of its preventive capacity if we already know that the vaccine is effective. This is how most of preventive interventions are measured through intermediate outcomes, like increase in condom use or reduction of STI incidence [108]. This could be useful either because HIV+ positive individuals are part of the study population, thus a change in risk

behaviour is desirable [109], or because the intermediate outcome is a known step in the causal pathway of events to acquire HIV. The choice between one and the other has been discussed before [109], but briefly, intermediate outcomes are more likely to be used in contexts of low HIV incidence like industrialized countries where estimating HIV incidence would require too large sample sizes [109, 110]. Choosing between primary and intermediate outcomes is particularly complex in concentrated epidemics among hard to reach populations like MSM. Also, measuring HIV incidence in any context, irrespective of the level of HIV incidence, is costly and requires following individuals for longer periods of time [109].

Two chapters of this thesis address the problem of evaluating the impact of ART for reducing HIV incidence in different contexts. Accordingly, a better understanding of how the preventive impact of ART has been evaluated is presented in the following section, describing the main findings and the possible limitations and gaps, building like this a framework to understand the possible contribution of this thesis.

5.1 Randomised Controlled Trials (RCTs) in ART prevention

RCTs are the gold standard for measuring the effect of interventions as they provide a highly controlled environment to observe differences in the outcomes across trial arms[95]. In this regard, HPTN 052 [83] provided definitive evidence of the effect of ART for preventing transmission of HIV at the individual level.

In August 2011 the HIV Prevention Trial Network (HPTN) officially announced that HPTN 052 was being halted three years before its intended date of termination due to an interim analysis showing a 96% risk reduction in HIV transmission among the intervention arm. HPTN 052 was a randomized controlled trial which enrolled 1763 serodiscordant couples

across 13 countries (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, USA and Zimbabwe). Serodiscordant couples were recruited if the HIV+ partner had a CD4 cell count between 350 and 500cell/mm³. HIV infected partners were randomized to receive either immediate antiretroviral treatment or delayed care according to the World Health Organization (WHO) recommendation (treat if CD4 < 250 cell/mm³). Both arms of the study received permanent counselling on safe sex, free condoms and treatment for other sexually transmitted diseases. The uninfected couples were frequently tested for HIV and when infection was detected they were redirected for clinical management. An early assessment of the trial outcomes revealed that 39 new infections were reported during the time of study, of which 28 could be genetically traced to the infected serodiscordant partner. Out of these 28 incident cases, 27 were part of the delayed treatment arm, which translates in a 96% reduction in the risk of transmission.

HPTN 052 was a controlled RCT which recruited serodiscordant couples and the evidence it produced is a landmark for the individual HIV transmission literature. But, what is the effect of ART at the population level? What would be the “real life” effect of this intervention? These were not answered by HPTN 052.

The context of a serodiscordant couple is as ideal a context as it could possibly be for observing and virologically linking HIV transmission events, but is not representative of the sexual behaviours that have previously explain –up to a point- the wide spread of HIV in Africa. Stable couples might not be the norm in contexts with a high frequency of multiplicity of sexual partners, in the short and the long-term (concurrency) and high rates of migration. Also, the uptake of testing and compliance to treatment not to mention the health system capacity to provide ART and retain individuals on treatment [111].

These are some of reasons why a new series of studies that explored the effect of treatment at the population level were urgently needed.

Cluster-Randomized Controlled Trials (C-RCTs) have been planned or are currently on-going to test the principle of TasP hypothesis at the community level. Three studies have been proposed, and a summary of their main characteristics can be seen in **table 3**.

Two of the studies (PopART and ANRS 12249) test effect of universal test and immediate ART regardless of CD4+ count on HIV incidence compared against standard of care according to WHO guidelines as of 2011 (i.e. treat only when CD4+ <350 cell/mm³) [112, 113]. The third study (CDC/HSPH in Botswana) took a different approach of test and treat, and was originally designed to compare the standard of care in the control arm against an intervention of HIV testing and provision of ART for all HIV-infected persons with CD4+ <350 cells/ml or with HIV-1 RNA >10,000 copies/ml [114]². This novel approach relies on the fact that individuals with higher viral load have a greater contribution to HIV transmission [115, 116].

5.2 *Observational studies of serodiscordant couples*

Several observational studies have produced estimates on the effect of ART for preventing HIV transmission in serodiscordant-couples and at the community level.

Studies of the effect of ART in serodiscordant couples have been systematically reviewed and pooled by Anglemyer et al. (**Figure 8**) [117]. This systematic review collected the evidence on the effect of ART for reducing the risk of HIV transmission within

² This information is as of 2012. No further information about this trial was made available. However, was recently referred by Wang et al. 114. Wang, R., et al., *Sample size considerations in the design of cluster randomized trials of combination HIV prevention*. Clin Trials, 2014. **11**(3): p. 309-318.

serodiscordant couples. Prospective and retrospective cohorts were included as well as one RCT (HPTN 052). The pooled estimate (Rate Ratio) when only observational studies that considered combined therapy (no mono or dual therapy) was 0.36 (95%CI 0.17 to 0.75). This is a mean reduction of 64% in HIV transmission.

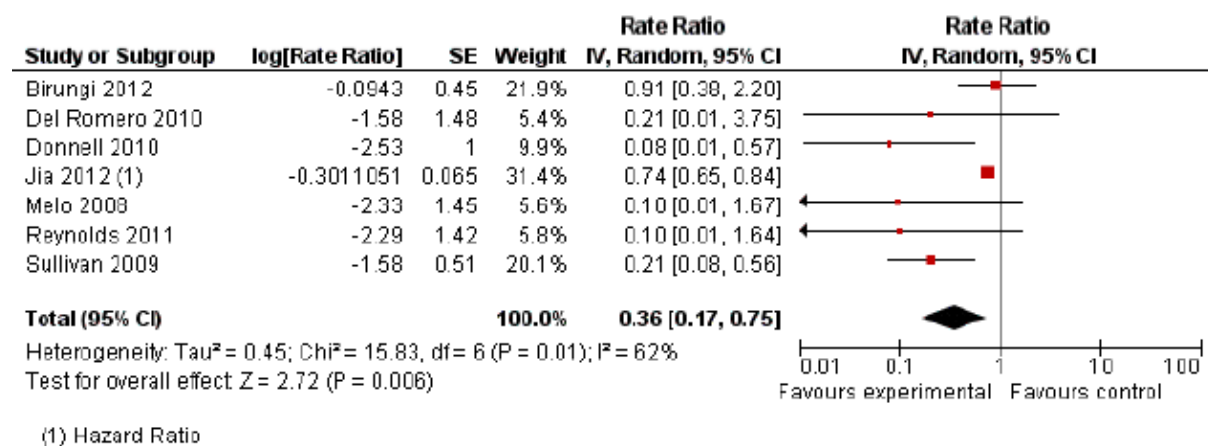


Figure 8 Forest plot of observational cohorts of ART in serodiscordant couples: pooled estimates when studies with mono and dual therapy were removed. Source: Anglemyer et al. [117]

Table 3 Summary of main characteristics of on-going C-RCTs of combined prevention

Study	PopART (HPTN 071)	CDC/HSPH ^a	ANRS 12249
Site	Zambia+South Africa (Western Cape)	Botswana	Hlabisa, KwaZulu-Natal, South Africa
Number of arms	3	2	2
Intervention arms	A: Universal community home-based testing;; active linkage of HIV+-positive individuals to care and immediate ART according to national guidelines and/or male circumcision (MC); B: Same as A but ART at CD4 < 350 cells/ml	A: Enhanced HIV testing (including mobile and home-based testing), active linkage to care and treatment; enhanced MC; ART for all HIV-infected persons with CD4 < 350 cells/μl or with HIV-1 RNA > 10,000 copies/ml; and point-of-care CD4 testing in antenatal clinics with universal HAART in pregnancy started by 28 wk gestation, as well as HIV retesting at delivery among women HIV-negative in second trimester or earlier	A: home-based HIV testing, active linkage to care and immediate ART initiation regardless of CD4 count and clinical stage.
Control arm	C: Enhanced standard of care ^d	B: Standard of care ^b	B: Standard of care ^b
Design	Triplet matched	Pair matched	Pair matched
Number of randomized clusters			
Total	24 (South Africa: 9, Zambia: 15)	30	34
Per arm	8	15	17
Average size of randomized cluster	50,000 (25,000 >18 y)	5,800	34,000
Overall cohort follow up			
Age eligibility	18–44 y	16–64 y	16 y or older
Size per cluster	~2,500 adults per cluster	~500 adults per cluster	~1000
Total size	60,000	15,000	27,000
Primary outcome	HIV incidence ^e	HIV incidence ^e	HIV incidence ^e
Follow up duration	2 y	3–4 y	2 y
HIV Incidence assumption	1.0–1.5 per 100 person-years	~1.5 per 100 person-years	~2.9 per 100 person-years
Anticipated HIV prevalence at baseline	15%	25%	~20%
Target reduction in incidence	In arm A versus C: ~50% to 60%; in arm B versus C: ~25% to 30%	In arm A versus B: ~50%	In arm A versus B: ~30%
Stages when modelling is currently planned	Start, final	Start	Start
Status	Running	Planning	Running

^a Data as of March 2012.^bStandard of care is ART for HIV-positive individuals with CD4 < 350 cells/μl or AIDS.^cStandard of care is standard referral to MC and ART according to Tanzania guidelines (this will soon change from CD4 < 200 cells/μl to CD4 < 350 cells/μl, initially focusing on HIV-positive people with tuberculosis and pregnant women).^dStandard of care is no home-based testing or home-based visit to facilitate linkage to ART. ART given according to country guidelines; standard referral to MC.^eCumulative HIV incidence measured over the trial duration.

CDC/HSPH, US Centers for Disease Control and Prevention/Harvard School of Public Health; HAART, highly active ART; JHU/USAID, Johns Hopkins University/United States Agency of International Development; PopART (HPTN 071), HIV Prevention Trials Network.

As can be seen in the **Figure 8**, only three studies had a significant effect. The observational cohorts by Donnell et al. [81], and Sullivan et al. were both prospective, as opposed to the study by Jia et al. [118] in which an observational cohort was reconstructed retrospectively and analysed.

Donnell et al. recruited 3480 couples in seven countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) where one partner was both positive for HIV+ and HSV-2. Couples were followed for 2 years and were part of an on-going RCT in that region. Sullivan et al. followed 2,993 serodiscordant couples in Rwanda and Zambia from 2002 to 2008.

On the other hand, Jia et al. reconstructed the largest serodiscordant couples cohort known to date, using records from China's HIV national programme from 2003 to 2011 about 38,862 serodiscordant couples [118].

It is interesting to note that the largest effects were observed with the prospective analysis of cohorts made by Donnell et al. and Sullivan et al. Prospective observational cohorts could provide a better and more direct assessment of the initial conditions of participants as well as a precise discrimination of events and the precise time of observation. On the other hand, the retrospective cohort Jia et al. offers a substantially bigger sample, and the retrospective nature of the analyses removes any observer effect as cited before. However, one major subject concern about these results is the lack of evidence to confirm that the infections observed correspond to the discordant partner and not a third party. This was not caused by the design of the study but by the fact that virological linkage was not feasible. This might severely underestimate the effect of ART. Only Donnell et al. performed tests to virologically link the events of transmission tests [81].

5.3 *Ecological studies and observational cohorts for the population effect of ART*

Other studies have performed ecological observations in an attempt to establish a relation between the presence of ART in the community and reductions in HIV incidence. The ecological nature of this analysis implies that different populations were assessed to establish the exposure and the effect of the intervention of interest. Three of these studies were carried out in San Francisco [119-121], other three in British Columbia, Canada [78, 122, 123] and one in Taiwan [124]. In the latter, Fang et al. analysed a retrospective cohort in Taiwan, finding that a policy of free ART delivery to every HIV+ citizen reduced HIV transmission by 53% [124].

Montaner et al. and Lima et al. [78, 122, 123], examined this case for the population of British Columbia in Canada concluding that an association between ART expansion, decreased community viral load and the reduction of new infections have been present in that community. They used unlinked datasets (one for new cases and other for viral load and CD4+ count data) from two different provincial centres.

Similarly, the studies in San Francisco assessed established a relation between coverage of ART in the community for a period of time and changes in HIV prevalence.

Several limitations can be pointed out about this analysis. First, their conclusions are vulnerable to ecological fallacy, since there is no causal relation between the exposure (ART in the community) and the event (reductions in HIV incidence). This allows for a myriad of factors not taken into account to be influencing the observed reductions. Furthermore, none of these studies observed real changes in HIV incidence, but surrogate markers of it like reported HIV cases and HIV prevalence, making it even more difficult to establish a temporal

correlation between variables. Also, in the cases of British Columbia and San Francisco where epidemics are strongly influenced by MSM and PWID respectively, this form of analysis largely overlooks the impact of the repeated preventive interventions in these key populations. These findings have been largely discussed and criticized elsewhere [125, 126].

A different form of evaluation was performed by Tanser et al. in South Africa [127]. This group followed 17,000 HIV negative individuals for a period of eight years (2004 to 2011). They observed the infection events by tracking individual seroconversion and establish a relationship between this event and the level of ART coverage in the community surrounding each individual. Their findings show that in areas of high ART coverage (30 to 40% of all PLHA) the risk of acquiring HIV infection was reduced in a 38%, compared to individuals living in low coverage areas. This study even when uses an ecological exposure variable, measures the effect individually, making the attribution more valid, as stated by the authors.

5.4 Mathematical modelling in HIV programme evaluation

Models can be used in evaluation within the range of designs discussed above in different ways. In RCTs and C-RCTs modelling can be used in initial phases for sample size calculation and in more advance phases for exploration of causal relations and interim analysis. Mathematical models can also be used in the evaluation of health programs when no specific design was used, but interventions were rolled-out in the community. In observational studies they can help to estimate primary endpoints from intermediate outcomes. Finally, modelling can explore the causal relations between ecological observations. Some examples will be discussed and a proposed framework for understanding the role of modelling in health programme evaluations.

Models have been part of programme evaluation in the past and their role has been growing. As mentioned before models are an increasing feature in many trials during the planning phase as they provide a dynamic and flexible tool to inform about baseline assumptions about incidence and demographic characteristics. Some trials like PopART are also planning to incorporate mathematical modelling as a projection strategy during an interim analysis of their results [128].

Garnett and others have proposed a framework for the role of modelling in the evaluation of health programmes [129]. According to this framework, modelling enters the evaluation process in three different ways: a) Estimate the effect of an intervention on a specific outcome when other factors are simultaneously taking place; b) Use changes in intermediate outcomes to predict impact on a final simulated endpoint of interest. This might be useful when primary outcomes are difficult or costly to measure; and c) Exploring the relation of interventions with the measured outcomes [129].

A good example of modelling in programme evaluation of HIV prevention is the case of the Avahan study in India [130, 131]. In this programme, several districts in south India where different types of epidemics take place (PWID, FSW), were intervened with strategies to improve access to health services, promote behaviour change within key populations and a large distribution of free condoms[130].Mathematical models have been used here to explore the causal effect of the intervention, as described in option a) of the framework proposed by Garnett et al. Modelling for Avahan was carried out in a specific district to explore to what extent an intervention in FSW could have explained the reductions observed in HIV prevalence in antenatal clinics (ANC). Their findings reported that even when a fraction of the effect is attributable to the interventions in FSW it was unlikely to explain completely by the programme, since very optimistic levels of intervention-uptake would be necessary to explain these changes [131].

Similarly, Hallett and others have addressed the subject of exploring causality, by exploring the relation between observed changes in behaviour change in Zimbabwe with drops in HIV prevalence, suggesting that earlier changes in risky behaviour over time was strongly related with declines in the epidemic trend in more recent years [132].

5.4.1 Models for estimating the impact of ART at the population level

Assessing the potential impact of ART as a preventive tool as well as its retrospective impact in settings where it has been widely available for many years is an interesting and classic example of a “modelling” question. Robust evidence at the individual level provided by HPTN 052 have opened a window of opportunity for modellers to explore all the possible barriers, co-factors and challenges of rolling-out TasP. Similarly, in the light of this evidence it has become a need to understand the past contributions of ART for prevention in many settings.

Modelling the use of antiretrovirals to stop transmission at the community level has been taking place many years before HPTN 052 or even many of the observational cohorts backing its effect [73, 84]. The most significant and commented cases is that of Granich and colleagues, already discussed in this chapter. But more recently, studies have used the available evidence to exploit its possibilities.

Eaton et al. [90] develop on the idea of ART as prevention within the framework of the 2013 WHO guidelines for the delivery of ART to every HIV+ person whose CD4+ count falls below the threshold of 500 cell/mm³[133]. They used models to simulate the epidemic in four different scenarios that combined different existing conditions of ART coverage and epidemic type: South Africa with a generalised epidemic and moderate ART coverage, Zambia with a generalised epidemic and high coverage, India where epidemic is concentrated

and the coverage is moderate, and Vietnam with a concentrated epidemic and low ART coverage. The analysis consisted of a prospective projection in a period of 20 years to explore not only health benefits but costs and cost-effectiveness. Comparisons were made by varying the threshold in CD4+ count at which individuals could receive ART. Their findings suggest that in addition to the substantial incidence reductions predicted, new recommendations for ART start (CD4+ <350cell/mm³) were very cost-effective compared to previous guidelines for ART initiation [90].

Models have also been used to explore past epidemic trends and assess the potential impact of ART and/or its relation with incidence patterns. Phillips and colleagues reproduced the epidemic of HIV among MSM in the UK where incidence in this group has remain unchanged or even increased despite high rates of testing and ART coverage[134]. Using stochastic individual base modelling, they explored the trends in incidence under assumptions of variability in the use of condoms and behaviour. Their main findings support the plausibility of an increase in incidence over time due to slight reductions of condom use even in the presence of ART. However, when compared to a counterfactual scenario, model results suggested that ART have been useful to control further epidemic expansion [134].

Many different forms of applying mathematical modelling to health programme evaluation have been described, and many advantages can be inferred from these examples. Models are capable of reproducing complex transmission dynamics while making use of robust evidence. The mechanistic nature of mathematical simulations provides powerful arguments to explain different phenomena where other evaluation methods fail (i.e. ecological studies). Furthermore, in the absence of RCTs and observational cohorts, mathematical models are the only form of assessment where counterfactual scenarios are reproducible, allowing the comparison of effect under the absence or presence of an intervention, and a wide range of possibilities for sensitivity analysis.

HIV research and prevention is a constantly expanding field of knowledge, producing large amounts of data, estimations and hypothesis each day. Processing and making appropriate use of this data is easier in the presence of mathematical modelling, for summarizing and translating this information into palpable outcomes.

5.5 The importance of HIV incidence estimation for assessing the impact of interventions.

As previously discussed, making the right choice of outcome for evaluation is an essential initial step of evaluation, and HIV incidence is the most natural and direct observation of effect for any HIV prevention method. In this section, some important considerations about the role of HIV incidence estimations are discussed in an attempt to create a framework for further research that will be presented in chapter four.

Estimates of HIV incidence are not always available and its estimation poses several challenges, related primarily to the scarcity of resources in most of contexts but also considerable methodological barriers.

Observational cohorts and RCTs are the natural source of incidence estimations, but the quantity and presence of these study designs around the world is extremely low contrasted with the widespread and urgent need of HIV incidence measures. For this reason, for many years incidence estimates for the purpose of monitoring HIV epidemics has been derived from indirect estimation methods, like back calculation from AIDS mortality, from consecutive HIV prevalence estimates and from modelling. All of these indirect methods presuppose the existence of information upon which infection rate estimates are built.

Back-calculation methods use surveillance data on AIDS mortality to infer past changes in the rate of infection by making assumptions about distribution of the incubation period [135].

Incidence have also been reconstructed from past HIV prevalence estimations structured by age, when there is a consistency in the sample population, and making a few assumption about survival, as Hallett et al. have demonstrated [136]. Finally, incidence has been recovered from mathematical simulations of transmission supported by detailed reconstruction of risk behaviours and individual contact patterns [137]. With its pros and cons all ultimately depend on the prior existence of a minimum level of information.

In this thesis we discuss the case of settings for which none of these methods is the optimal solution for estimating HIV incidence at a national due to three main reasons: a) inconsistency between samples of key populations making it impossible to infer incidence trends; b) underreporting and biases in AIDS mortality data; and c) lack of behavioural data. These points will now be described in more detail.

As described before in this chapter, HIV epidemics in Latin America are mostly concentrated and prevalence estimations come from key populations. Also, prevalence from ANC is not always periodically collected. The fundament for making inferences on incidence out of prevalence does not hold for these cases since the population samples are mostly inconsistent. Regarding AIDS mortality data, even when surveillance systems are in place and data is collected routinely – as in most of countries in Latin America-, the assumption that AIDS mortality actually reflects past trends in infection rate is very risky one, given the large amount of underreporting in collected mortality data and particularly for the initial years of AIDS mortality report which are at the end the most informative for this method [135, 138, 139]. Finally, detailed transmission models show indeed a very useful solution but are still unfeasible for many settings where behavioural and programmatic data, are not at hand to accurately reproduce HIV infection. Moreover, the demands of time and data of transmission models make that option unfeasible as a surveillance tool to be used regularly.

In this sense, disparities can be identified in the type and amount of data available or regularly collected according to the type of epidemic: broadly, we could say that the vast majority of states harbouring generalized epidemics have accumulated extensive information on risk behaviours. In many occasions this goes hand in hand with HIV seroprevalence studies, such is the case of Demographic Health Surveys (DHS) in most of Sub Saharan African states. DHS studies are also present in Latin America but HIV seroprevalence is not part of the surveys.

In general, HIV incidence can be harder to estimate in many Latin American settings due to incomplete data about behaviours, necessary to inform current estimations like the UNAIDS Estimation and Projection Package [140] and other mathematical models. Also, inferring HIV incidence from past prevalence might not be feasible since ANC prevalence collection is not the norm, and inconsistencies in sampling from key populations makes it difficult to use the method for this groups. For this reasons this thesis proposes a flexible modelling approach that does not make use of any behavioural data or prevalence estimation, and relies solely on case-report data to derive HIV incidence.

6 RATIONALE AND THESIS LAYOUT

This brief revision of many different aspects of HIV was intended to give an outlook of a specific region of the world in the context of the global efforts to contain the HIV epidemic. The current state of the epidemic in the contexts of Latin America and more specifically in Brazil and Colombia was described, noting that both countries have made important efforts to introduce ART and expand the coverage of ART as part as their response to the epidemic.

The impact of such efforts in the light of recent evidence about the transmission prevention effect of ART is still unknown for these settings.

Reviewing the importance of health programme evaluation and the role of modelling, it was made clear how essential it is for countries to have HIV incidence estimations at hand to evaluate the progress of their response to HIV. However, a gap between the type of information required for making use of the most popular methods for incidence estimation and the data actually collected, was identified for Latin American countries.

This thesis aims to fill the gaps of knowledge mentioned above and for this purpose; this work has been organized and carried out in the following order.

Chapters two and three study the cases of HIV transmission in Bogota, and Brazil, respectively. Transmission dynamics are reproduced through mathematical modelling in order to explain the main epidemiological trends among a heterogeneous population, to finally estimate the retrospective impact of ART and condoms for preventing new HIV infections.

Chapter four proposes a method for estimating HIV incidence in settings where surveillance data is more readily available than other sources of data used in transmission models. Relying only on case-report data a mathematical model that estimates infection rates with an alternative flexible spline function is validated and applied to the case of Colombia.

Chapter five discusses the main findings, limitations, challenges and the future prospects of this research.

7 REFERENCES

1. UNAIDS. *Report on the global AIDS epidemic*. 2012 February 6, 2013]; Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf.
2. UNAIDS. *Global Report: UNAIDS report on the global AIDS epidemic 2010*. May 5 2011]; Available from: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf.
3. Hahn, B.H., et al., *AIDS as a zoonosis: scientific and public health implications*. Science, 2000. **287**(5453): p. 607-14.
4. Barre-Sinoussi, F., et al., *Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)*. Science, 1983. **220**(4599): p. 868-71.
5. Crawford, D.H., *Virus hunt : the search for the origin of HIV*. 1st ed. 2013, Oxford: Oxford University Press. xi, 244 p.
6. Chen, Z., et al., *Genetic characterization of new West African simian immunodeficiency virus SIVsm: geographic clustering of household-derived SIV strains with human immunodeficiency virus type 2 subtypes and genetically diverse viruses from a single feral sooty mangabey troop*. J Virol, 1996. **70**(6): p. 3617-27.
7. Plantier, J.C., et al., *A new human immunodeficiency virus derived from gorillas*. Nat Med, 2009. **15**(8): p. 871-2.
8. Soares, M.A., et al., *A specific subtype C of human immunodeficiency virus type 1 circulates in Brazil*. Aids, 2003. **17**(1): p. 11-21.
9. Hemelaar, J., *The origin and diversity of the HIV-1 pandemic*. Trends Mol Med, 2012. **18**(3): p. 182-92.
10. Korber, B., et al., *Timing the ancestor of the HIV-1 pandemic strains*. Science, 2000. **288**(5472): p. 1789-96.
11. Buve, A., et al., *Multicentre study on factors determining differences in rate of spread of HIV in sub-Saharan Africa: methods and prevalence of HIV infection*. Aids, 2001. **15 Suppl 4**: p. S5-14.
12. Weiss, L., *[Immune-based therapies and HIV infection]*. Ann Med Interne (Paris), 2002. **153**(4): p. 227-36.
13. Boily, M.C., et al., *Incremental role of male circumcision on a generalised HIV epidemic through its protective effect against other sexually transmitted infections: from efficacy to effectiveness to population-level impact*. Sex Transm Infect, 2008. **84 Suppl 2**: p. ii28-34.
14. 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.
15. Gilbert, M.T., et al., *The emergence of HIV/AIDS in the Americas and beyond*. Proc Natl Acad Sci U S A, 2007. **104**(47): p. 18566-70.
16. Stevens, C.E., et al., *Human T-cell lymphotropic virus type III infection in a cohort of homosexual men in New York City*. Jama, 1986. **255**(16): p. 2167-72.
17. Jaffe, H.W., et al., *The acquired immunodeficiency syndrome in a cohort of homosexual men. A six-year follow-up study*. Ann Intern Med, 1985. **103**(2): p. 210-4.
18. Farmer, P., *AIDS and accusation : Haiti and the geography of blame*. Updated with a new preface. ed. Comparative studies of health systems and medical care. 2006, Berkeley: University of California Press. xxxii, 338 p.
19. Dodds, J.P., et al., *Increasing risk behaviour and high levels of undiagnosed HIV infection in a community sample of homosexual men*. Sex Transm Infect, 2004. **80**(3): p. 236-40.
20. Grov, C., *HIV risk and substance use in men who have sex with men surveyed in bathhouses, bars/clubs, and on Craigslist.org: venue of recruitment matters*. AIDS Behav, 2012. **16**(4): p. 807-17.

21. UNAIDS/WHO Working Group On Global HIV/AIDS and STI Surveillance, *Guidelines for second generation HIV surveillance*. Geneva: World Health Organization and Joint United Nations Programme on HIV/AIDS. . 2000.
22. Wilson, D. and D.T. Halperin, "Know your epidemic, know your response": a useful approach, if we get it right. *Lancet*, 2008. **372**: p. 423-6.
23. Mishra, S., et al., *Distinguishing sources of HIV transmission from the distribution of newly acquired HIV infections: why is it important for HIV prevention planning?* *Sex Transm Infect*, 2014. **90**(1): p. 19-25.
24. Blanchard, J.F. and S.O. Aral, *Program Science: an initiative to improve the planning, implementation and evaluation of HIV/sexually transmitted infection prevention programmes*, in *Sex Transm Infect*. 2011: England. p. 2-3.
25. UNAIDS, *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013*. 2013: Geneva.
26. UNAIDS, *Regional Fact Sheet: Latin America*. 2012: Geneva.
27. UNFPA. *Panorama del VIH/sida en Colombia 1983-2010*. 2012 6 February 2013]; Available from: <http://www.unfpa.org.co/uploadUNFPA/file/PANORAMA%20VIH%20SIDA%20COLOMBIA%201983-2010.pdf>.
28. Caceres, C.F., *HIV among gay and other men who have sex with men in Latin America and the Caribbean: a hidden epidemic?* *AIDS*, 2002. **16 Suppl 3**: p. S23-33.
29. Bautista, C.T., et al., *Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men*. *Sex Transm Infect*, 2004. **80**(6): p. 498-504.
30. Montano, S.M., et al., *Prevalences, genotypes, and risk factors for HIV transmission in South America*. *J Acquir Immune Defic Syndr*, 2005. **40**(1): p. 57-64.
31. Gomez, G.B., et al., *The potential impact of pre-exposure prophylaxis for HIV prevention among men who have sex with men and transwomen in Lima, Peru: a mathematical modelling study*. *PLoS Med*, 2012. **9**(10): p. e1001323.
32. Pulerwitz, J., et al., *HIV-related stigma, service utilization, and status disclosure among truck drivers crossing the Southern borders in Brazil*. *AIDS Care*, 2008. **20**(7): p. 764-70.
33. Wilson, D.P. and L. Zhang, *Characteristics of HIV epidemics driven by men who have sex with men and people who inject drugs*. *Curr Opin HIV AIDS*, 2011. **6**(2): p. 94-101.
34. Spire, B., I. de Zoysa, and H. Himmich, *HIV prevention: What have we learned from community experiences in concentrated epidemics?* *J Int AIDS Soc*, 2008. **11**(1): p. 5.
35. Sidibé, M. 2010 [cited 2011 13th June]; Available from: <http://www.unaids.org/en/resources/presscentre/featurestories/2010/march/20100316msmcaribbean/>.
36. Malebranche, D.J., et al., *Exploring the "bisexual bridge": a qualitative study of risk behavior and disclosure of same-sex behavior among black bisexual men*. *Am J Public Health*, 2010. **100**(1): p. 159-64.
37. Miguez-Burbano, M.J., et al., *High-risk behaviours in men from Bogota, Colombia and the spread of HIV*. *Int J STD AIDS*, 2001. **12**(11): p. 739-43.
38. ILGA. *State-sponsored Homophobia*. 2009 [cited 2011 13th June]; Available from: http://ilga.org/historic/Statehomophobia/ILGA_State_Sponsored_Homophobia_2009.pdf.
39. Prüss-Ustün, A., et al., *HIV Due to Female Sex Work: Regional and Global Estimates*. *PLoS ONE*, 2013. **8**(5): p. e63476.
40. Suárez, R., R. Sepúlveda, and J.F. Vesga, *Contextos socioculturales de riesgo para Contrar VIH en Cartagena*. *Antípoda*, 2008. **6**: p. 313-330.
41. Bautista, C.T., et al., *Immigration Status and HIV-risk Related Behaviors among Female Sex Workers in South America*. *AIDS and Behavior*, 2007. **12**(2): p. 195-201.
42. Bautista, C.T., *Seroprevalence of and risk factors for HIV-1 infection among female commercial sex workers in South America*. *Sexually transmitted infections*, 2006. **82**(4): p. 311-316.

43. Harm Reduction International, *The Global State of Harm Reduction: Towards an Integrated Response*. 2012: London.
44. Mesquita, F., et al., *Trends of HIV infection among injection drug users in Brazil in the 1990s: the impact of changes in patterns of drug use*. J Acquir Immune Defic Syndr, 2001. **28**(3): p. 298-302.
45. Rodriguez, C.M., L.F. Marques, and G. Touze, *HIV and injection drug use in Latin America*. AIDS, 2002. **16 Suppl 3**: p. S34-41.
46. Pando, M.A., et al., *Incidence of HIV type 1 infection, antiretroviral drug resistance, and molecular characterization in newly diagnosed individuals in Argentina: A Global Fund Project*. AIDS Res Hum Retroviruses, 2011. **27**(1): p. 17-23.
47. Carrion, G., et al., *Documentation of subtype C HIV Type 1 strains in Argentina, Paraguay, and Uruguay*. AIDS Res Hum Retroviruses, 2004. **20**(9): p. 1022-5.
48. Salemi, M., et al., *Different epidemic potentials of the HIV-1B and C subtypes*. J Mol Evol, 2005. **60**(5): p. 598-605.
49. Codazzi, I.G.A. *Political Map, Colombia*. 2011 [cited 2011 May 9th]; Available from: <http://190.254.22.44/ssigl2.0/visor/galeria.req?mapald=1&title=Mapa%20Base>.
50. García-Bernal, R., *Infección por VIH/SIDA en Colombia. Estado del Arte 2000-2005*, ed. UNAIDS. 2006, Bogota: UNAIDS.
51. Suarez R, N.N., Sepulveda R, Vesga JF, *HIV Risk Perception and Condom Use in the Sociocultural Context of Cartagena- Colombia*. Anthropol & H. J, 2008. **1**: p. 5.
52. Streicker, J., *Remaking race, class, and region in a tourist town*. Identities-Global Studies in Culture and Power, 1997. **3**(4): p. 523-555.
53. Streicker, J., *Sexuality, Power, and Social-Order in Cartagena, Colombia*. Ethnology, 1993. **32**(4): p. 359-374.
54. Internal Displacement Monitoring Centre. 2014 [cited 2014 23 September]; Available from: <http://www.internal-displacement.org/>.
55. Carrillo, A., *Internal displacement in Colombia: humanitarian, economic and social consequences in urban settings and current challenges* International Review of the Red Cross, 2009. **91**(857): p. 19.
56. Moreno, L., *Informe UNGASS 2010*, MPS, Editor. 2010, MPS: Bogota. p. 6-26.
57. Bautista, C.T., *Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men*. Sexually transmitted infections, 2004. **80**(6): p. 498-504.
58. MPS/UNFPA, *Comportamiento sexual y prevalencia de VIH en hombres que tienen relaciones sexuales con hombres en siete ciudades de Colombia*, Ministerio-de-la-protección-social/UNFPA, Editor. 2012: Bogota.
59. Berbesi, D., et al., *Estudio de prevalencia de VIH y comportamientos de riesgo asociados, en usuarios de drogas vía inyectada en Medellín y Pereira*. 2011, Universidad CES: Medellín.
60. Garavito, L. *Gasto Nacional en VIH-sida*. 2007 [cited 09 February 2013; Available from: http://www.minsalud.gov.co/salud/Documents/observatorio_vih/documentos/monitoreo_evaluacion/3_sistemas-informacion/Informe_MEGAS_FINAL__12_ago_2008_Mexico.pdf.
61. Plaza, B., A.B. Barona, and N. Hearst, *Managed competition for the poor or poorly managed competition? Lessons from the Colombian health reform experience*. Health Policy Plan, 2001. **16 Suppl 2**: p. 44-51.
62. ACIN, *Guía de práctica clínica basada en la evidencia científica para la atención de la infección por VIH en adolescentes y adultos hombres y mujeres, residentes en Colombia*. . 2012, Asociación Colombiana de Infectología: Bogota.
63. Departamento-de-DST-Aids-e-Hepatitis-Virais, *Boletim Epidemiológico*, M.d. Saúde, Editor. 2012, Ministério da Saúde: Brasília DF.
64. Nunn, A., *The politics and history of AIDS treatment in Brazil*. 2009, New York ; London: Springer.

65. Berkman, A., et al., *A critical analysis of the Brazilian response to HIV/AIDS: lessons learned for controlling and mitigating the epidemic in developing countries*. Am J Public Health, 2005. **95**(7): p. 1162-72.
66. Bueno, R.C., G. L. Paes, and F. C. Mesquita, *A Comparison of IVDU and Heterosexual Transmission in Sex Workers of Low Social-Economics Situation in Santos, Brasil*, in *VIII International Conference on AIDS*. 1992: Amsterdam
67. Levi, G.C. and M.A. Vitoria, *Fighting against AIDS: the Brazilian experience*. Aids, 2002. **16**(18): p. 2373-83.
68. Fazito, E., et al., *Analysis of duration of risk behaviour for key populations: a literature review*. Sex Transm Infect, 2012. **88 Suppl 2**: p. i24-32.
69. UNAIDS. *AIDSinfo Online Database*. [cited 2014 1 July]; Available from: <http://aidsinfoonline.org/devinfo/libraries.aspx/Home.aspx>.
70. Kerr, L.R., et al., *HIV among MSM in a large middle-income country*. AIDS, 2013. **27**(3): p. 427-35.
71. Saúde, M.d., *Brazilian Policy on addressing AIDS: results, progress and perspectives*, A.a.V.H. Department of STD, Editor. 2012: Brasilia.
72. Meiners-Chabin, C., et al., *Towards the sustainable implementation of treatment as prevention (TasP) in Brazil: investing in policy measures to cut down on ART costs*, in *AIDS conference*. 2014: Melbourne, Australia.
73. Garnett, G.P. and R.M. Anderson, *Antiviral therapy and the transmission dynamics of HIV-1*. J Antimicrob Chemother, 1996. **37 Suppl B**: p. 135-50.
74. Ho, D.D., et al., *Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection*. Nature, 1995. **373**(6510): p. 123-6.
75. Chigwedere, P., et al., *Efficacy of antiretroviral drugs in reducing mother-to-child transmission of HIV in Africa: a meta-analysis of published clinical trials*. AIDS Res Hum Retroviruses, 2008. **24**(6): p. 827-37.
76. Quinn, T., et al., *Viral Load And Heterosexual Transmission Of Human Immunodeficiency Virus Type 1*. The New England Journal of Medicine, 2000. **342**: p. 921-929.
77. 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.
78. Montaner, J.S., et al., *The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic*. Lancet, 2006. **368**(9534): p. 531-6.
79. Hosseinipour, M., et al., *Can antiretroviral therapy be used to prevent sexual transmission of human immunodeficiency virus type 1?* Clin Infect Dis, 2002. **34**(10): p. 1391-5.
80. Cohen, M.S., et al., *Use of antiretroviral drugs to prevent sexual transmission of HIV*. Curr Clin Top Infect Dis, 2002. **22**: p. 214-51.
81. Donnell, D., et al., *Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis*. Lancet, 2010. **375**(9731): p. 2092-8.
82. Tovanabutra, S., et al., *Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand*. J Acquir Immune Defic Syndr, 2002. **29**(3): p. 275-83.
83. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy*. N Engl J Med, 2011. **365**(6): p. 493-505.
84. Granich, R.M., et al., *Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model*. Lancet, 2009. **373**(9657): p. 48-57.
85. Cremin, I., *The Impact and Importance of Voluntary Counselling and Testing for HIV in sub-Saharan Africa*, in *Department of Infectious Disease Epidemiology*. 2010, Imperial College: London. p. 273.
86. Cohen, M.S., T.D. Mastro, and W. Cates, Jr., *Universal voluntary HIV testing and immediate antiretroviral therapy*. Lancet, 2009. **373**(9669): p. 1077; author reply 1080-1.

87. Dodd, P.J., G.P. Garnett, and T.B. Hallett, *Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings*. *AIDS*, 2010. **24**(5): p. 729-35.
88. 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.
89. Law, M.G., et al., *Modelling the effect of combination antiretroviral treatments on HIV incidence*. *AIDS*, 2001. **15**(10): p. 1287-94.
90. Eaton, J.W., et al., *Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models*. *Lancet Glob Health*, 2014. **2**(1): p. e23-34.
91. Cohen, M.S., *HIV treatment as prevention: to be or not to be?* *J Acquir Immune Defic Syndr*, 2010. **55**(2): p. 137-8.
92. Garnett, G.P. and R.F. Baggeley, *Treating our way out of the HIV pandemic: could we, would we, should we?* *Lancet*, 2009. **373**(9657): p. 9-11.
93. Ostrow, D.E., et al., *Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men*. *AIDS*, 2002. **16**(5): p. 775-80.
94. Stockman, J.K., et al., *HIV prevention fatigue among high-risk populations in San Francisco*. *J Acquir Immune Defic Syndr*, 2004. **35**(4): p. 432-4.
95. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
96. Fischl, M.A., et al., *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial*. *N Engl J Med*, 1987. **317**(4): p. 185-91.
97. Hammer, S.M., et al., *A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter*. *AIDS Clinical Trials Group Study 175 Study Team*. *N Engl J Med*, 1996. **335**(15): p. 1081-90.
98. Hammer, S.M., et al., *A controlled trial of two nucleoside analogues plus didanosine 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.
99. Gulick, R.M., et al., *Treatment with didanosine, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy*. *N Engl J Med*, 1997. **337**(11): p. 734-9.
100. Arno, A., et al., *Impact on the immune system of undetectable plasma HIV-1 RNA for more than 2 years*. *Aids*, 1998. **12**(7): p. 697-704.
101. Deeks, S.G., et al., *Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia*. *N Engl J Med*, 2001. **344**(7): p. 472-80.
102. Siliciano, J.D. and R.F. Siliciano, *A long-term latent reservoir for HIV-1: discovery and clinical implications*. *J Antimicrob Chemother*, 2004. **54**(1): p. 6-9.
103. Gallant, J.E., et al., *Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial*. *Jama*, 2004. **292**(2): p. 191-201.
104. van Leth, F., et al., *Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study*. *Lancet*, 2004. **363**(9417): p. 1253-63.
105. Ruel, T.D., et al., *Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy*. *J Acquir Immune Defic Syndr*, 2014. **65**(5): p. 535-41.
106. 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.

107. Artz, L., et al., *A randomized trial of clinician-delivered interventions promoting barrier contraception for sexually transmitted disease prevention*. Sex Transm Dis, 2005. **32**(11): p. 672-9.
108. Hayes, R., et al., *Randomised trials of STD treatment for HIV prevention: report of an international workshop*. HIV/STD Trials Workshop Group. Genitourin Med, 1997. **73**(6): p. 432-43.
109. Hallett, T.B., P.J. White, and G.P. Garnett, *Appropriate evaluation of HIV prevention interventions: from experiment to full-scale implementation*. Sex Transm Infect, 2007. **83 Suppl 1**: p. i55-60.
110. Boily, M.C., et al., *HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention*. PLoS Med, 2012. **9**(7): p. e1001250.
111. Shelton, J.D., *HIV/AIDS. ARVs as HIV prevention: a tough road to wide impact*. Science, 2011. **334**(6063): p. 1645-6.
112. Hayes, R., et al., *HPTN 071 (PopART): rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment - a study protocol for a cluster randomised trial*. Trials, 2014. **15**: p. 57.
113. Iwuji, C.C., et al., *Evaluation of the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence: the ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa: study protocol for a cluster randomised controlled trial*. Trials, 2013. **14**: p. 230.
114. Wang, R., et al., *Sample size considerations in the design of cluster randomized trials of combination HIV prevention*. Clin Trials, 2014. **11**(3): p. 309-318.
115. Novitsky, V. and M. Essex, *Using HIV viral load to guide treatment-for-prevention interventions*. Curr Opin HIV AIDS, 2012. **7**(2): p. 117-24.
116. Novitsky, V., et al., *HIV-1 subtype C-infected individuals maintaining high viral load as potential targets for the "test-and-treat" approach to reduce HIV transmission*. PLoS One, 2010. **5**(4): p. e10148.
117. Anglemyer, A., et al., *Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples*. Cochrane Database Syst Rev, 2013. **4**: p. Cd009153.
118. Jia, Z., et al., *Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study*. Lancet, 2012.
119. Das, M., et al., *Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco*. PLoS One, 2010. **5**(6): p. e11068.
120. Katz, M.H., et al., *Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco*. Am J Public Health, 2002. **92**(3): p. 388-94.
121. Porco, T.C., et al., *Decline in HIV infectivity following the introduction of highly active antiretroviral therapy*. Aids, 2004. **18**(1): p. 81-8.
122. Lima, V.D., et al., *Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic*. J Infect Dis, 2008. **198**(1): p. 59-67.
123. Montaner, J.S., et al., *Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study*. Lancet, 2010. **376**(9740): p. 532-9.
124. Fang, C.T., et al., *Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan*. J Infect Dis, 2004. **190**(5): p. 879-85.
125. Smith, M.K., et al., *HIV treatment as prevention: the utility and limitations of ecological observation*. PLoS Med, 2012. **9**(7): p. e1001260.
126. Smith, K., et al., *HIV-1 treatment as prevention: the good, the bad, and the challenges*. Curr Opin HIV AIDS, 2011. **6**(4): p. 315-25.

127. Tanser, F., et al., *High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa*. Science, 2013. **339**(6122): p. 966-71.
128. Cori, A., et al., *HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model*. PLoS One, 2014. **9**(1): p. e84511.
129. Garnett, G.P., et al., *Mathematical models in the evaluation of health programmes*. Lancet, 2011.
130. Boily, M.C., et al., *Evaluating large-scale HIV prevention interventions: study design for an integrated mathematical modelling approach*. Sex Transm Infect, 2007. **83**(7): p. 582-9.
131. Pickles, M., et al., *HIV prevention at scale: has it worked? Evaluation of the impact of the Avahan programme in South India*. The Lancet Global Health, 2013. **[Accepted]**.
132. Hallett, T.B., et al., *Assessing evidence for behaviour change affecting the course of HIV epidemics: a new mathematical modelling approach and application to data from Zimbabwe*. Epidemics, 2009. **1**(2): p. 108-17.
133. WHO, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection—recommendations for a public health approach*. 2013: Geneva.
134. Phillips, A.N., et al., *Increased HIV Incidence in Men Who Have Sex with Men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic*. PLoS ONE, 2013. **8**(2): p. e55312.
135. Gail, M.H. and R. Brookmeyer, *Methods for projecting course of acquired immunodeficiency syndrome epidemic*. J Natl Cancer Inst, 1988. **80**(12): p. 900-11.
136. Hallett, T.B., et al., *Estimating incidence from prevalence in generalised HIV epidemics: methods and validation*. PLoS Med, 2008. **5**(4): p. e80.
137. 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.
138. Gonzalez, M.A., et al., *Patterns, trends and sex differences in HIV/AIDS reported mortality in Latin American countries: 1996-2007*. BMC Public Health, 2011. **11**: p. 605.
139. Fazito, E., et al., *Identifying and quantifying misclassified and under-reported AIDS deaths in Brazil: a retrospective analysis from 1985 to 2009*. Sex Transm Infect, 2012. **88 Suppl 2**: p. i86-94.
140. Brown, T., et al., *Modelling HIV epidemics in the antiretroviral era: the UNAIDS Estimation and Projection package 2009*. Sex Transm Infect, 2010. **86 Suppl 2**: p. ii3-10.

Chapter 2: Estimating the Impact of Antiretroviral Treatment in the HIV epidemic of Bogota, Colombia

1 INTRODUCTION

The government of Colombia planned their response to HIV epidemic around four pillars: health promotion, prevention, counseling/testing and treatment. The first two pillars have been addressed through communication campaigns, educational workshops and distribution of condoms [1]. Bogota as the capital and most diverse city in the country has led the effort to direct the prevention campaigns to men who have sex with men (MSM) and female sex workers (FSW). NGOs like *Ligasida* have had a principal role in delivering HIV prevention in the city through activities such as mapping venues (baths, saunas, clubs and bars) and working closely with the vulnerable populations since its creation in 1983. Their activities included offering information and advice on sexually transmitted infections (STIs) and HIV, counseling and HIV testing, distribution of condoms and more importantly linking patients to HIV care [2]. Regarding the third pillar, HIV testing in Colombia is voluntary and with the very few exceptions where the health providers have tried to reach-out vulnerable populations, it has remained passive (*i.e.* available for those who seek the test) and only offered widely as part of the antenatal care package [3, 4]. Those who test positive flow through the system starting at the point of testing (*i.e.* Hospitals, primary-care centres and STI clinics) to be redirected to an HIV programme where confirmatory tests are performed (*i.e.* Western Blot). If a case is confirmed, a clinical assessment and laboratory appraisal – CD4 count and viral load among others - takes place in order to establish the stage of disease and the need of antiretroviral therapy (ART) [3]. Report of new HIV cases is mandatory and these are collected centrally by the Ministry of Health.

Antiretroviral therapy and HIV/AIDS-related medical care is provided for free in Colombia since 1997, with the list of therapeutic options increasingly growing over the years. According to UNAIDS estimations, by 2013 29% of people living with HIV and AIDS (PLHA) were receiving ART in the country. [5]

It can be said that Colombia's response has been strongly inclined towards the medical care and antiretroviral treatment delivery. This is supported by the national spending records, which showed that HIV prevention activities in Colombia are mainly funded by private and international sources (82% of the total spending) while the government is contributing with only 18% [6].

However, Colombia's Ministry of health (MoH) reported that 76% of HIV+ detected by the health system by 2007 were receiving ART [6], suggesting that detection is occurring during advance stages of the disease, when individuals are already in need of therapy. A brief analysis of data from MoH's *cuenta de alto costo*³ supports the latter, showing the distribution of detected cases in Bogota over time by CD4+ cell count at the time of diagnosis (**Figure 1**).

Bogota, as many other cities in Latin America, is the host of a highly concentrated epidemic among MSM but its response to it does not reflect this fact necessarily. Mainly focused on providing ART according to the changing international guidelines and lacking a solid policy that focuses on tackling the spread of the virus at its source, Colombia's approach might not be capitalizing from the preventive effects of both ART and targeted prevention strategies to its full potential.

The objective of this mathematical modelling analysis is to provide theoretical support to this argument, by estimating the retrospective impact of prevention interventions.

³ *Cuenta de alto costo* (high-cost account) is a special branch of MoH in Colombia which deals with high-cost diseases like HIV, Cancer and renal disease. available in the internet from <http://www.cuentadealtocosto.org/>

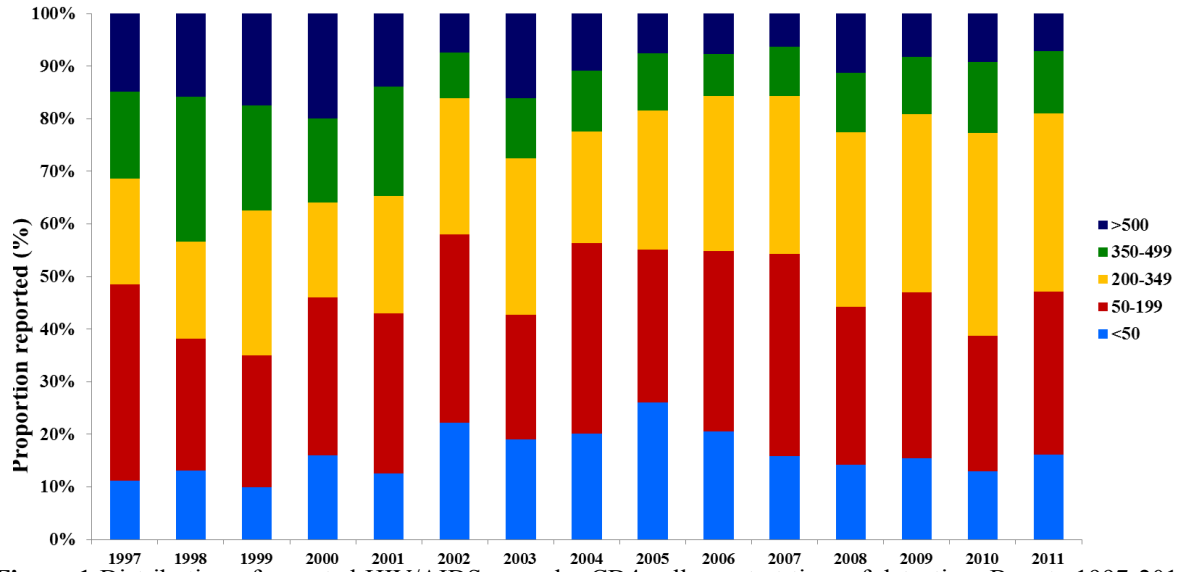


Figure 1 Distribution of reported HIV/AIDS cases by CD4 cell count at time of detection, Bogota 1997-2011. Source: *Cuenta de alto costo*, MPS (Ministry of Health).

2 METHODS

2.1 Model structure

A mathematical modelling approach was designed for the purposes stated above. A deterministic model that simulated the sexual transmission of HIV amongst sexually active population between 15 to 49 years old, while introducing the effects of preventive intervention over time (i.e. sex acts with condom and ART transmission effects) was developed.

The initial stage of the model represents the HIV infection event where susceptible individuals get in contact with infectious individuals at different rates according to their sexual activity group “ k ”, as will be better described later in this section. Those acquiring the virus progress through the model structure in a series of stages that intends to represent the average decay in CD4+ cell count that characterise the natural history of HIV infection [7].

Progression through stages of undetected infection competes with the rate of detection and recruitment into ART as seen in **Figure 2**. This rate of detection as will be explained later varies across disease stages and over the simulation time. Those who enter treatment start an alternative path that starts with a transient phase of un-suppressed viral load that was incorporated to capture the fact that the effect of ART on transmission depends on the extent of viral suppression. Afterwards, treated individuals move to a fully suppressed ART stage where progression to death is delayed according to the existent evidence on survival extension provided by ART. In these stages, individuals progress vertically (**Figure 2**) and not through CD4+ count stages. Failure on 1st line of treatment is allowed and implies a step back to natural progression of disease in the absence of ART which competes again with 2nd line ART recruitment.

All the stages of infection in the model represent the number of infectious individuals. This constantly changing “pool” of infectious individuals ultimately provides the risk of acquiring HIV infection for susceptible individuals at every point in time. However, infectiousness is not constant throughout the stages, and a transmission-modification factor was incorporated for the acute phase of infection and for the treatment stages. Despite the evidence provided by Hollingsworth et al. [8, 9] regarding increased transmissibility during the late phase of infection, here it was assumed that anyone with a CD4+ count $< 50 \text{ cell/mm}^3$ was too ill to engage in sexual activity.

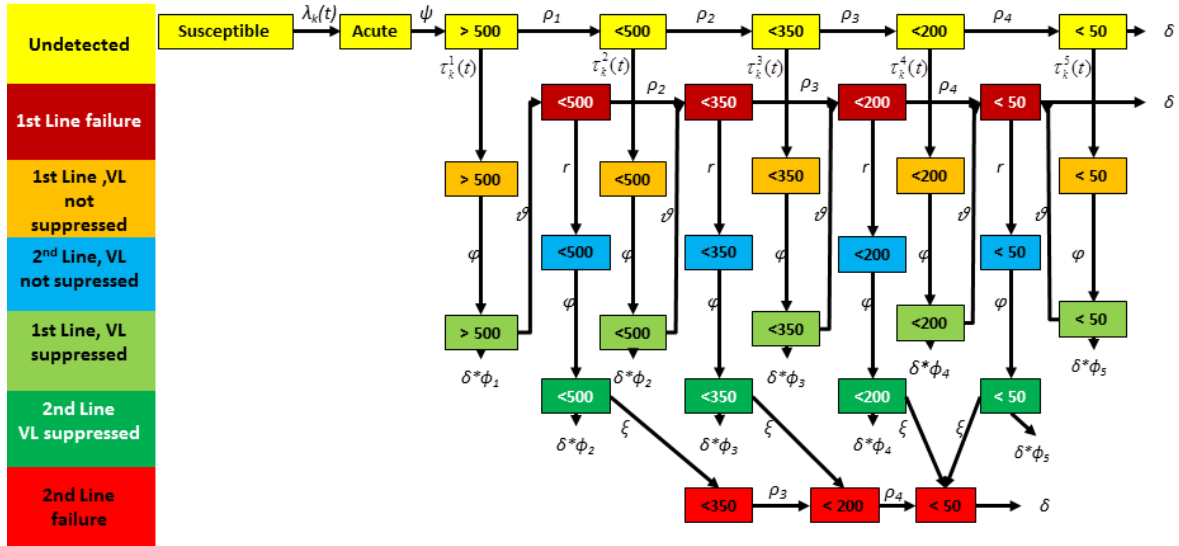


Figure 2 Model structure for the sexual transmission of HIV: Susceptible individuals get infected at rate $\lambda_k(t)$ (where k denotes the sexual activity group) progressing to Acute stage and leaving at a fixed rate ψ . Natural progression through CD4 count stages occurs at fixed rates ρ_1 to ρ_4 to finally progress to death at rate δ . Rates ρ_1 to ρ_4 are set to match an average CD4+ cell decay of 60cell/mm^3 per year. Recruitment into ART occurs at rate $\tau_k^s(t)$, varying by CD4+ count “s” and risk group “k”. Individuals set on ART spend an average of 6 months (φ) in a non-suppressed viral load phase. Vertical progression to death from ART suppressive stages occurs at rate $\delta * \phi_s$, where ϕ_s is the mortality hazard reduction according to the CD4 count stage “s” at the time of ART start. First line failure (ϑ) and second line failure (ξ) are allowed. Recruitment into second line ART occurs at fixed rate r , reflecting average retention rates for Colombia. First and second line failure stages progress to death at the same rate as the undetected stages.

Heterogeneity in behaviour was introduced by stratifying the sexually active population of Bogota into eight different sexual-activity groups, using Demographic Health Survey data [10] (**table 1**) (**Figure 3**). The proportion in the sexually active population was estimated from data as one minus the proportion of people (men and woman) reporting no sexual activity in the last year, according to DHS data. Following others [11], heterosexual activity for men and women was stratified into two different groups: high activity for those with 2 or more partners in the past year, and a low activity group, estimated as the remaining proportion of the population after estimating all other subpopulation sizes. The latter group is assumed to reflect stable heterosexual couples and consequently one partner per year was attributed to this group, and levels of condom use according to those reported for contraceptive purposes in the national health surveys.

FSWs population was previously estimated to be around 0.7% (CI 95% 0.61% to 0.87%) in Colombia in 2001 [12]. Since no local estimations for population size of clients of FSW were available, regional estimations were used. According to Carael et al. between 0.3% and 7% of men in Latin America and the Caribbean have paid for sex in the last year in 2002 [13]. MSM were subdivided into bisexual-MSM (MSM_{bi}) and exclusive-MSM (MSM_{ex}) to incorporate risk heterogeneity within the group and also bridging transmissions between subpopulations. MSM population size was previously estimated to be 4.4% (95% CI 2% to 6.6%) of male population in Bogota. The relative size of sub-group MSM_{bi} was estimated as $\sim 26\%$ of the complete MSM group according to reports on the fraction of MSM reporting female partners in the past year in a behavioural-survey carried out in Bogota in 2011 [14].

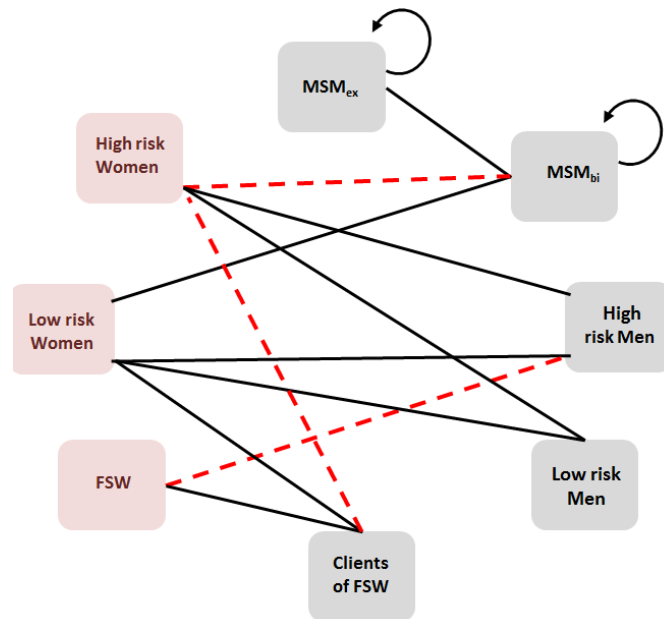


Figure 3 Population stratification according to sexual behaviour and gender: Black solid line reflect preferential mixing which depends on the fraction of partners assigned to each subpopulation, abased on available evidence of mixing preferences or otherwise, based on assumptions. In the case of proportionate mixing, sex acts can occur with partners not necessarily preferred. These contacts depend on availability of partners, and are represented as “allowed partnerships” in the figure by red dotted lines.

2.2 Model Equations

2.2.1 Ordinary Differential Equations

Equations 1 to 32:

The following equations are the mathematical representation of the model stages shown in

Figure 2. For parameter and symbol description see **Table 1**

1. $\frac{dS_k(t)}{dt} = \left[(\sigma + \mu) \left(\sum_a I_k^{a,s}(t) + S_k(t) \right) + \left(\delta \sum_{a=0,3,6}^{s=6} I_k^{a,s}(t) \right) + \delta \phi_1 I_k^{2,2}(t) + \left(\delta \phi_2 \sum_{a=2,5}^{s=3} I_k^{a,s}(t) \right) + \left(\delta \phi_3 \sum_{a=2,5}^{s=4} I_k^{a,s}(t) \right) + \left(\delta \phi_4 \sum_{a=2,5}^{s=5} I_k^{a,s}(t) \right) + \left(\delta \phi_5 \sum_{a=2,5}^{s=6} I_k^{a,s}(t) \right) + \gamma(t) \left(\sum_a I_k^{a,s}(t) + S_k(t) \right) + W_k(t) + E_k(t) \right] - S_k(t) \sum_j (\lambda_{k,j}(t)) ; \text{Susceptible}$
2. $\frac{dI_k^{0,1}(t)}{dt} = S_k(t) \sum_j (\lambda_{k,j}(t)) - I_k^{1,0}(t)(\psi + \mu + \sigma) ; \text{Acute HIV Infection undetected}$
3. $\frac{dI_k^{0,2}(t)}{dt} = I_k^{0,1}(t)\psi - I_k^{0,2}(t)(\rho_1 + \tau_k^1(t) + \mu + \sigma) ; \text{HIV Positive with CD4} > 500, \text{undetected}$
4. $\frac{dI_k^{0,3}(t)}{dt} = I_k^{0,2}(t)\rho_1 - I_k^{0,3}(t)(\rho_2 + \tau_k^2(t) + \mu + \sigma) ; \text{HIV Positive with CD4 } 499\text{-}350, \text{undetected}$
5. $\frac{dI_k^{0,4}(t)}{dt} = I_k^{0,3}(t)\rho_2 - I_k^{0,4}(t)(\rho_3 + \tau_k^3(t) + \mu + \sigma) ; \text{HIV Positive with CD4 } 349\text{-}200, \text{undetected}$
6. $\frac{dI_k^{0,5}(t)}{dt} = I_k^{0,4}(t)\rho_3 - I_k^{0,5}(t)(\rho_4 + \tau_k^4(t) + \mu + \sigma) ; \text{HIV Positive with CD4 } 199\text{-}50, \text{undetected}$
7. $\frac{dI_k^{0,6}(t)}{dt} = I_k^{0,5}(t)\rho_4 - I_k^{0,6}(t)(\delta + \tau_k^5(t) + \mu + \sigma) ; \text{AIDS, CD4} < 50, \text{undetected}$
8. $\frac{dI_k^{1,2}(t)}{dt} = I_k^{0,2}(t)\tau_k^1(t) - I_k^{1,2}(t)(\varphi + \mu + \sigma) ; \text{CD4} > 500, \text{on 1st Line ART, non-suppressed VL}$
9. $\frac{dI_k^{1,3}(t)}{dt} = I_k^{0,3}(t)\tau_k^2(t) - I_k^{1,3}(t)(\varphi + \mu + \sigma) ; \text{CD4 } 350\text{-}499, \text{on 1st Line ART, non-suppressed VL}$
10. $\frac{dI_k^{1,4}(t)}{dt} = I_k^{0,4}(t)\tau_k^3(t) - I_k^{1,4}(t)(\varphi + \mu + \sigma) ; \text{CD4 } 200\text{-}349, \text{on 1st Line ART, non-suppressed VL}$
11. $\frac{dI_k^{1,5}(t)}{dt} = I_k^{0,5}(t)\tau_k^4(t) - I_k^{1,5}(t)(\varphi + \mu + \sigma) ; \text{CD4 } 50\text{-}199, \text{on 1st Line ART, non-suppressed VL}$
12. $\frac{dI_k^{1,6}(t)}{dt} = I_k^{0,6}(t)\tau_k^5(t) - I_k^{1,6}(t)(\varphi + \mu + \sigma) ; \text{CD4} < 50, \text{on 1st Line ART, non-suppressed VL}$

13. $\frac{dI_k^{2,2}(t)}{dt} = I_k^{1,2}(t)\varphi - I_k^{2,2}(t)(\delta\phi_1 + \vartheta + \mu + \sigma)$; *CD4 >500, on 1st Line ART, suppressed VL*
14. $\frac{dI_k^{2,3}(t)}{dt} = I_k^{1,3}(t)\varphi - I_k^{2,3}(t)(\delta\phi_2 + \vartheta + \mu + \sigma)$; *CD4 350-499, on 1st Line ART, suppressed VL*
15. $\frac{dI_k^{2,4}(t)}{dt} = I_k^{1,4}(t)\varphi - I_k^{2,4}(t)(\delta\phi_3 + \vartheta + \mu + \sigma)$; *CD4 200-349, on 1st Line ART, suppressed VL*
16. $\frac{dI_k^{2,5}(t)}{dt} = I_k^{1,5}(t)\varphi - I_k^{2,5}(t)(\delta\phi_4 + \vartheta + \mu + \sigma)$; *CD4 50-199, on 1st Line ART, suppressed VL*
17. $\frac{dI_k^{2,6}(t)}{dt} = I_k^{1,6}(t)\varphi - I_k^{2,6}(t)(\delta\phi_5 + \vartheta + \mu + \sigma)$; *CD4 50-199, on 1st Line ART, suppressed VL*
18. $\frac{dI_k^{3,3}(t)}{dt} = I_k^{2,2}(t)\vartheta - I_k^{3,3}(t)(\rho_2 + r + \mu + \sigma)$; *CD4 350-499, on 1st Line ART failure*
19. $\frac{dI_k^{3,4}(t)}{dt} = I_k^{2,3}(t)\vartheta + I_k^{3,3}(t)\rho_2 - I_k^{3,4}(t)(\rho_3 + r + \mu + \sigma)$; *CD4 200-349, on 1st Line ART failure*
20. $\frac{dI_k^{3,5}(t)}{dt} = I_k^{2,4}(t)\vartheta + I_k^{3,4}(t)\rho_3 - I_k^{3,5}(t)(\rho_4 + r + \mu + \sigma)$; *CD4 50-199, on 1st Line ART failure*
21. $\frac{dI_k^{3,6}(t)}{dt} = I_k^{2,5}(t)\vartheta + I_k^{2,6}(t)\vartheta + I_k^{3,5}(t)\rho_4 - I_k^{3,6}(t)(\delta + r + \mu + \sigma)$; *CD4 <50, on 1st Line ART failure*
22. $\frac{dI_k^{4,3}(t)}{dt} = I_k^{3,3}(t)r - I_k^{4,3}(t)(\varphi + \mu + \sigma)$; *CD4 350-499, on 2nd Line ART, non-suppressed VL*
23. $\frac{dI_k^{4,4}(t)}{dt} = I_k^{3,4}(t)r - I_k^{4,4}(t)(\varphi + \mu + \sigma)$; *CD4 200-349, on 2nd Line ART, non-suppressed VL*
24. $\frac{dI_k^{4,5}(t)}{dt} = I_k^{3,5}(t)r - I_k^{4,5}(t)(\varphi + \mu + \sigma)$; *CD4 50-199, on 2nd Line ART, non-suppressed VL*
25. $\frac{dI_k^{4,6}(t)}{dt} = I_k^{3,6}(t)r - I_k^{4,6}(t)(\varphi + \mu + \sigma)$; *CD4 <50, on 2nd Line ART, non-suppressed VL*
26. $\frac{dI_k^{5,3}(t)}{dt} = I_k^{4,3}(t)\varphi - I_k^{5,3}(t)(\delta\phi_2 + \xi + \mu + \sigma)$; *CD4 350-499, on 2nd Line ART, suppressed VL*
27. $\frac{dI_k^{5,4}(t)}{dt} = I_k^{4,4}(t)\varphi - I_k^{5,4}(t)(\delta\phi_3 + \xi + \mu + \sigma)$; *CD4 200-349, on 2nd Line ART, suppressed VL*
28. $\frac{dI_k^{5,5}(t)}{dt} = I_k^{4,5}(t)\varphi - I_k^{5,5}(t)(\delta\phi_4 + \xi + \mu + \sigma)$; *CD4 50-199, on 2nd Line ART, suppressed VL*
29. $\frac{dI_k^{5,6}(t)}{dt} = I_k^{4,6}(t)\varphi - I_k^{5,6}(t)(\delta\phi_5 + \xi + \mu + \sigma)$; *CD4 <50, on 2nd Line ART, suppressed VL*
30. $\frac{dI_k^{6,4}(t)}{dt} = I_k^{5,3}(t)\xi - I_k^{6,4}(t)(\rho_3 + \mu + \sigma)$; *CD4 200-349, on 2nd Line failure*
31. $\frac{dI_k^{6,5}(t)}{dt} = I_k^{5,4}(t)\xi + I_k^{6,4}(t)\rho_3 - I_k^{6,5}(t)(\rho_4 + \mu + \sigma)$; *CD4 50-199, on 2nd Line ART, suppressed VL*
32. $\frac{dI_k^{6,6}(t)}{dt} = I_k^{5,5}(t)\xi + I_k^{5,6}(t)\xi + I_k^{6,5}(t)\rho_4 - I_k^{6,6}(t)(\delta + \mu + \sigma)$; *CD4 <50, on 2nd Line ART, suppressed VL*

S_k are the susceptible in each risk category k ($k=1$ no risk women, $k=2$ low risk women, $k=3$ high risk women, $k=4$ female sex workers, $k=5$ no risk men, $k=6$ low risk men, $k=7$ high risk men, $k=8$ bisexual MSM, $k=9$ exclusive MSM, $k=10$ clients of FSW). $I_k^{a,s}$ is used for all HIV+ stages, where superscript a indicates the treatment status in the model, ($a=0$ is No ART, $a=1$ is 1st line ART non-suppressed VL, $a=2$ is 1st line ART suppressed VL, $a=3$ is 1st line failure, $a=4$ is 2nd line ART non-suppressed VL, $a=5$ is 2nd line ART suppressed VL, $a=6$ is 2nd line failure). Superscript s , indicates the CD4+ count stage of disease: $s=1$ is Acute HIV Infection, $s=2$ is CD4+ count >500 cell/mm³, $s=3$ is CD4+ count 350 to 499 cell/mm³, $s=4$ is CD4+ count 200 to 349 cell/mm³, $s=5$ is CD4+ count 50 to 199 cell/mm³, $s=6$ is CD4+ count <50 cell/mm³.

2.2.2 Force of Infection

The expression for force of infection ($\lambda_{k,j}(t)$), contains the specific transmission rate for any given individual of risk category k who establishes effective contact with other individual from category j , where k is the choosing partner and j is the chosen one.[15]. Equations 33 to 35 describe this process for three forms of sexual transmission allowed in the model, namely female to male, male to female, and male to male.

Equation 33: Force of infection for the transmission of HIV-1 from females (j) to males (k),

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum \left(\left(\frac{I_j^{a,s}}{\sum I_j^{a,s} + S_j} \right) \left(\left(1 - \left((1 - \beta_f L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_f L^{a,s} \zeta)^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ for } j=2, 3, 4.$$

And $k= 6, 7, 8, 10$.

Equation 34: Force of infection for the transmission of HIV-1 from males (j) to females (k),

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum \left(\left(\frac{I_j^{a,s}}{\sum I_j^{a,s} + S_j} \right) \left(\left(1 - \left((1 - \beta_m L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_m L^{a,s} \varsigma)^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ for } j=6, 7, 8, 10, \text{ and } k=2, 3, 4.$$

Equation 35: Force of infection for the transmission of HIV-1 from females (j) to males (k),

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum \left(\left(\frac{I_j^{a,s}}{\sum I_j^{a,s} + S_j} \right) \left(\left(1 - \left((1 - \beta_{msm} L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_{msm} L^{a,s} \varsigma)^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ for } j=8, 9, \text{ and } k=8, 9.$$

Irrespective of the type of exposure, the principle in these equations stays the same as the changing rate in susceptible and infectious individuals at each point in time determines the overall probability of transmission.

Condom effectiveness is incorporated with the term $\left(1 - \beta_f L^{a,s} (1 - \varsigma)\right)^{\alpha_{k,j}(v_k(t))}$. The first part of this term reflects the reduction in the probability of infection in a single act with an infected partner and using a condom. Here the symbol ς is the risk reduction in HIV transmission given the use of condom [16]. This term is raised to the numbers of acts $\alpha_{k,j}$ occurring in the partnership between individual k and j , multiplied by the annual proportion of sex acts protected with condom for any person in group k , $v_k(t)$, according to local data (Table 1).

On the other hand, risk ratios for transmission due to use of ART are incorporated with matrix $L^{a,s}$. This term multiplies the transmission probability per act (β_m, β_f or β_{msm})

according to the disease stage and treatment status (s and a) of contact in category j . Specific transmission cofactor values can be consulted in **Table 1**.

2.2.3 Mixing matrix and contact patterns in the model

In equation 35 the term $p_{k,j}$ indicates the matrix of mixing between different risk categories in the model.

Equation 36: probability of interaction for a given individual of category k , with someone from risk group j .

$$P_{k,j} = (eM_{k,j}) + \left[i_{k,j}(1 - e) \left(\frac{N_j c_j}{\sum_j N_j c_j} \right) \right]$$

Here, e is the assortativeness parameter. When mixing is fully assortative (i.e. with like) $e = 1$, and $e = 0$ when mixing is completely proportionate. Equation 36, includes a slight modification of the system proposed by Garnett et al. (1999)[11], since it includes a mixing preference matrix $M_{k,j}$ which means that during a fully assortative scenario ($e=1$) individuals from risk group k choose the partner exclusively according to their preference, as opposed to proportional mixing where coupling happens as a function of availability of partners in the sexually active pool of category j , when j is one of the “allowed” partnerships in the system. This restriction is reflected with the identity matrix $i_{k,j}$. A graphical description of identity and preference matrix can be found in **Figure 3**. c_j is the partner change rate in group j . N_j is the sum of people in all stages included in sexual mixing, this means, available for coupling between k and j .

Equation 37: Matrix of available partners for each risk category j .

$$N_j = \sum_{s=1}^5 I_k^{a,s} + S_j$$

The mixing matrix described in equation 36 is calculated separately for each partnership formed between risk groups, leaving the possibility of imbalances given that risk group k might demand more or less partnerships than risk group j can provide. For this reason the mixing matrix is adjusted, following the methods described by Garnett et al.[11].

Equation 38: mixing matrix balancing

$$\Delta_{kj} = \frac{c_j p_{j,k} N_j}{c_k p_{k,j} N_k}$$

$$c_k = c_k \Delta_{kj}^\eta$$

$$c_j = c_j \Delta_{kj}^{-(1-\eta)}$$

According to this system, the disparity between risk groups is first estimated (Δ_{kj}) and then use to redefine the partnership formation rates of groups j and k . Symbol η is the balancing coefficient and determines the extent at which each partner commits to balance (i.e. adjust) the partnership formation rates.

2.2.4 Initial conditions and numerical solution

Ordinary differential equations (ODE) were programmed and solved numerically using MATLAB® R2012b and the Runge-Kutta integration algorithm. The solution involves an algorithm coded to iterate in a loop according to a start point, time-step and stop time defined along with the epidemic initial conditions. The model considers a start point or times zero (t_0) in 1975 with a time-step of 0.05 years. The simulation was run until 2014.

The start of the epidemic is introduced as a seed or initial HIV prevalence in 1975. This initial prevalence was let to vary in the calibration process within the limits seen in **Table 1**. This seed was only applied for high risk groups, namely $MSM_{exclusive}$, $MSM_{bisexual}$ and FSW, considering the initial reports of the epidemic in the country [1].

Equation 39: Seeding of HIV epidemic in the model in FSW, $MSM_{exclusive}$ and $MSM_{bisexual}$

$$I_k^{a,s}(t_{start}) = f \Omega_k(seed) N_0, \text{ for } a=0, s=2 \text{ and } k=4$$

$$I_k^{a,s}(t_{start}) = (1 - f) \Omega_k(seed) N_0, \text{ for } a=0, s=2 \text{ and } k= 8, \dots, 9$$

Here, f is the proportion of females in the total population of Bogota (**table 1**), and Ω_k is a matrix containing the proportion of each subpopulation k in population N_0 . t_{start} is the time of the start of the epidemic, and N_0 is the total population in the model at time 0.

2.3 Data and parameterization

A thorough search for demographic, biological, epidemiological, behavioral and programmatic data of HIV in Bogota was carried to parameterize the model. Table 1 synthesizes the search results while stating which parameters were used for calibration.

2.3.1 Behavior change: condom use in the model

Behavior changes have been shown to have modified the course of the HIV epidemic, such as for example, a reduction of sexual partners in Uganda and Zimbabwe [17, 18], and the drastic increases in condom use among sex workers in Thailand [19].

In this model, behaviors are summarized by the partner change rates in each modelled sub-population and the rates of condom use. The first component was set to be fixed over time in the simulation, mainly because of the lack of evidence to reproduce a varying time-trend of partner change rates. Condom use on the other hand was incorporated with risk-group and time variations, by interpolating point estimations of proportion of acts protected per year in each category, as reported by several surveys cited in **Table 1**.

Table 1: Parameters and calibration information

	Symbol	Value	Calibration Range		Prior Distribution	Source
			Low	High		
Demographic and Initial Model Conditions						
Total Population 15 to 49 years at time 0 (1970)	N_0	906000	-	-	-	[20]
Population growth rate	$Y(t)$	See below	-	-	-	[20]
Background mortality rate	μ	1/65 years	-	-	-	[20]
Rate of ceasing sexual activity	σ	1/34 years	-	-	-	[20]
Proportion of Female population	f	0.52	-	-	-	[20]
Fraction of Sexually Active Women	$1 - \Omega_1$	0.842	-	-	-	[20]
Fraction of FSW in female population	Ω_4	calibrated	0.005	0.02	Uniform	[12]
Fraction FSW out to Low Risk Group	$postSW$	0.5				Assumption
FSW turnover rate	γ	Calibrated	1	20	Triangle	[21]
Fraction of female in High Activity category	Ω_3	0.0298	-	-	-	[10]
Fraction of female Low Activity category	Ω_2	$1 - (\Omega_1 + \Omega_3 + \Omega_4)$	-	-	-	Assumption
Fraction male High Activity category	Ω_7	Calibrated	0.09	0.14	Uniform	[10, 22]
Fraction of male in MSM category	Ω_8	Calibrated	0.021	0.067	Uniform	[14]
Fraction of MSM in Bisexual activity category	Ω_9	Calibrated	0.11	0.43	Uniform	[14]
Fraction of male in CFSW in category	Ω_{10}	Calibrated	0.05	0.15	Uniform	[23]
Fraction of male in Low Activity category	Ω_6	$1 - (\Omega_5 + \Omega_7 + \Omega_8 + \Omega_9 + \Omega_{10})$	-	-	-	Assumption
Year of Start of the epidemic		1975	-	-		Assumption

Chapter 2: Estimating the impact of Antiretroviral Treatment in the HIV epidemic of Bogota

Seed (HIV prevalence at time 0)	seed	-	0.0001	0.0025	Uniform	Assumption
Behaviour parameters						
Proportion testing for HIV per year ($H_k(t)$)	$H_{msm}(2006)$	Calibrated	0.122	0.177	Uniform	[24]
	$H_{msm}(2010)$	Calibrated	0.197	0.305	Uniform	[14]
	$H_{fsw}(2007)$	Calibrated	0.421	0.506	Uniform	[25]
	$H_{fsw}(2012)$	Calibrated	0.463	0.537	Uniform	[21]
	$H_{men}(2007)$	Calibrated	0.049	0.065	Uniform	[26]
	$H_{women}(2005)$	Calibrated	0.040	0.045	Uniform	[27]
	$H_{women}(2005)$	Calibrated	0.086	0.098	Uniform	[28]
HIV testing cofactor according to CD4 count (F_s)	$F1$ (CD4 >500)	Calibrated	0.01	1	Uniform	Assumption
	$F2$ (CD4 350-500)	Calibrated	0.01	1	Uniform	Assumption
	$F3$ (CD4 200-349)	Calibrated	0.01	1	Uniform	Assumption
	$F4$ (CD4 50-199)	Calibrated	1	3	Uniform	Assumption
Proportion of sex acts protected with condom per year by risk group ($v_k(t)$)	$v_{all}(<1984)$	Calibrated	0.010	0.100	Uniform	Assumption
	$v_{msm}(2006)$	Calibrated	0.590	0.667	Uniform	[24]
	$v_{msm}(2010)$	Calibrated	0.530	0.650	Uniform	[14]
	$v_{fsw}(2007)$	Calibrated	0.739	0.811	Uniform	[25]
	$v_{fsw}(2012)$	Calibrated	0.956	0.982	Uniform	[21]
	$v_{hetero}(1995)$	Calibrated	0.072	0.101	Uniform	[29]
	$v_{low}(2000)$	Calibrated	0.104	0.136	Uniform	[30]
	$v_{high}(2000)$	Calibrated	0.020	0.24	Uniform	[30]
	$v_{low}(2005)$	Calibrated	0.121	0.148	Uniform	[27]
	$v_{high}(2005)$	Calibrated	0.200	0.415	Uniform	[27]
	$v_{low}(2010)$	Calibrated	0.146	0.170	Uniform	[28]
	$v_{high}(2010)$	Calibrated	0.260	0.444	Uniform	[28]
Year of Condom use increase (Behaviour change)	condyear80	Calibrated	1984	1994	Uniform	Assumption
Partner Change Rate by risk group per year (c_k)	c_{low_women}	0.9522	-	-	-	[10]
	c_{high_women}	Calibrated	2	4	Uniform	[10]
	c_{low_men}	1	-	-	-	[10]
	c_{high_men}	Calibrated	2	4	Uniform	[10]
	c_{fsw}	638	159	1117	Triangle	[21]
	c_{bi}	10	2	45	Triangle	[14]
	c_{msm}	10	2	45	Triangle	[14]
Average number acts per partnership by risk grouper year (α_k)	c_{cfsw}	-	2	30	Uniform	Assumption
	α_{low}	53	-	-	-	[31]
	α_{high}	2	-	-	-	Assumption
	α_{fsw}	1	-	-	-	Assumption
Assortativeness coefficient	α_{msm}	4	-	-	-	[14]
	e	-	0	1	Uniform	Assumption
Natural History of Disease						
Per-Act Female to Male HIV transmission probability	β_f	Calibrated	0.00114	0.009	Uniform	[9]
Per-Act Male to female HIV transmission probability	β_m	Calibrated	0.0008	0.002	Uniform	[9]
Per-Act MSM HIV transmission probability (combined)*	β_{msm}	Calibrated	0.002	0.025	Uniform	[32]
Average time in Early HIV infection stage (years)	ψ	0.25	-	-	-	[8]
Progression rates through CD4 stages (years)	P_1, P_2, P_3, P_4	2.4	-	-	-	[7]
Progression rate to death when CD4 <50 cell/mL (years)	δ	0.75	-	-	-	[8]
Relative Infectiousness during Early HIV Infection	$L^{0,1}$	calibrated	4.47	18.18	Uniform	[9]
Interventions						
Recruitment rate into ART by stage of disease per year $C_s(t)$	$C_5(2001)$	calibrated	0.56	5.98	Uniform	(30)
	$C_4(2001)$	Calibrated	0.23	3.96	Uniform	(30)
	$C_3(2001)$	Calibrated	0.23	2.53	Uniform	(30)
	$C_2(2001)$	Calibrated	0.19	1	Uniform	(30)
	$C_1(2001)$	Calibrated	0.16	1.02	Uniform	(30)
	$C_5(2009)$	Calibrated	2.97	11.7	Uniform	(30)
	$C_4(2009)$	Calibrated	1.99	11.7	Uniform	(30)
	$C_3(2009)$	Calibrated	1	2.99	Uniform	(30)
	$C_2(2009)$	Calibrated	0.52	2.96	Uniform	(30)
	$C_1(2009)$	Calibrated	0.43	2.96	Uniform	(30)
Annual retention rate into ART	r	Calibrated	0.4	0.9	Uniform	[33]
Year of ART start	-	1997	-	-	-	[34]
HIV transmission proportional reduction due to ART	$L^{0,5}$ For $a=2,5$	Calibrated	0.73	0.99	Uniform	[35]
HIV transmission proportional reduction non-suppressed ART	$L^{0,5}$ For $a=1,4$	0.5	-	-	-	Assumption
Annual rate of failure on 1 st line ART	ϑ	Calibrated	0.05	0.25	Uniform	[36]
Annual rate of failure on 2 nd & 1 st line ART	ξ	0.23	-	-	-	[37]
Average time spent in non-suppressed VL with ART (years)	φ	0.5	-	-	-	[38]
Relative disease progression reduction caused by ART by stage of disease	Φ_3	95%	-	-	-	[7]
	Φ_4	91%	-	-	-	[7]
	Φ_5	72%	-	-	-	[7]
Condom efficacy on HIV transmission	ζ	Calibrated	0.8	0.95	Uniform	[39, 40]

Equation 40: Linear interpolation,

$$f(x) = Y_a + (Y_b - Y_a) \frac{X - X_a}{X_b - X_a}$$

Linear interpolation finds intermediate values from a function underlying the known data points. Thus, for two given data points (X_a, Y_a) and (X_b, Y_b) , and a point in time X between X_a and X_b .

However, the amount of information available to reconstruct this trend was not enough to confidently reproduce changes in condom use in the first years of the epidemic. It is likely, and has been observed elsewhere [41], that the recognition of HIV virus as the cause of AIDS could have prompted an increase in condom use. This increase in risk perception might have had an important role in shaping the early epidemic, and as such it was included in this model by calibrating the start of condom use increase, between 1983 and the time of the first point estimation of condom use per risk group.

2.3.2 Modelling ART

The event of enrolling HIV+ individuals into ART is a complex process that involves many steps and implies several barriers encountered between the moment of diagnosis and the final delivery of antiretroviral drugs. It was not the purpose of this research to investigate and reproduce the cascade of care (but rather to assess the impact of those known to be treated) therefore this process was simplified here. Making use of the relevant programmatic indicators and some assumptions based in previous observations, recruitment into ART was modelled based in three fundamental sources of variation/information: changes in the time trend of ART scale-up over time, differential rates by CD4+ count stage, and differential access by risk group.

The first and more important source of information was the dataset from *Cuenta de alto costo*⁴. This dataset collects periodical programmatic information of HIV patients around the country. For Bogota 7161 records were retrieved, and data regarding CD4+ count at the time of diagnosis and at the time of ART initiation was analysed [33]. The first observation from this analysis was that the expansion in the number of HIV+ on ART in Bogota increased exponentially over time (**Figure 4**).

Looking more closely into the characteristics of individuals receiving ART behind these numbers, we can find a changing pattern in the CD4+ count at which people had been recruited into treatment. The median time to ART (i.e. the time difference between date of HIV diagnosis and date of treatment initiation) was estimated and stratified by CD4+ cell count range at the time of ART initiation. This calculation was performed over 2351 records eligible after excluding those records without all the required information (**Figure 5**).

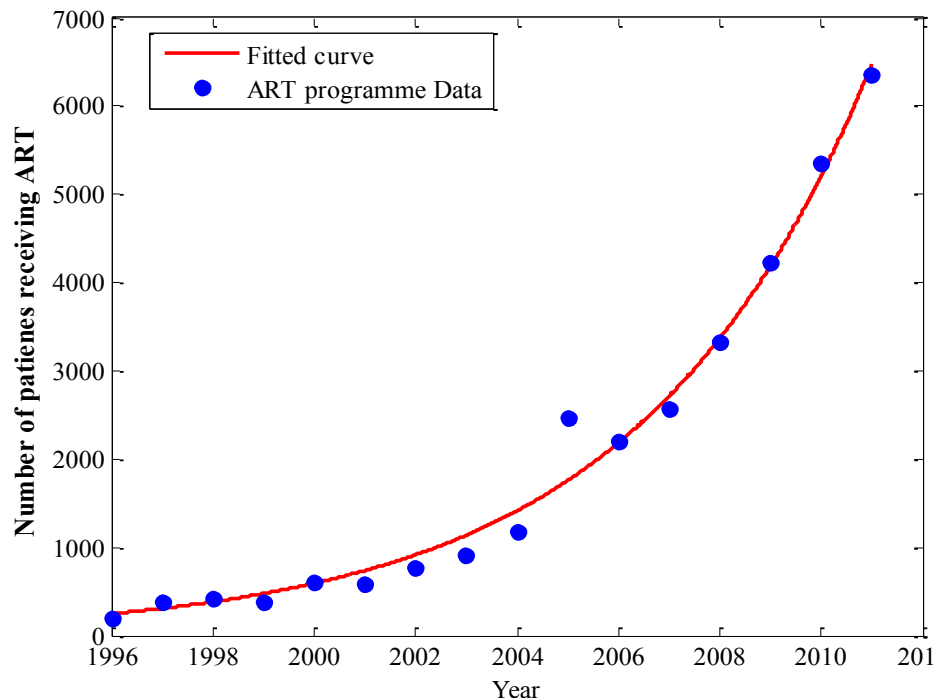


Figure 4 Number of new patients receiving ART in Bogota, 1997-2011: Blue dots represent the annual number of people recruited into ART from 1997 to 2011, according to Ministry of health records for Bogota. Red line is the exponential function fitted to the observed data.

⁴ *Idem*

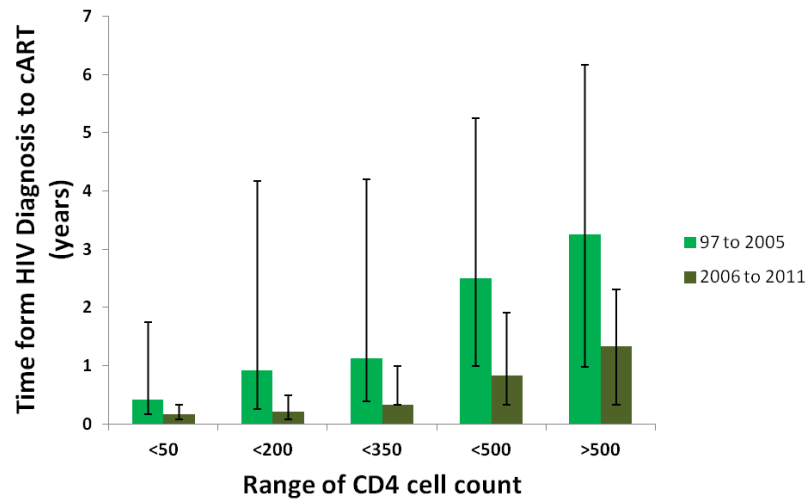


Figure 5 Median times between HIV diagnosis and ART initiation in Bogota, by time period: Estimated from a sample of 2351 records eligible for analysis in MoH datasets. Light green bars present the median time in years for individuals diagnosed between 1997 and 2005. Dark green bars for those diagnosed between 2006 and 2011. Error bars reflect the Inter-quartile Range (25 percentile and 75 percentile).

The median time between HIV diagnosis and ART decreased overtime and across all CD4+ ranges shown in **Figure 5**. This observation suggested that time-varying rates of recruitment by clinical stage were an important variable to account for when modelling ART scale-up in Bogota. It is worth noting that ART was allowed at every disease stage following this observation, contrary to what is stated in the national guidelines as the threshold for starting an HIV+ adult into ART in Colombia(i.e. symptomatic illness or CD4+ count less than 350 cell/mm³) [42].

The third component considered as a source of variation in ART delivery (i.e. variations in access to ART according to group of exposure) was approximated through estimations of HIV testing in different sub-populations. Using data from cross-sectional studies performed in Bogota among MSM, FSW and the general population (**table 1**), time-trends of HIV testing rates per year were reconstructed, by linearly interpolating point estimations as available. Testing trends for male and female were applied equally to both high and low activity classes.

These components were brought together in a single term $\tau_k^s(t)$. This is explained below in equation 41. Thus, recruitment rate works as a function of individual HIV-testing behaviours and programmatic efforts to link PLHA to care. Equation 41 describes and puts together the pieces of information mentioned before.

Equation 41: Recruitment rate into ART over time in the model

$$\tau_k^s(t) = H_k(t) F_s G_s(t)$$

HIV testing by
risk group
Testing co-factor
by stage of
disease
Reflects waiting
time between
diagnosis and ART
by CD4+ stage

Where $H_k(t)$ is the function of HIV-testing rates/year, F_s is a factor included to reflect the possible variations in testing rates by clinical stage, considering that symptomatic disease might lead to health-seeking behaviours (values can be found in **Table 1**). Finally, $G_s(t)$ incorporates the information about time-to-ART as shown before in **Figure 5**. As explained above, the scale-up of ART appear to have followed an exponential trend over time, thus $G_s(t)$ was formulated as the exponential interpolation of times to ART (rates) (**Figure 5**) for periods 1997 to 2005, and 2006 to 2011. The median point of this time ranges was used for interpolation.

Equation 42: Exponential interpolation

$$C_s(t) = \exp \left[\ln(C_s(2001)) + [\ln(C_s(2009)) - \ln(Y_a)] \frac{t - 2001}{2009 - 2001} \right]$$

This equation was solved for each disease stage s (for $s = 2, \dots, 6$), using data points for 2001 and 2009 that were also calibrated, with prior ranges shown in **Table 1**.

2.4 Model Calibration

2.4.1 Parameter sampling

Model calibration was carried out by fitting model outcomes to data on HIV prevalence among FSW, MSM and antenatal clinics, as well as numbers of deaths due to AIDS and patients receiving ART. Parameters were sampled from prior ranges obtained from the original sources of information or assumed in some cases. Complete details of prior ranges can be found in **Table 1**. A *Latin Hypercube Sampling (LHS)* technique was used, which provides a computationally efficient approach to sampling multidimensional parameter space [43, 44]. Briefly, *LHS* starts with an iterative process of drawing parameter values to populate a table -LHS table-, sized $p \times i$, where p is the number of parameters to be sampled and i is the number of desired runs. Sampling is made by stating a prior distribution of the parameter sample space, which is then sliced in equi-probable sections. These sections are sampled without replacement, and a value is chosen from within that range. A total of 61 parameters were chosen for calibration.

2.4.2 Fitting model outcomes to data

Model outcomes were systematically compared against data from the city as follows.

a. HIV prevalence in MSM:

HIV prevalence estimations from available cross-sectional studies in Bogota were used as shown in table 2. The modelling outcome fitted here was overall HIV prevalence amongst all MSM (i.e. MSM_{ex} and MSM_{bi} combined).

Table 2: HIV prevalence studies among MSM in Bogota

<i>Year of observation</i>	<i>Sample size</i>	<i>Prevalence</i>	<i>Source</i>
1999	643	20.4%	[45]
2002	660	19.7%	[46]
2006	630	11%	[47]
2010	485	15%	[14]
2012	1000	12%	[48]

b. HIV Prevalence among FSW:

Similarly, information regarding HIV prevalence among female sex workers was available from studies carried out in Bogota, as can be seen in table 3.

Table 3: HIV prevalence studies among FSW in Bogota

<i>Year of observation</i>	<i>Sample Size</i>	<i>Prevalence</i>	<i>Source</i>
2002	514	0.78%	[49]
2007	529	0.76%	[25]
2012	706	0.20%	[50]

c. *HIV Prevalence in Antenatal Clinics (ANC):*

Data from antenatal clinics was fitted to overall HIV prevalence among women in the model, irrespective of their risk category. Data can be seen in **table 4**.

Table 4: HIV prevalence studies among pregnant women in Bogota

<i>Year of observation</i>	<i>Sample size</i>	<i>Prevalence</i>	<i>Source</i>
2003	139	0.72%	[51]
2009	2847	0.035%	[52]

d. *Mortality due to HIV/AIDS:*

Time-series of reported annual numbers of deaths due to AIDS (total and among males) were available from *Observatorio Nacional de la Gestión en VIH* (National Observatory of HIV Management)⁵. Full dataset can be seen in **table 5**.

Mortality reports by general causes and AIDS in Colombia have been shown to be susceptible to underreporting [53, 54]. For this reason, the matching modelling outcome to data on reported deaths was a modification of total AIDS mortality in the model, by including one parameter that incorporates variation in underreporting over time (M_{report}). Therefore:

⁵ *Observatorio Nacional de la Gestión en VIH* routinely collects and publishes data on HIV report cases, mortality and care. Available in the internet at http://www.minsalud.gov.co/salud/Paginas/Observatorio_menu_monitoreo_evaluacion_vigilancia_salud_b.aspx

Equation 43. Model outcome for reported deaths due to AIDS

$$ModelAIDSdeaths(t) = TotalAIDSmortality(t) \times Underreport(t)$$

Underreporting over time was assumed to have followed a linear trend connecting the points

$M_{report} \sim U(0, 0.9)$ in 1983 and 90% in 2010 according previous estimations [55]

e. Number of people recruited into ART:

Similarly, *Observatorio Nacional de la Gestión en VIH* provided time-series data on annual numbers of people recruited into ART from 1997 to 2011. (**Table 5**)

Table 5: Reported mortality due to AIDS and people receiving ART in Bogota

<i>Year</i>	<i>Reported Deaths caused by AIDS</i>	<i>Number recruited into ART</i>
1991	108	-
1992	290	-
1993	273	-
1994	396	-
1995	405	-
1996	435	-
1997	310	203
1998	286	159
1999	353	133
2000	422	163
2001	388	202
2002	404	205
2003	391	260
2004	415	331
2005	368	402
2006	348	452
2007	328	495
2008	329	584
2009	272	794
2010	-	883
2011	-	1011

2.4.3 Goodness of fit

The selection of the set of model simulations that better reproduce the data described above, was carried out using Likelihood Estimation.

Likelihoods were independently estimated for each data point and summed to obtain a global likelihood for each simulation. Prevalence data was compared against the matching model outcome using the Log-Likelihood binomial distribution function.

Equation 44: Log-Likelihood function for binomial distribution

$$- \ln L(y, \theta) = \sum_i N_i \theta_i \ln(y_i) + N_i (1 - \theta_i) \ln(1 - y_i)$$

Here, θ the observed prevalence and y is the predicted model prevalence. N is the sample size for prevalence data θ .

For AIDS mortality and ART data, the *Poisson* distribution was assumed:

Equation 45: Log-likelihood estimation for Poisson distributed data

$$\ln \mathcal{L}(y|\theta) = \sum_{i=1}^n (\theta_i \log y_i - y_i - \log \theta_i!)$$

Here, the data-point (θ_i) (e.g. number of AIDS deaths) is being matched against the i_{th} modelled outcome (y_i).

Log Likelihood estimations for each set of parameters were sorted in descending order to select the runs that summed-up up to 95% of the overall probability of the model reproducing the data. These runs are shown in the calibration section of *Results* in this document.

2.5 Plan of analysis

2.5.1 Characterization of HIV epidemic in Bogota

Using the series of fits coherent with data, we use model results to help characterize the epidemic in Bogota as follows.

- A) Determine the distribution of new HIV infection annually Per risk groups.
- B) Determine the source of infections, by determining the distribution of new HIV infections each year that originated from the different risk groups and stages of HIV infections.
- C) Estimated the Population attributable fraction for risk groups in the model.

The first step of analysis was focused on trying to extract useful epidemiological insights out from the calibrated model of HIV transmission in Bogota. More than intending to provide definitive evidence about infection dynamics in this context, this analysis was made as means to explain the posterior results on HIV incidence reduction estimations, while “dissecting” the model mechanics of these simulations.

The simulated epidemic in Bogota was characterized by assessing the distribution of cumulative new HIV infections by sub-population, and also by establishing the source of these infections over time by both risk group and clinical stage of the virus donor in the model. This was carried out in order to provide two points of view on transmission: the relative size of the epidemic in each risk category and unveiling the more active “spreaders” of HIV.

Drivers of the simulated HIV epidemic were identified by estimating Population Attributable Fraction (PAF). In this analysis, a simulated scenario where transmission was removed from specific subpopulations was performed for observing the proportional reduction in cumulative HIV incidence when contrasted against the calibrated model, for each pair of simulation with and without transmission from the relevant risk group

2.5.2 Estimation of retrospective impact of interventions

The impact of antiretroviral treatment was assessed by estimating total and proportional reductions in cumulative incidence of HIV over a period from 1997 to 2014. Three counterfactual scenarios were built to assess the retrospective impact of interventions:

- 1) Baseline scenario - Combined intervention (calibrated model): This is the resulting set of simulations resulting from the model calibration process to all available data from Bogota. In this scenario the level of ART and condom use reflect those reported from the data over time. This scenario represents the best possible representation of the epidemic in Bogota according to this model.
- 2) Condoms only (counterfactual 1): In this scenario, we use the same sets of parameters as in 1) with the exception that we assume that ART was not introduced in the population at all for the whole period between 1997 (when it started) and 2014, therefore the resulting projection shows the epidemic as it would look like if only condoms had been made available. We used this counterfactual for estimating incidence reductions due to ART use.
- 3) ART only (counterfactual 2): In this scenario, condom use in all populations was removed from 1997, meaning that only ART use was represented (starting in 1997 as in 1). This counterfactual was used for estimating incidence reductions due to condom use.

4) No intervention (counterfactual 3): This scenario assumes that neither condom nor ART were allowed in the simulation. This counterfactual was used for estimating total HIV incidence reductions.

To make all the scenarios comparable, and considering that condom use had historically been available as prevention for longer than ART, the above mentioned scenarios were compared from 1997 to date. This means that model projections are exactly the same as the calibrated model for all scenarios until 1997 when interventions were either applied or removed.

These scenarios were implemented initially in all the population in the model, and then were applied over specific risk groups. The first approach explores the overall contribution of each intervention scenario on the subsequent reduction in HIV incidence irrespective of who is intervened. The second approach intends to dissect these contributions by risk group and to establish which component had the largest impact at a population level.

The outcome of choice was always the same for all comparisons, and it was cumulative HIV infections averted in the total population between 1997 and 2014. Absolute and proportional reductions are presented.

Equation 46: Absolute Cumulative HIV infections averted

$$CHIA = \int_a^b \sum_{j,k} S_k^0(t) (\lambda_{k,j}^0(t)) dt - \int_a^b S_k^n(t) \sum_{j,k} (\lambda_{k,j}^n(t)) dt$$

The term $S_k(t) \sum_j (\lambda_{k,j}^0(t))$ is the number of new HIV infections per unit time dt under the No-Intervention counterfactual scenario, symbolized by the superscript 0 over λ . Superscript n in the second term reflects any of the other three scenarios where interventions took place (*i.e.* Condoms only, ART only, and Combined). A proportional estimation of CHIA was also calculated by dividing the expression above by the first term, this is, the cumulative number of cases seen with the No-Intervention counterfactual scenario.

This outcome was estimated for each of the n simulations obtained in the calibration process. Uncertainty around point estimations, in this case the median, is presented with interquartile range (IQR).

To research further the source of HIV incidence reductions in the model, a final modification to the combined scenario was made by setting ART transmission effectiveness to zero. This was done to discriminate between the impact of ART's transmission and survival effects on incidence reduction.

3 RESULTS

3.1 Calibration results

After 500,000 model iterations (*i.e.* combination of parameters), the calibration procedure yielded 412 runs that were accepted under the criteria of the prior limits set on the model

outcomes. From these, 232 sets of parameters were selected as these represented the 95% weight of the cumulative likelihood. **Figures 6** synthesize calibration results.

The posterior distribution from the subset of sampled parameters sets can be seen in Appendix **Figures S1 and S2**. These figures show that transmission probabilities as well as partner change rates among FSW and MSM and the assortativeness parameter (e) were the distributions most influenced (informed) by the calibration procedure in contrast with their prior distribution. No major correlations between parameters were found as can be seen in the correlation matrix in **Figure S3**.

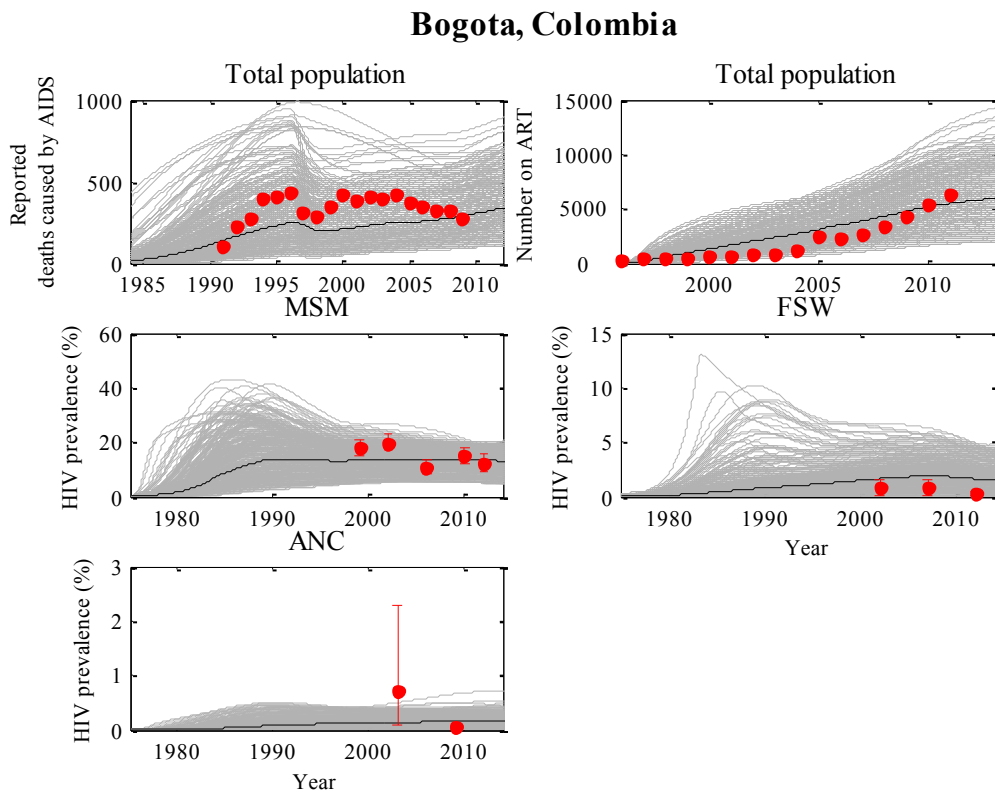


Figure 6 Calibration results to reported mortality by AIDS data (top left), number of patients receiving ART (top right), HIV prevalence among MSM (middle-left), FSW (middle right) and pregnant women (bottom left), in in Bogota.. Grey lines reflect simulations for the 95% of the cumulative likelihood and black solid line is the median of this distribution. Red dots are data points available in each dimension.

3.2 HIV Epidemic Characterization

From this model, it is estimated that a median of 26,200 cumulative HIV infections (IQR 13120) have occurred in Bogota from the beginning of the epidemic to 2014.

The model suggests that HIV incidence may have peaked in 1986 at an estimated median rate of 0.054% person-year (0.03 – 0.09) give uncertainty range with a smooth decline until date. A peak in HIV prevalence in Bogota shows a slight delay with respect with HIV incidence rate as can be seen from **Figure 7**.

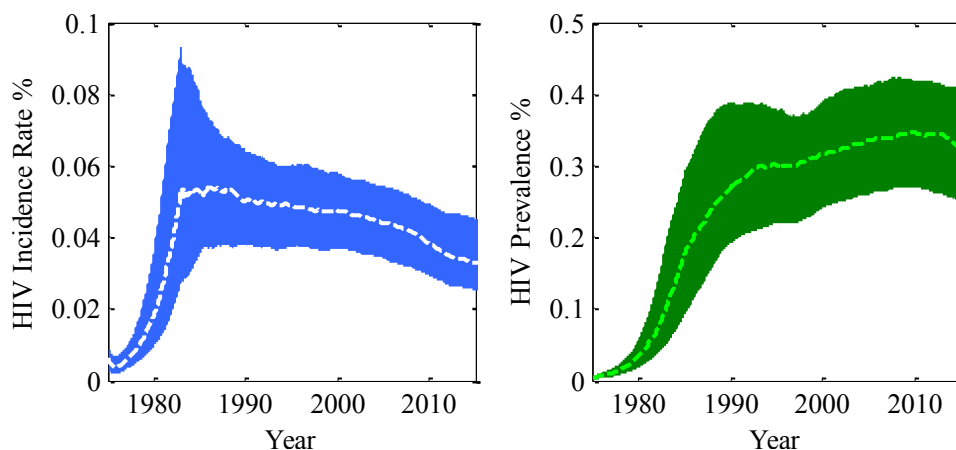


Figure 7 Modelled HIV incidence and prevalence in Bogota, 1975 2014: Left panel shows median HIV incidence estimation with 25/75 percentile around. Right panel shows median estimation of HIV prevalence with 25/75 percentile.

3.2.1 3.2.1. HIV infections by risk group

Distribution of cumulative HIV infections overtime by risk group in the model suggests that over 72% (IQR 17%) of cumulative incidence infections in Bogota have occurred among MSM. It also suggests that heterosexuals (non-sex work related) contributed with around 7% (IQR 6%) of infections until 1980, and reaching 22% by 2014, at the expense of a decrease in

cumulative contribution by the bisexual MSM sub-group. FSW and their clients show a stable contribution (6% to 10%) over time (**Figure 8**).

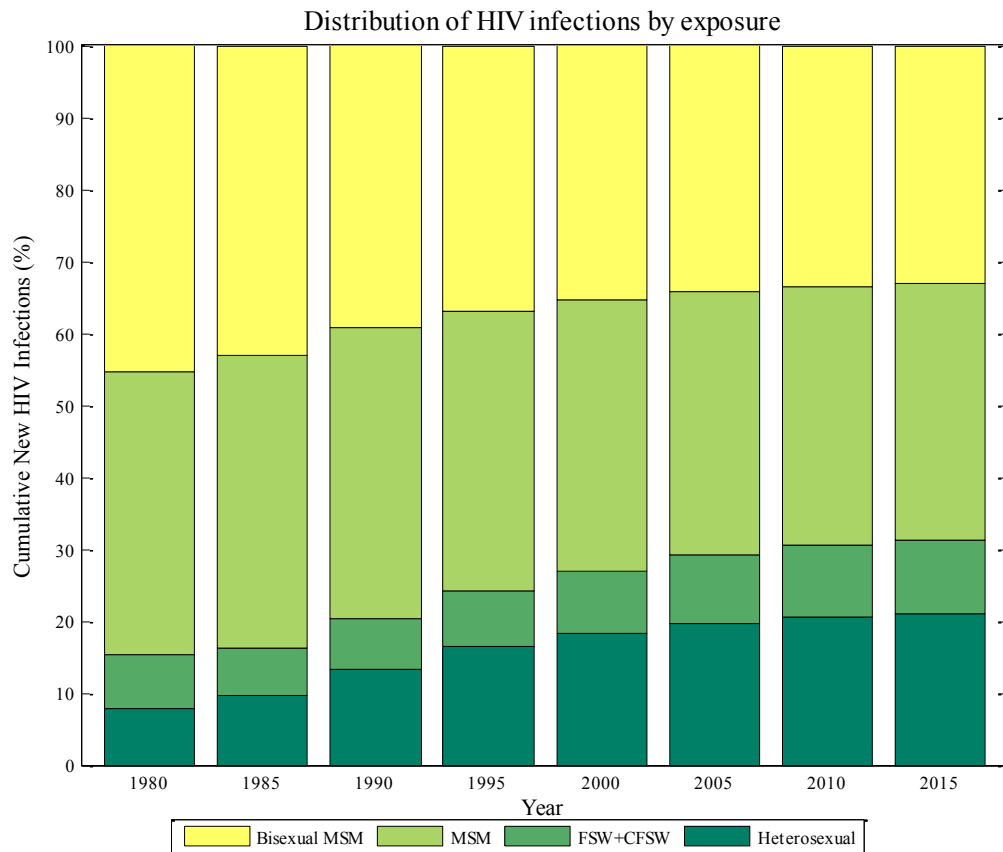


Figure 8: Distribution of cumulative HIV infections by risk group in Bogota, 1975-2015. Proportions showed reflect the median estimation.

3.2.2 Sources of transmission

Approximately 29% (IQR 27%) of new HIV infections in the model arose from infected individuals who were in the Acute stage of infection being this the major source of transmission cumulatively, followed by clinical stages with $CD4^+ > 500 \text{ cell/mm}^3$ (25%, IQR 24%), and the least coming from the stage with $CD4^+ 50-199 \text{ cell/mm}^3$ (11%, IQR 12%)(**Figure 9**).

From the start of the epidemic until 2014, 80% (IQR 16%) of all HIV infections had its source at MSM groups. The most noticeable change is the cumulative number of infections coming from heterosexual groups, with less than 5% in the first decade to increase to 13% (IQR 10%) in the last decade (**Figure 9**).

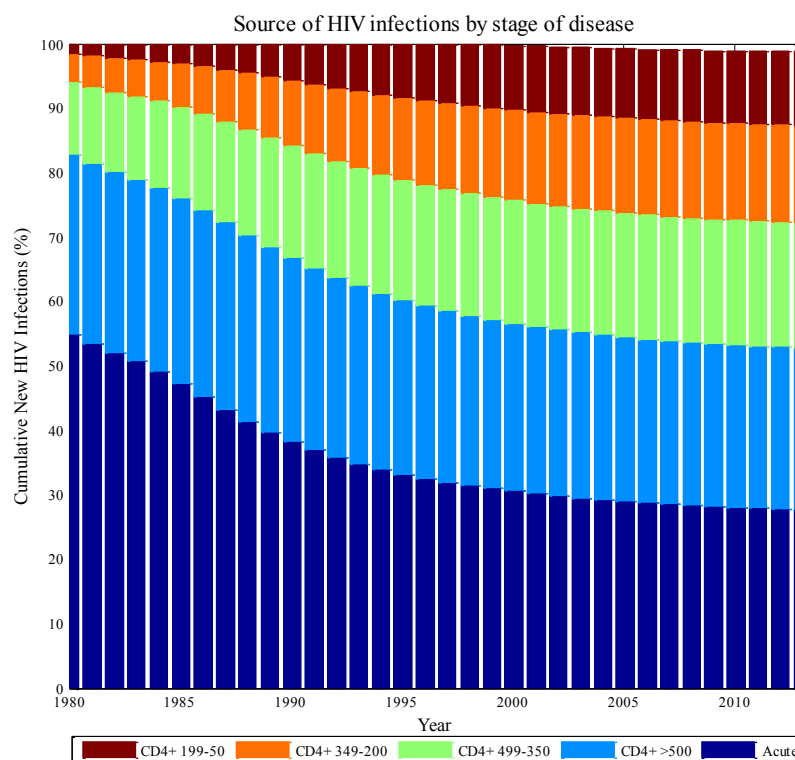


Figure 9 Source of HIV transmission by clinical stage of infection: median cumulative fraction of new infections since the beginning of the epidemic, as distributed by the CD4+ count stage of the HIV donor.

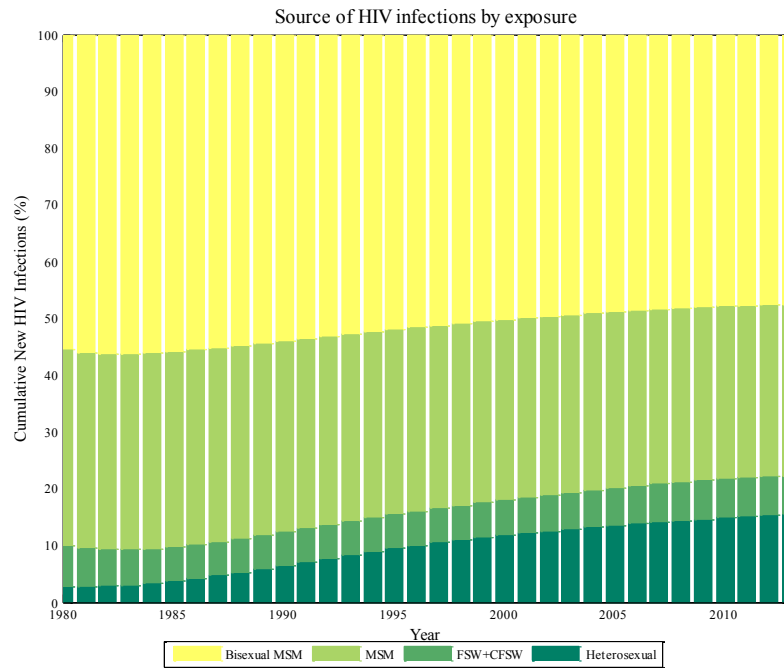


Figure 10: Source of HIV transmission by risk category: median cumulative fraction of new infections since the start of the epidemic, as distributed by the risk group of the HIV donor.

3.2.3 Drivers of HIV epidemic

Population Attributable Fraction from 1975 to 2014 was estimated for main risk-groups (MSM_{ex} , MSM_{bi} , FSW and grouped low-risk and high-risk heterosexuals) as can be seen in

Table 6.

Table 6: Population Attributable Fraction of cumulative HIV incidence by risk group

Exposure group	PAF	IQR
Exclusive MSM	90.2%	34%
Bisexual MSM	99%	12%
Female Sex Workers	8.5%	15%
Heterosexual	14%	10%

Table 6 Population Attributable Fraction of cumulative HIV incidence by risk group: Proportional and absolute median reduction in cumulative HIV infections from the beginning of epidemic to 2014.

PAF estimations suggest that both MSM_{bi} and MSM_{ex} are major drivers of HIV epidemic in the model, being particularly for the bisexual subgroup of MSM.

3.2.4 Estimation of retrospective impact of interventions

The scenario analysis shows that according to this model, the combination of condom use and ART (calibrated model) in Bogota may have averted a median of 54,200 (IQR 52000) new HIV infections from 1997 to 2014, when compared against a No-Intervention simulated scenario. If only ART would have been available for the same period, only 12800 (IQR 9300) cumulative infections could have been averted, compared to 52431 (IQR 46000) for a scenario with only condoms (Figure 11).

Proportional reduction of cumulative HIV infections, Bogota 1997-2014

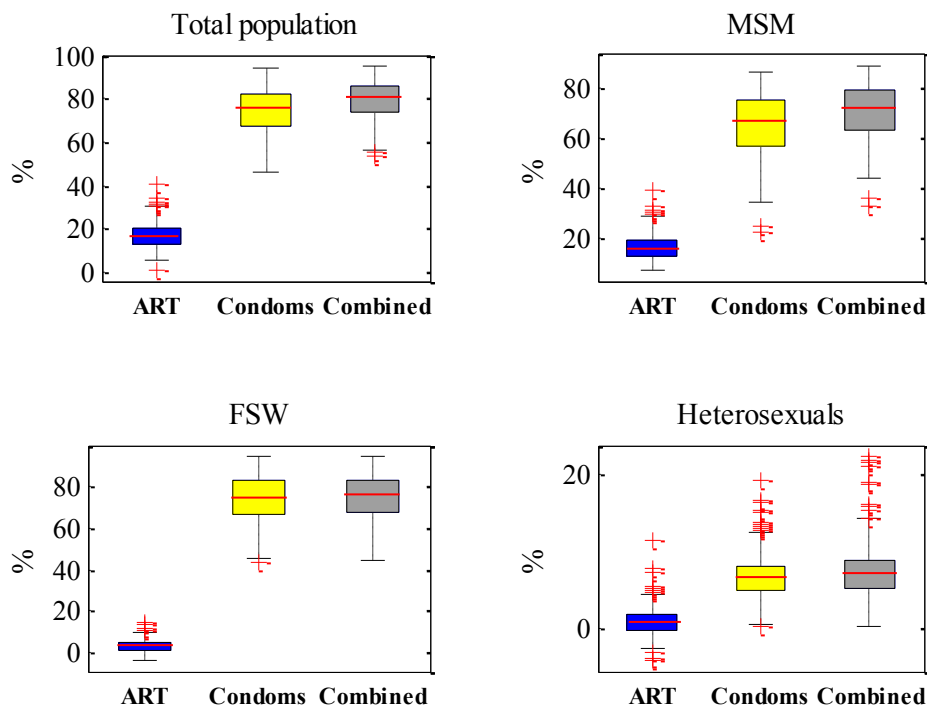


Figure 11 Box Plot for the total number of cumulative HIV infections averted from 1997 to 2014: Cumulative HIV infections averted with three analysed scenarios of intervention in the total population (top-left), only targeted to MSM (top-right), only targeted to FSW (bottom-left) and targeted to heterosexuals (bottom right).

These results suggest that condom use was the main factor behind HIV incidence reduction in the model, and across all groups.

When the analysis of simulated scenarios was performed by targeting specific risk groups, interesting conclusions were drawn from the visual comparison (**Figures 12 & 13**): removing ART from a single group would have had a noticeable impact in the overall epidemic only if done for MSM. Removing use of condoms in the same period showed a great impact when done for both FSW and MSM, but it is only when removed only from FSW that incidence levels reach the levels seen when condoms were removed in the total population. This suggests that condoms are the main factor preventing the emergence of a bigger epidemic amongst this group. On the other hand, is worth noting that targeted removal of interventions in the grouped-heterosexual category did not produce any noticeable change in HIV incidence in the general population (**Figure 12**).

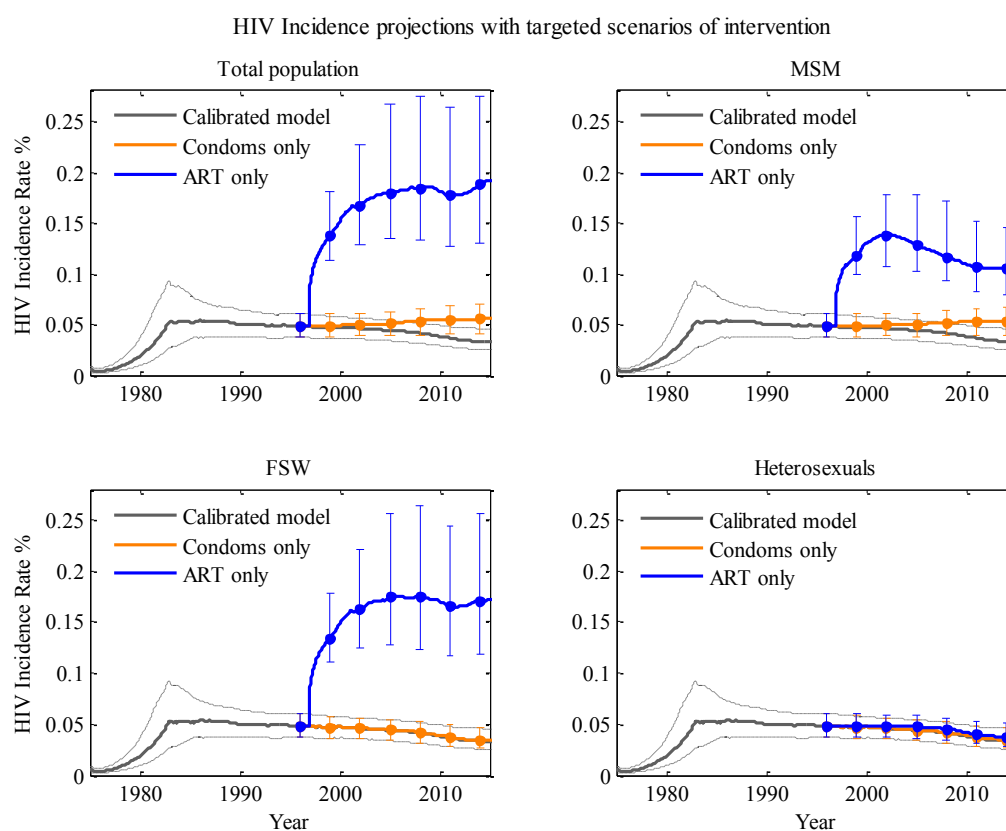


Figure 12 Modelling results of effect of interventions over HIV epidemic in Bogota: Epidemic projections for four scenarios of intervention in Bogota, from 1997 to 2014. In orange, only condoms scenarios while the calibrated model and the ART scenarios are shown in solid grey and blue respectively. Panels for specific populations reflect incidence rates in the Total population when interventions were exclusively applied to that group.

4 DISCUSSION

Transmission of HIV in Bogota was simulated using a mathematical model calibrated to local data. This model was able to reproduce epidemic trends and surveillance data, providing a plausible interpretation of what HIV transmission could have been in Bogota in the last four decades. According to these results, interventions had an important role in shaping the epidemic, with condoms being the main driver of epidemic control. ART in the model plays an additional role contributing with an important number of HIV infections averted, and its effect was more evident among MSM. A targeted analysis exploring the population effect of adding and removing interventions into specific groups raise interesting thoughts about how maximization of effectiveness could be achieved in epidemics with high transmissibility concentrated in small sub populations. In this model, removing all preventive interventions from the MSM groups (keeping other populations unchanged), resulted in an increment of 70% in cumulative HIV incidence from the calibrated model results. This is consistent with the PAF analysis which suggests that MSM groups have an attributable fraction of the HIV incidence as big as 90% since the start of the epidemic. In conclusion, the epidemic representation of Bogota's epidemic shows intense transmissibility within MSM, with a major role of bisexual activity males, and a high dependency on interventions to find the slowing in epidemic growth seen in the recent years.

Incidence reduction due to treatment in this model is not insignificant (~ 20%) but was not very large, and a number of factors come to mind when trying to explain the constrained impact of antiretroviral drugs on transmission in this context: First, from the programmatic point of view and as exposed in the introduction of this chapter, the biggest portion of cases

detected and set on ART come from the more advanced phases of infection, while the modelled source of infection shows a distribution strongly skewed towards the early stages of infection. In summary, it is possible that ART is also not reaching the sub-populations generating the majority of infections, undermining the prevention potential of antiretroviral drugs. In this simulation the fraction of individuals receiving ART who belonged to the MSM group (**Figure S4**) matches the fraction of MSM affected by HIV (**Figure 8**). However, HIV testing rates are used here as a proxy of the possible variations in access to ART across risk groups in the city, which might underestimate the real barriers found by the most vulnerable groups.

Another point to consider is related to the data used to calibrate the model in the ART delivery dimension: The city records for numbers of patients on ART only consider people receiving medical care from of the national health services. Even when coverage of such system is high among the population –around 75% in 2007- [6], there is still a small fraction of individuals getting their treatment out-of-pocket, and therefore not included in such records. In 2006 it was estimated that only 5.6% of all detected PLHA were not affiliated to the national health system. This figure came down to 0% by 2007 [6]. However, changes in more recent years could not be foreseen.

The stage of infection could play an important role in the potential impact of ART as has been shown and debated elsewhere [56-59]. Here, the fraction of cases arising -cumulatively- from acutely infected individuals was around 25%. A very simple reasoning around this figure, suggests that any attempt to prevent HIV transmission by means of treating those infected in this context will not achieve effectiveness levels greater than 75%, and that is assuming optimal levels of detection and treatment delivery for those HIV+ with over 500 CD4-cells/mm³.

Condom use displayed a significant impact in the simulated epidemic for Bogota, with reductions as high as 76% in cumulative HIV incidence for the period 1997 to 2014. This figure could be even higher if we consider that our analysis was restricted to the period 1997-2014, for comparability reasons. This means that the previous impact of condom use during the early years of the epidemic was removed from this estimation.

The first limitation about this approach is the restriction imposed in the model by not allowing other forms of behaviour change over the years, such as reduction of partners. This will tend to overestimate the impact of condoms as it will have to absorb and reproduce the impact of all other alternatives in HIV prevention. This restrictiveness in behaviour change is also found in the way that condom use was introduced. Even when it seems plausible to assume that a drastic decline in transmission might have appeared in several contexts given the start of the HIV testing era and increased risk awareness [41, 60], this could have happened to different extents according to the form of exposure. This is not allowed in the model, in part because there is little evidence to support the contrary. As a result, this “forced” change in behaviour could be one of the factors why this model finds it difficult to produce epidemics that saturate and reach equilibrium with less help from external forces like ART and condoms. Besides, for an epidemic driven so strongly by MSM such as the one in Bogota, the risk heterogeneity within this group portrayed by the model is rather limited. It is indeed possible to conclude that a lack of risk heterogeneity within MSM groups in the model might be leading to an overestimation of the impact of condoms in this group, given that protection rates in this group are particularly high. Ideally, a more detailed specification of the MSM spectrum of behaviours would drive transmission to its equilibrium by means of natural dynamics of HIV transmission. Incorporating one or several more categories of risk within the MSM group would have a buffer effect in the model by diverting transmission from the very high risk pools to low or intermediate risk MSM sub-groups. Given a less

intense transmission within the lower risk groups, the epidemic would progress more smoothly from the early epidemic outburst to the endemic phase. Also, one would expect less protected acts within stable MSM couples than in the casual ones, thus decreasing the overall impact of condoms on incidence. Nevertheless, changing these features was bounded by the absence of information on the diversity and nuances of MSM population in Bogota, which is in itself an important finding of this research.

The characterisation of the simulated epidemic in Bogota showed it was highly concentrated among MSM and elucidated very high levels of dependency on HIV transmission coming from this population. This is evident from PAF calculation by risk group displayed in **Table 6**, suggesting that HIV transmission would die out if MSM groups were removed from the infectious pool.

Analysis of the source of infection by stage of disease reveals that in the early years of the simulated epidemic in Bogota more than 50% of new infections could be ascribed to transmission during the acute stage, whereas by 2014 ~25% were attributable to that stage of infection. This is consistent with previous findings, which highlighted the importance of the epidemic phase when estimating of the role of early HIV infection (EHI) in HIV transmission [57]. A greater contribution of the early phase to transmission in early epidemics is thought to be caused by an outburst of new cases, thus producing a higher proportion of infected individuals in acute and early stages. This proportion decays as epidemic approaches its endemic phase as does the role of the early HIV infection on transmission [61].

Here, it is also important mentioning the role of number of sexual partners per year in the extent of incidence ascribed to the early HIV infection (EHI). Koopman, Kretzschmar and others [62-64] have already observed how the fraction of cases coming from primary HIV infection donors increases in the presence of concurrency and multiple partners. Xiridou et al.

[65] and Kim et al.[66] used modelling techniques to incorporate complexity around sexual partnership formation –durations, dissolution rates, concurrency- and found that this nuances were of central importance for accurately estimating the role of EHI in MSM driven epidemics. This model assumes a more simple approach, using an instant partnership formation at different rates according to the sexual partnership information available at the time this model was designed. Also, incorporation of further complexity around partnership formation was not only constrained by the paucity of data in Bogota but beyond the scope of our initial objectives.

It is important to highlight that these results are the first and more in depth approach to estimate the role of ART and condom use in the sexual transmission of HIV in Bogota. Exploring the dynamics between sub-populations in this context can provide a theoretical base for better understanding the overall effect of programmatic efforts of the past. Therefore, these findings come to enrich the body of knowledge for understanding the epidemiological trends of HIV in Latin America and also other contexts where HIV remains hyper-endemic among MSM groups.

Future efforts should be focused on applying methods with more flexible systems for reproducing behavioural nuances. Using future data on the more complex details about the structure of high transmissibility groups is a central part of research in concentrated epidemics.

This model's results led in some way to reflect about the urgent need of more evidence about targeted prevention interventions based on ART tailored to fit the needs of concentrated epidemics. Future work should explore different aspects of such interventions.

The era of abundant international resources dedicated to HIV response world-wide might be coming to an end, especially in a number of states where health systems and infrastructure is

already in place to withstand the impact of the changing epidemic. The wisest move for these countries starts by understanding their own needs for designing those strategies that maximize their resources and exploits the potential of the available prevention technologies. Hopefully this work contributes in building the path in that direction.

5 REFERENCES

1. García-Bernal, R., *Infección por VIH/SIDA en Colombia. Estado del Arte 2000-2005*, ed. UNAIDS. 2006, Bogota: UNAIDS.
2. Fernandez, M.I., et al., *HIV prevention programs of nongovernmental organizations in Latin America and the Caribbean: the Global AIDS Intervention Network project*. Rev Panam Salud Publica, 2005. **17**(3): p. 154-62.
3. Arrivillaga, M., et al., *HIV testing and counselling in Colombia: evidence from a national health survey and recommendations for health-care services*. Int J STD AIDS, 2012. **23**(11): p. 815-21.
4. Gómez, M., *Comparación de tres estrategias de tamizaje para la prevención de la infección perinatal por VIH en Colombia: análisis de decisiones*. Revista Panamericana de Salud Pública, 2008. **24**(4).
5. UNAIDS. *AIDSinfo Online Database*. [cited 2014 1 July]; Available from: <http://aidsinfoonline.org/devinfo/libraries.aspx/Home.aspx>.
6. Garavito, L. *Gasto Nacional en VIH-sida*. 2007 [cited 09 Februray 2013; Available from: http://www.minsalud.gov.co/salud/Documents/observatorio_vih/documentos/monitoreo_evaluacion/3_sistemas-informacion/Informe_MEGAS_FINAL__12_ago_2008_Mexico.pdf.
7. Sterne, J.A., et al., *Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies*. Lancet, 2009. **373**(9672): p. 1352-63.
8. Hollingsworth, T.D., R.M. Anderson, and C. Fraser, *HIV-1 transmission, by stage of infection*. J Infect Dis, 2008. **198**(5): p. 687-93.
9. Boily, M.C., et al., *Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies*. Lancet Infect Dis, 2009. **9**(2): p. 118-29.
10. PROFAMILIA, *1a Encuesta distrital de demografía y salud*. 2011, Profamilia: Bogota.
11. Garnett, G.P., et al., *The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey*. Philos Trans R Soc Lond B Biol Sci, 1999. **354**(1384): p. 787-97.
12. UNAIDS, *Sex Work and HIV.UNAIDS Technical Update*. June 2002, UNAIDS: Geneva.
13. Carael, M., et al., *Clients of sex workers in different regions of the world: hard to count*. Sex Transm Infect, 2006. **82 Suppl 3**: p. iii26-33.
14. MPS/UNFPA, *Comportamiento sexual y prevalencia de VIH en hombres que tienen relaciones sexuales con hombres en siete ciudades de Colombia*, Ministerio-de-la-protección-social/UNFPA, Editor. 2012: Bogota.
15. Anderson, R.M. and R.M. May, *Infectious diseases of humans : dynamics and control*. Oxford science publications. 1991, Oxford ; New York: Oxford University Press. viii, 757 p.
16. Pinkerton, S.D. and P.R. Abramson, *Occasional Condom Use and HIV Risk Reduction*. Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology, 1996. **13**: p. 13-16.

17. Stoneburner, R.L. and D. Low-Beer, *Population-level HIV declines and behavioral risk avoidance in Uganda*. Science, 2004. **304**(5671): p. 714-8.
18. Hallett, T.B., et al., *Assessing evidence for behaviour change affecting the course of HIV epidemics: a new mathematical modelling approach and application to data from Zimbabwe*. Epidemics, 2009. **1**(2): p. 108-17.
19. 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.
20. DANE. *Estadísticas Vitales*. [cited 10 Nov 2012; Available from: http://www.dane.gov.co/index.php?option=com_content&view=article&id=73&Itemid=119.
21. The-Global-Fund-to-fight-AIDS-Tuberculosis-and-Malaria, *Comportamiento sexual y prevalencia de VIH de las mujeres trabajadoras sexuales en 5 ciudades de Colombia*, T.G. Fund, Editor. 2012: Bogota D.C.
22. Miguez-Burbano, M.J., et al., *High-risk behaviours in men from Bogota, Colombia and the spread of HIV*. Int J STD AIDS, 2001. **12**(11): p. 739-43.
23. Miller, G.A., et al., *Clients of female sex workers in Lima, Peru: a bridge population for sexually transmitted disease/HIV transmission?* Sex Transm Dis, 2004. **31**(6): p. 337-42.
24. Ligasida and Secretaria-Distrital-de-Salud. *Informe final centinela de conocimientos comportamientos sexuales y prevalencia de vih y otras its en hombres que tienen sexo con hombres, Bogotá 2006*. 2006; Available from: <http://www.portalsida.org/repos/Centinela%20Final%20HSH.pdf>.
25. Ligasida and Secretaria-Distrital-de-Salud. *Estudio de comportamiento sexual y prevalencia de VIH y otras ITS en mujeres trabajadoras sexuales en Bogota D.C.* 2007 [cited 25 March 2012; Available from: http://www.minproteccion-social.gov.co/salud/Documents/observatorio_vih/documentos/monitoreo_evaluacion/1_vigilancia_salud_publica/b_estudios_comportamiento/Estudio%20MTS%202007%20Bogot%C3%A1.pdf.
26. MPS, *Encuesta Nacional de Salud 2007*, CENDEX, Editor. 2007, CENDEX: Bogota.
27. DHS, M., *Demographic Health Survey, Colombia*. 2005.
28. DHS, M., *Demographic Health Survey, Colombia*. 2010.
29. DHS, M., *Demographic Health Survey, Colombia*. 1995.
30. DHS, M., *Demographic Health Survey, Colombia*. 2000.
31. Stover, J., J.T. Bertrand, and J.D. Shelton, *Empirically Based Conversion Factors for Calculating Couple-Years of Protection*. Evaluation Review, 2000. **24**(1): p. 3-46.
32. Baggaley, R.F., R.G. White, and M.C. Boily, *HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention*. Int J Epidemiol, 2010. **39**(4): p. 1048-63.
33. High-Cost-Accounts/Ministry-of-Health, *HIV Dataset*. 2011.
34. CNSSS, *Manual de Medicamentos y Terapéutica del Sistema General de Seguridad Social, Acuerdo 83 de 1997*, MPS, Editor. 1997, MPS: Bogota.
35. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy*. N Engl J Med, 2011. **365**(6): p. 493-505.
36. Mocroft, A., et al., *Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group*. J Infect Dis, 2004. **190**(11): p. 1947-56.
37. Ajose, O., et al., *Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis*. AIDS, 2012. **26**(8): p. 929-38.
38. Vo, T.T., et al., *Durability and outcome of initial antiretroviral treatments received during 2000--2005 by patients in the Swiss HIV Cohort Study*. J Infect Dis, 2008. **197**(12): p. 1685-94.
39. Pinkerton, S.D. and P.R. Abramson, *Effectiveness of condoms in preventing HIV transmission*. Soc Sci Med, 1997. **44**(9): p. 1303-12.

40. Pinkerton, S.D., P.R. Abramson, and M.E. Turk, *Updated estimates of condom effectiveness*. J Assoc Nurses AIDS Care, 1998. **9**(6): p. 88-9.
41. Bezemer, D., et al., *27 years of the HIV epidemic amongst men having sex with men in the Netherlands: An in depth mathematical model-based analysis*. Epidemics, 2010. **2**(2): p. 66-79.
42. MPS. *Guías de manejo del VIH/Sida*. 2006; Available from: <http://www.minproteccion-social.gov.co/Documentos%20y%20Publicaciones/GUIA%20PARA%20EL%20MANEJO%20DE%20VIH%20SIDA.pdf>.
43. McKay, M.D., B. R.J., and C. W.J., *A comparison of three methods for selecting values of input variables in the analysis of output from a computer code*. Technometrics, 1979. **21**(2): p. 6.
44. Blower, S. and H. Dowlatabadi, *Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV model, as an example*. International Statistical Review, 1994. **62**: p. 229 - 243.
45. Russell, K.L., et al., *Molecular epidemiology of HIV-1 in South America*, in *XIIIth International AIDS Conference*. 2000: Durban, SA.
46. Bautista, C.T., *Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men*. Sexually transmitted infections, 2004. **80**(6): p. 498-504.
47. Secretaria Distrital de Salud, U., *Ligasida, Conocimientos, comportamientos sexuales y prevalencia de VIH y otras ITS en hombres que tienen sexo con hombres, Bogotá 2006*. 2007, Secretaria Distrital de Salud: Bogota.
48. Zea, M.C., et al., *Prevalencia del VIH, comportamiento sexual, y circuncisión en hombres que tienen sexo con hombres en Bogotá*. 2013, The George Washington University: Bogota.
49. Bautista, C.T., *Seroprevalence of and risk factors for HIV-1 infection among female commercial sex workers in South America*. Sexually transmitted infections, 2006. **82**(4): p. 311-316.
50. Global-Fund-to-Fight-AIDS-Tuberculosis-and-Malaria, *Comportamiento sexual y prevalencia de VIH de las mujeres trabajadoras sexuales en cinco ciudades de Colombia, 2012*. 2012: Bogota.
51. Prieto, F., A. Osorio, and M. De Neira, *Prevalencia de vih en población general de Colombia 2003: VI Estudio Nacional Centinela de VIH 2003-2004*. . Informe Quincenal Epidemiológico, 2003. **9**(24).
52. Instituto-Nacional-de-Salud, *VII Estudio nacional centinela de VIH en gestantes*. 2009.
53. Gallardo, H. and J. Rodriguez-Garcia, *La Carga de la Enfermedad en Santa Fe de Bogotá*. 1 ed. 1999, Bogota: Alcaldía Mayor de Bogota/Secretaria de Salud.
54. Rodrigues, J. and H.N. Gallardo, *Estimación de la Cobertura del sistema de notificación nacional de VIH/SIDA*. 1995, Ministerio de Salud. p. 7-15.
55. Gonzalez, M.A., et al., *Patterns, trends and sex differences in HIV/AIDS reported mortality in Latin American countries: 1996-2007*. BMC Public Health, 2011. **11**: p. 605.
56. Powers, K.a., et al., *The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study*. Lancet, 2011. **378**: p. 256-68.
57. Cohen, M.S., et al., *HIV treatment as prevention: debate and commentary--will early infection compromise treatment-as-prevention strategies?* PLoS Med, 2012. **9**(7): p. e1001232.
58. Cohen, M.S., et al., *Acute HIV-1 Infection*. N Engl J Med, 2011. **364**(20): p. 1943-54.
59. Smith, K., et al., *HIV-1 treatment as prevention: the good, the bad, and the challenges*. Curr Opin HIV AIDS, 2011. **6**(4): p. 315-25.
60. Katz, M.H., *AIDS epidemic in San Francisco among men who report sex with men: successes and challenges of HIV prevention*. J Acquir Immune Defic Syndr Hum Retrovirol, 1997. **14 Suppl 2**: p. S38-46.

61. Miller, W.C., et al., *Role of acute and early HIV infection in the sexual transmission of HIV*. Curr Opin HIV AIDS, 2010. **5**(4): p. 277-82.
62. Koopman, J.S., et al., *The role of early HIV infection in the spread of HIV through populations*. J Acquir Immune Defic Syndr Hum Retrovirol, 1997. **14**(3): p. 249-58.
63. 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.
64. 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.
65. Xiridou, M., et al., *Primary HIV infection as source of HIV transmission within steady and casual partnerships among homosexual men*. AIDS, 2004. **18**(9): p. 1311-20.
66. Kim, J.H., R.L. Riolo, and J.S. Koopman, *HIV transmission by stage of infection and pattern of sexual partnerships*. Epidemiology, 2010. **21**(5): p. 676-84.

Chapter 3: Estimating the retrospective impact of Antiretroviral Treatment scale-up in Brazil

1 INTRODUCTION

In November 1996 the government of Brazil began one of the biggest ventures of public health in a middle income country by guaranteeing free and universal access to antiretroviral therapy (ART) to people living with AIDS. Brazil opted for the expansion of treatment amidst criticism from donors and international agencies which considered that developing countries should invest more in prevention interventions than treatment [1]. As a result, Brazil's became the first and largest public AIDS programme in a middle income country.

Brazil has a population of 202 million people [2], and its AIDS programme has reported over 656,000 cases of AIDS since the first case in 1980 to 2012 [3]. According to the latest epidemiologic bulletin, by 2012 720,000 people were estimated to be living with HIV/AIDS in Brazil. Of these, 80% (574,000) had been diagnosed, 74% (531,000) linked to care, 61% (436,000) retained in the system, 44% (313,000) were receiving ART, and 33% (236,000) had an undetectable viral load ($VL < 50$ RNA-copies/mL) [4]. Reaching such numbers requires an infrastructure and a well-functioning system in place to not only deliver drugs but to detect new cases, link patients to care, perform clinical assessment and retain individuals in the programme.

Sistema Único de Saúde (Unified Health System) known in Brazil by its acronym, *SUS*, was created in 1990 after several years of political and social struggle in the country. After 21 years of military regime (1964 to 1985), the start of the AIDS epidemic found Brazil in the middle of its transition to democracy, and the country's definitive turn towards socially oriented governments [1]. With a new health system in place, the development of new drugs capable of keeping the virus in check, and the increasing need to respond to the growing

number of cases, one could say that Brazil's AIDS universal treatment programme was a product of political will, social mobilization and "good timing".

Brazil's ART programme is frequently portrayed as a "success story" of treatment scale-up, and rightly so: in a paper by Marins et al., [5] the authors report the striking increase in survival time from AIDS within individuals diagnosed in 1996 and starting combined ARV therapy (58 months) compared to those diagnosed between 1982-1985 (5 months) and 1995 (18 months). Similar results have been observed at the regional level and in studies conducted in the major cities of Brazil [6]. Moreover drastic reductions in morbidity by opportunistic infections [7] and even tropical endemic diseases like malaria, Chagas disease and leishmaniasis were observed among HIV patients in Brazil [8].

However, Brazil can hardly be taken as a single unit, and to understand the dynamics of HIV transmission as well as the impact of interventions as a whole, it is necessary to increase the level of detail at least to the regional dimension. Brazil is divided into five geographic regions, namely: North, Northeast, South, Southeast, and Central-west. The coasts of the country are densely populated in contrast to the centre and Amazonian regions, with the largest urban settlements (Sao Paulo, Rio de Janeiro, Belo Horizonte) located in the Southeast (**Figure 1**). Consequently, the South and Southeast regions not only represent the vast majority of urban Brazil, but also concentrate the economic wealth of the country.

Distribuição da população em 2000

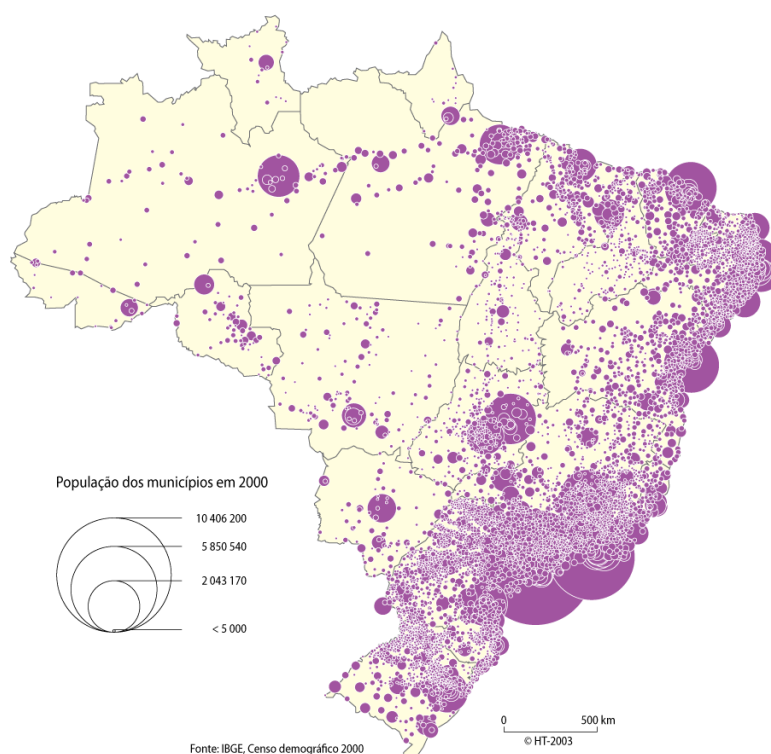


Figure 1 Population distribution of Brazil: proportional circles map showing population density in populated centres across the country in the year 2000.

Source: Sampaio et al, 2008.[9]. *Image reproduced with permission of the rights holder, Confins Revue* ©.

The populated urban centres in southeast Brazil offered the conditions for the spread of HIV across the country in the early years of the epidemic. Hosting the largest majority of men who have sex with men (MSM) as well as people who inject drugs (PWID) and a large rate of population mobility, the cities of São Paulo and Rio de Janeiro became the epicentre of the Brazilian HIV epidemic. The first AIDS case was reported in 1980 in São Paulo [10] and from there on the epidemic expanded with over 50% of cases detected occurring amongst MSM living in the southeast [1, 11]. An important number of cases emerged as well in PWID during the early 1990s, particularly in urban areas of the south, but different factors like a shift in drug use behaviours slowed transmission in this group [12, 13]. Despite an observable change in the male to female ratio of new infections and a greater role of rural Brazil in the distribution of new cases, the epidemic is still predominantly urban and concentrated among

MSM. Prevalence among the general population has been stable at 0.6% since 2004 [14, 15] while the estimate in different settings among MSM has ranged between 6% and 26% for the last 5 years (**Table 1**).

There has been much debate about Brazil's bold decision of choosing universal access to treatment instead of following international trends to invest in prevention [1]. However, evidence from HPTN 052 [16] on the effect of antiretrovirals for preventing HIV transmission bridged the gap between prevention and treatment, providing fresh arguments for this debate. In a country where the response to AIDS epidemic is synonym of AIDS-treatment-expansion, establishing how much of that unprecedented approach actually ended up in preventing new HIV infections is a burning question for decision-makers and an interesting opportunity for HIV researchers.

To answer the above question, this chapter aims to retrospectively estimate the HIV incidence reduction in Brazil in the context of a large scale intervention of free and universal access to ART for those in need. For this purpose, a mathematical model was designed and applied to the main five geographical regions in Brazil.

2 METHODS

The sexual transmission of HIV in Brazil since the beginning of the epidemic to date was reproduced through a compartmental deterministic mathematical model, calibrated separately for each major region in the country. This geographical approach was chosen based on two important considerations: first and more importantly, spread of infection patterns and HIV mortality have been shown to be closely related with the geographical macro-regions in the country [17]. The second argument is the systematic report of surveillance data in Brazil

which follows the regional distribution adopted in this chapter. The same approach of geographical division is widely used to inform and report research results in Brazil [18-21].

Sexually active individuals over 15 years of age were simulated in a system that involves sexual mixing according to sexual behaviour. Interventions (*i.e.* condom and ART) were introduced in the model based on regional data. The mathematical expression of the models consists of a set of ordinary differential equations coded in MATLAB®, and solved numerically using the Runge-Kutta method.

A comparison of model *versus* data was made in a Bayesian statistical framework, which incorporates the prior knowledge about the distribution of parameters to the overall probability of the model given the data.

Equation 3.1: Posterior probability

$$p(\theta, y) = p(\theta)p(y|\theta),$$

Here, θ represents the model or parameter set and y is the given data. Prior probability $p(\theta)$ adds towards the posterior probability of the model explaining the data $p(\theta, y)$, together with our evidence provided by model comparison, summarized here as $p(y|\theta)$, and translated as the likelihood.

2.1 Model Structure

As can be seen in **Figure 2**, some changes were made to the model structure described in Chapter 2 for the sexual transmission of HIV in Bogota: CD4 count stages less than 50

cell/mL were removed, with the CD4 count < 200 cell/mL compartments now representing the final stage of disease. Infected individuals arriving at the acute infection compartment are allowed to move to any CD4 count stage, according to evidence on post-acute progression as reported by Lodi et al., [22]. Finally, the flow through treatment stages was simplified, now consisting of a single line of treatment stages and therefore a single set of “failure” stages.

These changes obey to the need of simplifying the structure of the model considering the differences in data availability.

2.2 Population Structure and risk heterogeneity

Sexual mixing in the model follows the system developed by Garnett et al., [23], described in detail in Chapter two of this document. The modelled population was subdivided by main sexual activity group according to gender, sexual orientation and number of sexual partners in the last year (**Figure 3**). Sexually active population over 15 years was estimated for each region as the arithmetic complement of the No-Risk population (*i.e.* individuals with no sexual contacts in the last year) as reported in national surveys (**Table 4**).

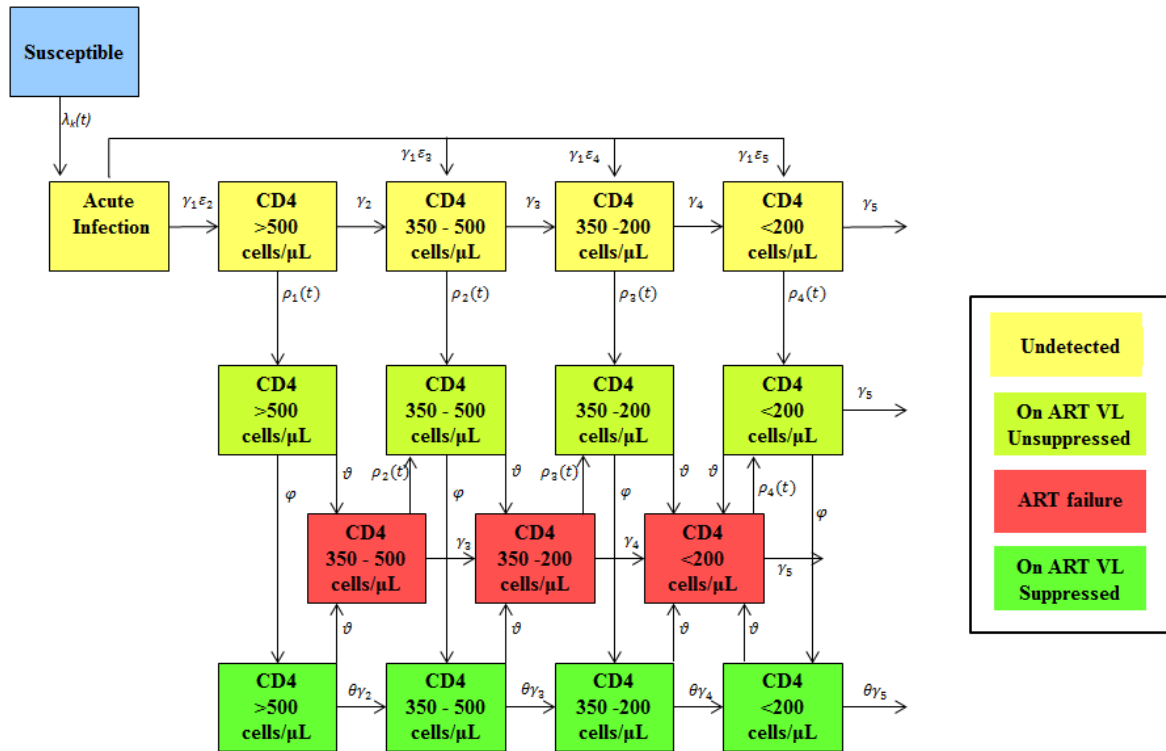


Figure 2 Model structure: Susceptible individuals get infected at rate $\lambda_k(t)$ progressing to acute infection and flowing through natural history of disease and ART. Full description of symbols and parameter values can be found in parameters table.

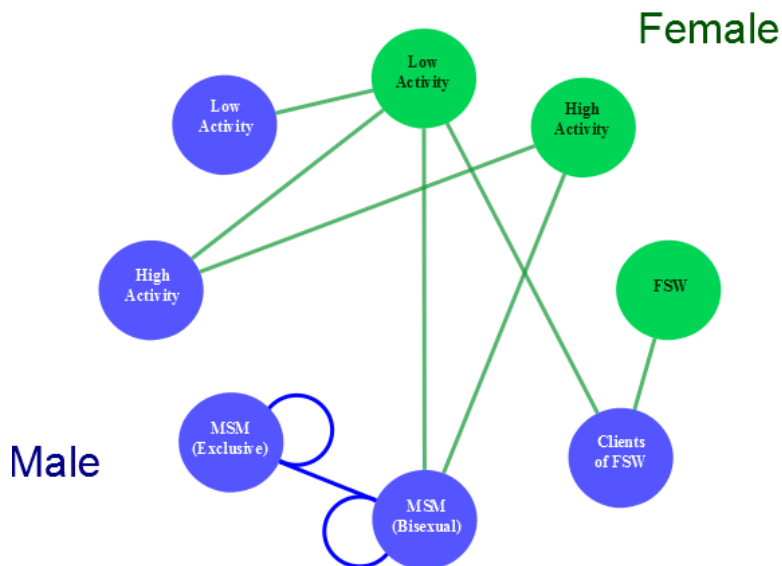


Figure 3 Sexual mixing in the model: In solid lines are sexual contacts allowed between male and female sub-populations. Same colour and loops reflect same sex contacts.

2.3 Model Equations

2.3.1 Ordinary Differential Equations

The dynamic system of compartments is mathematically expressed in equations 3.1 to 3.17, as follows:

1. Susceptible

$$\frac{dS_k(t)}{dt} = E_k + W_k^1 - S_k(t) \sum_j (\lambda_{k,j}(t)) - S_k(t)(\sigma + \mu),$$

2. Acute HIV Infection

$$\frac{dI_k^{0,1}(t)}{dt} = S_k(t) \sum_j (\lambda_{k,j}(t)) + W_k^2 - I_k^{0,1}(t)(\gamma_1 + \mu + \sigma),$$

3. HIV Positive with CD4 > 500 cell/ μ L, undetected

$$\frac{dI_k^{0,2}(t)}{dt} = I_k^{0,1}(t)(\gamma_1 \varepsilon_1) + W_k^3 - I_k^{0,2}(t)(\rho_1(t) + \gamma_2 + \mu + \sigma),$$

4. HIV Positive with CD4 350 to 499 cell/ μ L, Undetected

$$\frac{dI_k^{0,3}(t)}{dt} = I_k^{0,1}(t)(\gamma_1 \varepsilon_2) + I_k^{0,2}(t)\gamma_2 + W_k^4 - I_k^{0,3}(t)(\rho_2(t) + \gamma_3 + \mu + \sigma),$$

5. HIV Positive with CD4 200 to 349 cell/ μ L, Undetected

$$\frac{dI_k^{0,4}(t)}{dt} = I_k^{0,1}(t)(\gamma_1 \varepsilon_3) + I_k^{0,3}(t)\gamma_3 + W_k^5 - I_k^{0,4}(t)(\rho_3(t) + \gamma_4 + \mu + \sigma),$$

6. HIV Positive with CD4 < 200 cell/ μ L, Undetected

$$\frac{dI_k^{0,5}(t)}{dt} = I_k^{0,1}(t)(\gamma_1 \varepsilon_4) + I_k^{0,4}(t)\gamma_4 + W_k^6 - I_k^{0,5}(t)(\rho_4(t) + \gamma_5 + \mu + \sigma),$$

7. *CD4 >500 cell/μL, on 1st Line ART, Non-suppressed VL*

$$\frac{dI_k^{1,2}(t)}{dt} = I_k^{0,2}(t)\rho_1(t) + W_k^7 - I_k^{1,2}(t)(\varphi + \vartheta + \mu + \sigma),$$

8. *CD4 350-499 cell/μL, on 1st Line ART, non-suppressed VL*

$$\frac{dI_k^{1,3}(t)}{dt} = I_k^{0,3}(t)\rho_2(t) + W_k^8 + I_k^{3,3}(t)\rho_2(t) - I_k^{1,3}(t)(\varphi + \vartheta + \mu + \sigma),$$

9. *CD4 200-349 cell/μL, on 1st Line ART, non-suppressed VL*

$$\frac{dI_k^{1,4}(t)}{dt} = I_k^{0,4}(t)\rho_3(t) + W_k^9 + I_k^{3,4}(t)\rho_3(t) - I_k^{1,4}(t)(\varphi + \vartheta + \mu + \sigma),$$

10. *CD4 <200 cell/μL, on 1st Line ART, Non-suppressed VL*

$$\frac{dI_k^{1,5}(t)}{dt} = I_k^{0,5}(t)\rho_4(t) + W_k^{10} + I_k^{3,5}(t)\rho_4(t) - I_k^{1,5}(t)(\varphi + \vartheta + \mu + \sigma),$$

11. *CD4 >500 cell/μL, on ART, Suppressed VL*

$$\frac{dI_k^{2,2}(t)}{dt} = I_k^{1,2}(t)\varphi + W_k^{11} - I_k^{2,2}(t)(\theta\gamma_2 + \vartheta + \mu + \sigma),$$

12. *CD4 350 to 499 cell/μL, on ART, Suppressed VL*

$$\frac{dI_k^{2,3}(t)}{dt} = I_k^{1,3}(t)\varphi + W_k^{12} + I_k^{2,2}(t)\theta\gamma_2 - I_k^{2,3}(t)(\theta\gamma_3 + \vartheta + \mu + \sigma),$$

13. *CD4 200 to 349 cell/μL, on ART, Suppressed VL*

$$\frac{dI_k^{2,4}(t)}{dt} = I_k^{1,4}(t)\varphi + W_k^{13} + I_k^{2,3}(t)\theta\gamma_3 - I_k^{2,4}(t)(\theta\gamma_4 + \vartheta + \mu + \sigma),$$

14. *CD4 <200 cell/μL, on ART, Suppressed VL*

$$\frac{dI_k^{2,5}(t)}{dt} = I_k^{1,5}(t)\varphi + W_k^{14} + I_k^{2,4}(t)\theta\gamma_4 - I_k^{2,5}(t)(\theta\gamma_5 + \vartheta + \mu + \sigma),$$

15. CD4 350 to 499 cell/ μ L, on ART failure

$$\frac{dI_k^{3,3}(t)}{dt} = I_k^{1,2}(t)\vartheta + I_k^{2,2}(t)\vartheta + W_k^{15} - I_k^{3,3}(t)(\rho_2(t) + \gamma_3 + \mu + \sigma),$$

16. CD4 200 to 349 cell/ μ L, on ART failure

$$\frac{dI_k^{3,4}(t)}{dt} = I_k^{1,3}(t)\vartheta + I_k^{2,3}(t)\vartheta + I_k^{3,3}(t)\gamma_3 + W_k^{16} - I_k^{3,4}(t)(\rho_3(t) + \gamma_4 + \mu + \sigma),$$

17. CD4 <200 cell/ μ L, on ART failure

$$\begin{aligned} \frac{dI_k^{3,5}(t)}{dt} = & I_k^{1,4}(t)\vartheta + I_k^{2,4}(t)\vartheta + I_k^{1,5}(t)\vartheta + I_k^{2,5}(t)\vartheta + I_k^{3,4}(t)\gamma_4 + W_k^{17} - \\ & I_k^{3,5}(t)(\rho_4(t) + \gamma_5 + \mu + \sigma), \end{aligned}$$

Where $s_k(t)$ are all individuals in category k that are susceptible at time t . Stages named I represent all the HIV positive stages, with indexing code as follows:

$I_k^{a,s}$: Superscript “ a ” denotes the status of the HIV positive individual regarding ART with $a=1$ for those on treatment but unsuppressed viral load (VL); When $a=2$ for those on ART with suppressed VL, and $a=3$ for those in treatment failure. Superscript “ s ” denotes the stage of disease, taking values from 1 to 5, namely: 1 = acute infection, 2 = CD4 >500 cell/ μ L, 3 = CD4 350 to 499 cell/ μ L, 4 = CD4 200 to 349 cell/ μ L, and 5 = CD4 <200 cell/ μ L.

In equation 1, the term $E_k(t)$ is the expression to represent the input of new individuals entering the susceptible pool in each category k at time t . This number results from re-introducing the same number of individuals “lost” from the system at time $t-1$ (i.e. mortality due to AIDS, background mortality, and individuals leaving sexual activity). A population

growth rate is added $\epsilon(t)$, in accordance to population projections for each Brazilian region, as reported by IBGE⁶. The mathematical expression as follows:

Equation 3.18:

$$\frac{dE_k(t)}{dt} = (\sigma + \mu + \epsilon(t)) \left(\sum_{\frac{s}{a}} I_k^{a,s}(t) + S_k(t) \right) + \gamma_5 (I_k^{0,5}(t) + I_k^{1,5}(t) + I_k^{3,5}(t)) + \gamma_5 \theta I_k^{2,5}(t)$$

Another important consideration regarding the population structure and its balance in the system has to do with the rate at which women enter or leave the sex work category (turnover). Here, it is represented with the symbol W_k^c , where k is risk category, and c takes the value of the corresponding compartment in the system (*i.e.* from 1 to 17). It is assumed that female sex workers spend a given time in sex work activity (**Table 1**) and leave this category in equal proportions to both the Low and High Activity categories, and irrespective of their HIV status or stage of disease. An equal number of women enter sex work, moving from the susceptible compartments of low and high activity women to become susceptible female sex workers. This guarantees the preservation of the relative population size in female subpopulations over the simulation time. Equally proportional recruitment into sex work according to activity group was considered given that no consistent evidence was available to support the contrary.

2.3.2 Force of Infection

As described in Chapter two, the force of infection ($\lambda_{k,j}(t)$) was defined as the probability of HIV transmission given an effective contact between two individuals of risk category k and j [24]. In this case, the force of infection must reflect three forms of sexual contact and transmission, namely, male to female, female to male and male to male.

⁶ (IBGE) Brazilian Institute of Geography and Statistics. In the internet: <http://www.ibge.gov.br>

Equations 19 to 21 show the representation of these contacts, summarized in the matrix $\lambda_{k,j}(t)$, which contains the specific force of infection for each group k with contact j . This matrix is solved for every possible contact within activity groups using indices k , and j , where k is the choosing partner and j is the chosen one.

Equation 3.19: Force of Infection for HIV transmission from females (j) to males (k)

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum_a^s \left(\left(\frac{I_j^{a,s}(t)}{\sum_a^s I_j^{a,s}(t) + S_j(t)} \right) \left(\left(1 - \left((1 - \beta_f L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_f L^{a,s} (1 - \varsigma))^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ (for } j = 2, 3, 4, \text{ and } k = 6, 7, 8, 10),$$

Equation 3.20: Force of Infection for HIV transmission from males (j) to females (k)

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum_a^s \left(\left(\frac{I_j^{a,s}(t)}{\sum_a^s I_j^{a,s}(t) + S_j(t)} \right) \left(\left(1 - \left((1 - \beta_m L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_m L^{a,s} (1 - \varsigma))^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ (for } j = 6, 7, 8, 10, \text{ and } k = 2, 3, 4),$$

Equation 3.21: Force of Infection for HIV transmission from males (j) to males (k)

$$\lambda_{k,j}(t) = c_k p_{k,j} \left[\sum_a^s \left(\left(\frac{I_j^{a,s}(t)}{\sum_a^s I_j^{a,s}(t) + S_j(t)} \right) \left(\left(1 - \left((1 - \beta_{msm} L^{a,s})^{\alpha_{k,j}(1-v_k(t))} \right) (1 - \beta_{msm} L^{a,s} (1 - \varsigma))^{\alpha_{k,j}(v_k(t))} \right) \right) \right) \right], \text{ (for } j = 8, 9, \text{ and } k = 8, 9),$$

Condom effectiveness per act was incorporated with the term $\left(1 - \beta_f L^{a,s} (1 - \varsigma)\right)^{\alpha_{k,j} (v_k(t))}$, where ς is the relative risk reduction in HIV transmission with condom use [25], raised to the power of numbers of acts $\alpha_{k,j}$ between k and j , multiplied by the annual proportion of sex acts protected with condom in group k , $v_k(t)$.

The matrix $L^{a,s}$ incorporates coefficients that increase or reduce transmissibility within the couple according to the stage of infection (superscript “ s ”) (*i.e.* acute infection) and ART status of the contact (superscript “ a ”). Full description of symbols and its values can be found in parameters **Table 4**.

For a description of the mixing matrix $(p_{k,j})$ please refer to the methods section in chapter two in this manuscript.

2.4 Initial conditions

The start of the epidemic was fixed in 1975. To reflect a delay in the start of transmission or different sizes of the early epidemic, the seed was calibrated as a proportion of individuals infected. The epidemic was only seeded in female sex workers, their clients, and both categories of MSM, considering that these were the groups with the highest risk.

2.5 Condom use in the model

Different sources of data were consulted to recreate plausible time trends of condom use among risk groups in each of the five regions of Brazil. The information retrieved were point estimates of proportion of sex acts protected with condom for a given period across regions and risk groups. However, condom use is thought to have changed over time, and for this

reason it was modelled in a way that allowed the exploration of different plausible scenarios of condom uptake and variation over time and across risk groups.

Condom use before the AIDS era (*i.e.* before 1984 when HIV was recognized as causing AIDS) is thought to have been very low and fairly similar in all subpopulations. With the widespread knowledge of HIV being sexually transmitted and the HIV testing era after 1984 it is plausible that the frequency of condom use increased radically, particularly among the groups with the highest sexual activity. Changes in behaviour affecting HIV epidemics have been observed and suggested in other contexts [26, 27].

Following this reasoning, rates of condom use were modelled as the linear interpolation between pre-AIDS rates and the point estimations found in the literature review. However, the lack of consistent data about condom use in these decisive years of the epidemic was overcome by calibrating a parameter ($cond_{start}$) for the possible time spent between pre-AIDS era (before 1983) levels of use and the rates found in the first data point reported in the literature for each group.

Point estimates of condom use carry uncertainty, and this uncertainty was controlled with a global parameter ($cond_{scenario}$) that determined which value within this range would be used during interpolation of data points. This parameter had a prior range between 0 and 1. It was applied to all data points and uncertainty ranges across groups. This means that values near to 1 resulted in a “high condom use scenario” overall and those values near 0 resulted in the opposite.

Equation 3.22: Condom use by sex group and according to uncertainty factor

$$v_k(t) = lowEstimate_k(t) + (cond_{scenario}(lowerEstimate_k(t) - upperEstimate_k(t)))$$

Figure 4 exemplifies the range of possibilities in condom use trajectories allowed in the calibration process.

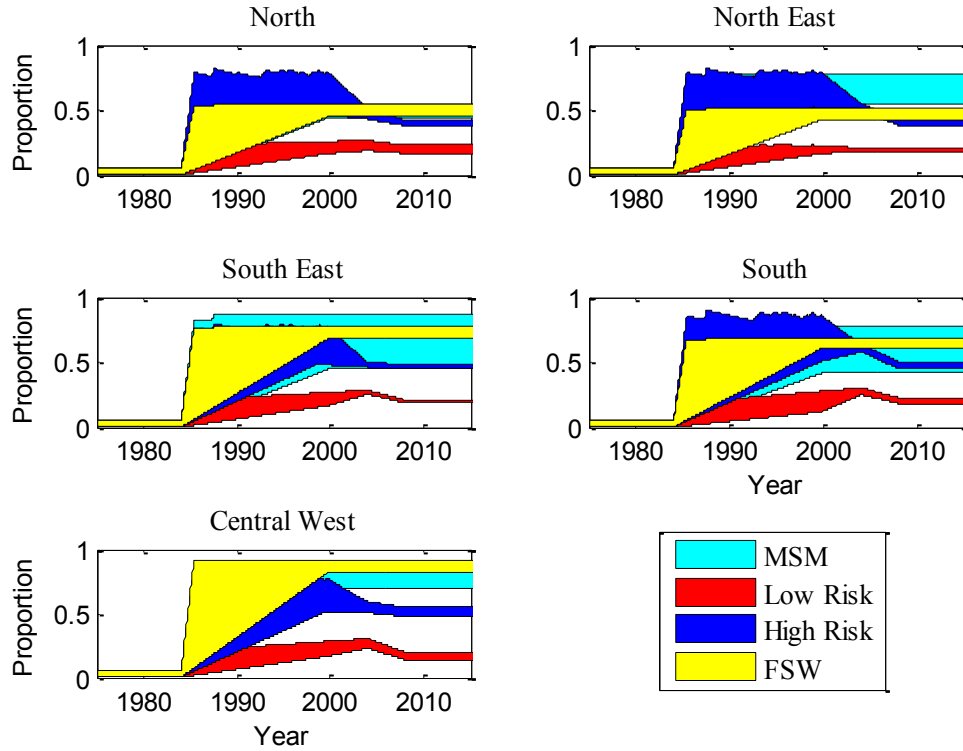


Figure 4 Modelled proportions of acts protected by condom by risk group and region: results from 100 simulations varying $cond_{start}$ and $cond_{scen}$ parameters according to calibration ranges.

2.6 Antiretroviral therapy in the model

The access to antiretroviral drugs in Brazil has varied across regions and also by stage of disease as has been documented elsewhere [21, 28, 29]. However, the true shape of the function behind treatment expansion in each region and the possible fluctuations over time is unknown.

Addressing ART scale-up is central for the aims of this research, and as such, a flexible and comprehensive approach was chosen for this task.

The rate at which HIV-infected are recruited into ART is expressed as $\rho_j(t)$, and is allowed to vary by CD4 cell count category j and calendar time t :

Equation 3.22: ART recruitment rate

$$\rho_j(t) = \left((m\omega)T_j + \rho_5(0) \right) \sigma(t)$$

Where T_j is the average time (years) to reach CD4+ count category <200 cell/ μ L ($j=5$) for those in CD4 cell count category $j=1, \dots, 4$ ($T_1=8.17$; $T_2=7.93$; $T_3=6.74$; $T_4=3.74$; $T_5=0$).

This parameterization sets the rate of detection to vary linearly as the time to reach CD4 <200 cell/ μ L decreases. The slope of this line is specified by parameter ω , which allows the linear relationship to be either positive or negative. With $\omega > 0$, individuals with low CD4 counts are more likely to be recruited into, which may be true if HIV testing is prompted by increasing experience of illness. However, with $\omega = 0$, the rate at which individuals move into the treatment compartments is the same across CD4 categories. The prior on ω reflects that both of these possibilities are equally likely: $\omega \sim U(0,1)$. Parameter m is a constant scaling parameter which ensures that the ART rate is greater than zero for all CD4 categories, irrespective of the value of ω .

Rate of recruitment into ART for those in CD4 cell count category <200 cell/ μ L (ρ_5) has a prior distribution such that the average interval from infection to treatment is uniformly distributed between 0.5 and 10 years: $\sim U\left(\frac{1}{10}, \frac{1}{0.5}\right)$.

$\sigma(t)$ describes the change in the rates of treatment uptake over time. Here it is assumed that this change can be represented by the logistic function: $\sigma(t) = \frac{1}{1+e^{-r(t-t_{50})}}$, where r is the rate of increase, and t_{50} is the time to reach half the upper limit rate. Parameter r is set at 0.003

and a prior was placed on t_{50} that allows a wide range in shapes in $\sigma(t)$ from a stable trend over time ($t_{50}=1$) to a sharp increase in this rate from close to zero at the start of ART scale up in 1997 ($t_{50}=0.1$): $t_{50} \sim U(0.1,1)$.

ART eligibility criteria have changed over time in Brazil [6]. However, different reports have shown that despite a trend towards late entry into care, many individuals started on ART with greater CD4+ counts than those established in the guidelines over the years [21]. The way in which ART was modelled, as explained above, favours trends where the ART is provided at later stages in the first years and increasing the threshold of CD4+ over the years, but for the reasons mentioned before, it was not restricted to strict cut-off limits.

2.7 Data and sources of information

2.7.1 HIV prevalence among key populations

The model was fitted to HIV prevalence estimates from different surveys and other cross-sectional studies carried out in several locations of Brazil. HIV prevalence among female sex workers and MSM was collected and classified according to the main geographical region where the study was located. **Table 1** describes in detail each study and the data point used during model comparison.

2.7.2 Surveillance data

HIV and AIDS information in Brazil is managed through a network of datasets that record information of different nature: SINAN dataset collects information on epidemiological variables; SICEL holds laboratory and clinical records; SICLOM contains data from the ART programme, and SIM gathers mortality reports. Two dimensions of data used in the

calibration process come from this network of information (*i.e.* reported deaths due to AIDS and numbers of people on ART).

The first dimension corresponds to the annual number of reported deaths due to AIDS, and reflects the annual number of deaths caused by HIV and AIDS and reported for each region between 1995 and 2011.

This data is periodically published in epidemiology bulletins by Brazil's Ministry of Health [3] (**Table 2**). However, this data is thought to be susceptible to several forms of bias, particularly under-reporting, defined as absence of cases in the official records, and misclassification (the attribution of a different cause of death or omission of HIV/AIDS in the records). Fazito et al., have studied the percentage of misclassified and under-reported AIDS deaths in Brazil[20], and Pacheco et al., have done an exhaustive and equally extensive job for the major AIDS reference centre in Rio de Janeiro [30].

Table 1 HIV prevalence studies among FSW and MSM in Brazil

Year	Region	Study location	HIV Prevalence (%)	95% CI		Sample Size	Reference
				Lower	Upper		
Female Sex Workers							
2006	North	Amazonas	2.6	0.0	10.7	114	[31]
2006	North	Amazonas	2.6	0.1	5.1	154	[32]
1988	Northeast	Salvador	13.3	0.0	27.9	15	[33]
1993	Northeast	Fortaleza	1.6	14.8	23.0	496	[34]
2000	Northeast	Maranhão	3.0	0.4	5.6	164	[35]
2000	Northeast	Paraíba	3.0	0.4	5.7	169	[35]
2000	Northeast	Sergipe	1.2	0.0	2.8	165	[35]
1987	Southeast	Rio de Janeiro	6.0	1.3	10.7	100	[36]
1987	Southeast	Rio de Janeiro	3.0	0.0	6.3	101	[37]
1987	Southeast	Santos	3.0	1.5	4.5	470	[38]
1988	Southeast	Campinas	10.8	5.8	15.8	148	[39]
1989	Southeast	São Paulo State	2.8	1.1	4.5	347	[38]
1990	Southeast	São Paulo	11.0	8.5	13.5	600	[40]
1991	Southeast	Santos	35.0	26.6	43.4	125	[41]
1994	Southeast	Espírito Santo	8.6	4.0	13.2	140	[42]
1996	Southeast	São Paulo	8.3	6.3	10.4	697	[43]
2000	Southeast	Minas Gerais	5.9	2.2	9.6	153	[35]
2000	Southeast	São Paulo	2.4	0.6	4.7	164	[35]
2006	Southeast	Rio de Janeiro	12.9	6.1	19.7	93	[44]
2006	Southeast	São Paulo	5.7	2.3	9.1	175	[45]
1992	South	Paranaguá	4.6	1.0	8.1	132	[46]
2000	South	Paraná	3.9	1.0	6.8	168	[35]
2000	South	Santa Catarina	5.4	1.3	7.6	164	[35]
2000	South	Rio Grande do Sul	19.5	13.5	25.5	166	[35]
2000	South	Porto Alegre	4.8	3.5	6.1	980	[47]
2003	South	Santa Catarina	6.7	1.5	11.9	90	[48]
2009	South	Santa Catarina	5.2	1.4	9.0	134	[49]
2010	Central-west	Campo Grande	1.0	0.1	2.6	402	[50]
Men who have sex with men							
2006	North	Manaus	2.6	0.0	5.5	116	[31]
2009	North	Manaus	8.3	6.0	10.9	350	[19]
1986	Northeast	Salvador	19.0	11.6	26.4	109	[51]
1988	Northeast	Salvador	40.0	29.5	50.8	82	[33]
1989	Northeast	Bahia State	12.0	5.5	18.5	96	[51]
1993	Northeast	Salvador	10.0	7.5	12.5	550	[52]
2009	Northeast	Recife	5.2	2.7	8.2	350	[19]
2009	Northeast	Salvador	8.9	5.5	12.7	350	[19]
1986	Southeast	Belo Horizonte	9.6	5.5	13.8	197	[53]
1987	Southeast	Rio de Janeiro	25.0	17.5	32.5	128	[37]
1994	Southeast	Rio de Janeiro	24.0	21.6	26.4	1165	[54]
1994	Southeast	Belo Horizonte	8.8	6.6	11.0	642	[55]
1994	Southeast	São Paulo	12.5	6.1	18.9	104	[56]
1994	Southeast	Belo Horizonte	6.6	2.8	10.4	167	[57]
1995	Southeast	Rio de Janeiro	11.7	9.5	13.8	855	[58]
1995	Southeast	São Paulo	13.9	10.7	17.1	453	[59]
2002	Southeast	Belo Horizonte	9.5	7.4	11.6	746	[60]
2005	Southeast	Campinas	8.4	6.3	10.5	658	[61]
2009	Southeast	Belo Horizonte	10.6	4.2	16.1	350	[19]
2009	Southeast	Rio de Janeiro	18.3	10.9	24.9	350	[19]
2009	Southeast	Santos	9.0	5.2	13.5	350	[19]
1996	South	Porto Alegre	24.0	20.0	28.0	461	[62]
2009	South	Curitiba	18.9	12.6	25.9	350	[19]
2009	South	Itajaí	12.3	5.3	21.1	350	[19]
1999	Central-west	Goiânia	16.2	4.3	28.1	37	[63]
2009	Central-west	Brasília	23.7	16.6	31.5	350	[19]
2009	Central-west	Campo Grande	6.7	3.5	10.7	350	[64]

Table 2: Number of reported AIDS deaths by region, Brazil 1995-2011

Year	North	Northeast	Southeast	South	Central-west
1995	209	1159	11310	1787	691
1996	270	1200	10914	1972	661
1997	220	984	8488	1811	575
1998	231	954	7167	1866	552
1999	245	989	6796	1945	546
2000	309	1147	6773	1961	540
2001	390	1263	6634	2115	546
2002	415	1341	6496	2246	557
2003	495	1404	6409	2356	619
2004	490	1393	6190	2354	593
2005	579	1498	6009	2433	581
2006	605	1603	5786	2417	635
2007	691	1744	5752	2469	716
2008	759	1887	5883	2585	725
2009	799	2089	5872	2631	704
2010	939	2061	5788	2589	774
2011	922	2180	5682	2561	699

Source: [2]

In order to overcome the possible presence of biases, the annual numbers of deaths caused by AIDS, as estimated with the model, were adjusted to match the data reported by MoH. Firstly, with a parameter that incorporated the estimated proportion of deaths due to AIDS that were being reported in 1984 ($Mort_{1984}$). This was the year when the official report of AIDS deaths started in Brazil. $Mort_{1984}$ was calibrated with bounds between 0 and 1, with 1 reflecting a 100% report of the total AIDS deaths occurred at time t . The increment over time of this reported proportion was modelled by linearly interpolating $Mort_{1984}$ to a future expected report proportion $Mort_{2016}$. The increment between these two points is introduced with a second parameter called $Mortslope \sim U(0,1)$. When $Mortslope = 1$, the future report

proportion in 2016 increases to 100%. If $Mortslope = 0$, this proportion stays the same up to 2016.

Equation 3.23: proportion of AIDS deaths reported in 2016

$$Mort_{2016} = Mort_{1984} + (1 - Mort_{1984})Mortslope$$

The other component of surveillance used in the model comparison was the annual number of people on ART (**Table 3**). As stated before, this information comes from SICLOM information system⁷. The modelling outcome matching this data is the total number of individuals on ART stages in the model per year.

Table 3: Number of people receiving ART by region, Brazil 2008-2012

Year	North	Northeast	Southeast	South	Central-west
2008	5,291	21,797	102,555	43,903	10,454
2009	6,492	26,820	118,749	48,594	11,932
2010	7,573	32,549	133,225	53,574	14,028
2011	8,894	37,496	144,906	60,077	16,213
2012	11,173	42,249	158,392	66,622	18,211

Source: Made available by A. Pascom at Departamento de DST, Aids e Hepatites Virais

2.8 Parameter sampling

An extensive literature review was carried out in order to inform the parameter selection. Regional data was used when available, and the absence of local estimates was resolved by using national estimates with wide prior ranges. **Table 4** describes all the parameters in the

⁷ Information on numbers on ART by region was retrieved and kindly made available by Ana Roberta Pascom at Departamento de DST, Aids e Hepatites Virais, and Francisco Inacio Bastos at Fundação Oswaldo Cruz.

model by region. Values are presented for fixed parameters and prior ranges for calibrated parameters.

A total of 29 parameters were randomly sampled using a Latin Hypercube Sampling algorithm, as explained in Chapter 2, section 2.5.1 of this manuscript. All parameters were drawn from the uniform distribution, bounded according to values described in table 1.

Table 4 Parameters table

		Value/Prior Range					
Symbol	Description	North	Northeast	Southeast	South	Central-west	Reference
Demographic and Initial Model Conditions							
N_0	Total population >15 years at 1970 [†]	1,915,943	15,410,702	24,453,223	9,448,452	2,784,704	[2]
$\epsilon(t)$	Population growth rate per annum	0.04	0.022	0.022	0.02	0.031	Manual calibration to IBGE data [2]
μ	Background mortality rate			1/65 years			
σ	Rate of ceasing sexual activity			1/34 years			Assumption
F	Proportion of female population			0.5			[2]
$NoRW$	Fraction of women out of sexually activity	0.21	0.263	0.235	0.17	0.189	[65]
$Ffsw$	Proportion of women in sex work			$\sim U(0.007, 0.021)$			[65]
$Turnfsw$	FSW turnover rate			$\sim U(10, 20) \text{ year}^{-1}$			[66]
HRW	Proportion of women in high activity group (> 5 partners in the last year)	0.055	0.041	0.043	0.026		[67]
LRW	Proportion of women in low activity group.			$LRW = 1 - (NRW + Ffsw + HRW)$			Assumption
HRM	Proportion of men in high activity group (> 5 partners in the last year)			0.132			[65]
$Fmsm$	Proportion of men exclusive MSM			$\sim U(0.013, 0.027)$			[65]
$Fbismsm$	Proportion of men bisexual MSM			$\sim U(0.008, 0.017)$			[65]
$Fcfsw$	Proportion of men clients of FSW			$\sim U(0.067, 0.089)$			[65]
$NoRM$	Fraction of women out of sexually activity			0.19			
LRM	Proportion of women in low activity group.			$LRM = 1 - (NRM + Fmsm + Fbismsm + Fcfsw + HRM)$			Assumption
t_0	Year of epidemic			1975			Assumption

<i>Seed</i>	start Fraction HIV+ at t_0	$(1e^{-6}$ to 0.0025)					<i>Assumption</i>
Sexual Behavior							
C_k	Partner change rate by activity group (pryr)	$C_{lowrisk} = 1$ $C_{highrisk} \sim U(2,5)$ $C_{sexwork} \sim U(52,2000)$ $C_{clients} \sim U(2,50)$ $C_{msm+bi} \sim U(2,50)$					<i>Assumption</i> [35, 65, 67] <i>Assumption</i> [68] [69]
$Cond_fac$	Scaling condom parameter	$\sim U(0,1)$					<i>Assumption</i>
$\alpha_{k,j}$	Number of sex acts per partnership	Low Risk: 83 High Risk: 8 MSM $\sim U(2,30)$ FSW & Clients $\sim U(1,2)$					[70] <i>Assumption</i>
$M_{k,j}$	Preferential mixing matrix	MSM to MSM $\sim U(0.1,0.9)$ MSMbi to MSMbi= 0.5					<i>Assumption</i>
$v_k(t)$, for $k =$ 2, ...10	Proportion of acts protected with condom in all groups before 1983	(0 to 0.05)					<i>Assumption</i>
$v_k(t)$, for $k =$ 2,6	Proportion of acts protected with condom in low activity	1998: (0.16 -0.23) 2004: (0.16 - 0.23) 2008 : (0.18 - 0.26)	(0.16 to 0.23) (0.18 to 0.21) (0.18 to 0.21)	(0.16 to 0.22) (0.25 to 0.28) (0.18 to 0.21)	(0.11 to 0.20) (0.25 to 0.30) (0.18 to 0.22)	(0.16 to 0.22) (0.2 to 0.30) (0.13 to 0.19)	[71] [67]
$v_k(t)$, for $k =$ 3,7	Proportion of acts protected with condom in high activity	1998: (0.5-0.8) 2004: (0.47-0.52) 2008: (0.44- 0.55)	(0.5-0.8) (0.50-0.55) (0.38- 0.42)	(0.5-0.8) (0.46-0.50) (0.45- 0.48)	(0.5-0.9) (0.58-0.64) (0.44- 0.5)	(0.51-0.8) (0.5-0.59) (0.47- 0.55)	[71]
$v_k(t)$, for $k =$ 8,9	Proportion of acts protected with condom in MSM 1999	(0.44 to 0.55)	(0.55 to 0.78)	(0.44 to 0.87)	(0.41 to 0.78)	(0.7 to 0.87)	[19]
$v_k(t)$, for $k =$ 4	Proportion of acts protected with condom in FSW 2000	(0.45 to 0.54)	(0.42 to 0.51)	(0.68 to 0.67)	(0.60 to 0.68)	(0.82 to 0.92)	[35, 50]
e	Assortativeness coefficient	$\sim U(0,1)$					<i>Assumption</i>
$Cond_{start}$	Year of condom use rates increase	$\sim U(1985,2000)$					<i>Assumption</i>
Natural History of Disease and transmission probabilities							
β_f	Per-act female to male HIV transmission coefficient	$\sim U(0.0014,0.009)$					[72]
β_m	Per-act male to female HIV transmission coefficient	$\sim U(0.0008,0.002)$					[72]
β_{msm}	Per-act male to male HIV transmission coefficient††	$\sim U(0.002, 0.025)$					[73]
γ_s	Average time spent in disease compartments (years)	Acute Stage : $\gamma_1 = 0.25$ CD4 >500 : $\gamma_2 = 2.86$ CD4 350-499 : $\gamma_3 = 2.86$ CD4 200-349 : $\gamma_4 = 3.54$ CD4 <200 : $\gamma_5 = 2.3$					[74]Adapted from[22]
ε_s	Post-acute progression rate (years)	To CD4 >500 : $\varepsilon_2 = 0.58$ To CD4 350-499 : $\varepsilon_3 = 0.23$ To CD4 200-349 : $\varepsilon_4 = 0.16$ To CD4 <200 : $\varepsilon_5 = 0.03$					[22]
$L^{0,1}$	Relative infectiousness coefficient during acute HIV infection	$\sim U(0.47,18.8)$					[72]
ARV therapy and intervention effectiveness							
ρ_A	Recruitment	$\sim U(0.1,2)$					<i>Assumption</i>

	rate into ART at CD4+ <200cell/ μ L (year ⁻¹)		
m	Slope scaling parameter. Is the slope for the line crossing (0, ρ_4) and (0, ρ_1)	$m = \frac{0 - \rho_4(0)}{9.25 - 0}$	Assumption
ω	Relative slope variation factor.	$\sim U(0,1)$	Assumption
$\sigma(t)$	Function for the variation of ART recruitment rate over time	$\sigma(t) = \frac{1}{1 + e^{-r(t-t_{50})}}$, for $r=0.003$	Assumption
t_{50}	Shape parameter in function $\sigma(t)$	$\sim U(0.1,1)$	Assumption
t^{art}	Year of ART introduction	1997	[1]
$L^{a,s}$ For $a=2$ and $s=2,\dots,5$	Relative HIV transmission reduction due to ART (with suppressed viral load)	$\sim U(0.73,0.99)$	[16]
$L^{a,s}$ For $a=1$ and $s=2,\dots,5$	Relative HIV transmission reduction due to ART (with unsuppressed viral load)	0.5	Assumption
ζ	HIV transmission relative reduction due to condom use	$\sim U(0.35,0.94)$	[75]
ϑ	Average ART failure rate (pryr)	0.17	[76]
φ	Average time spent in non-suppressed VL compartments (years)	0.5	[77]
θ	Relative progression rate reduction due to ART	$\sim U(0.1,0.5)$	[5]
$Mortslope$	Slope of underreporting function	$\sim U(0,1)$	Assumption
$Mort_{1984}$	Mortality reporting capacity in 1984	$\sim U(0,1)$	Assumption

† Population at time zero (1975) was found by interpolation of decennial estimations.

†† Combined unprotected receptive and insertive anal intercourse

2.9 Model calibration

The model was run with 1,200,000 randomly drawn parameter sets for each region. According to the priors on inputs described above calibration was carried out as a three-step process which ended in the selection of the parameters sets eligible for further analysis.

2.9.1 Prior Limits on output

The first part of this process consisted in placing *a priori* constraints (or prior limits) upon simulated HIV prevalence in MSM and FSW. These prior limits were informed by the 95% confidence intervals around point estimates found in each region. Since the quality and quantity of point prevalence estimates for these groups varied greatly across regions, the final placement of limits was made case-by-case, as can be seen in **Figures 5 to 9**. Another constraint was set to reject those runs which incidence projections were not stabilizing by 2016, when the simulation ends. This was incorporated simply by finding the maximum value in modelled incidence and comparing against the last value of incidence in the simulation. This last condition was intended to select plausible epidemic scenarios where incidence reached equilibrium via natural dynamics or with the help of interventions.

2.9.2 Likelihood Estimation

The second phase was applied to all runs that passed the initial step of the calibration procedure. HIV prevalence among MSM and FSW, annual number of people on ART and annual AIDS deaths reported, were produced from the selected parameter sets, and were systematically compared against regional data of the same nature.

The likelihood function was applied for each dimension of the data and its matching model outcome (*i.e.* HIV prevalence in MSM and FSW, number receiving ART, and number of AIDS deaths reported).

For comparisons of binomially distributed data, such as HIV prevalence, the likelihood function for binomial distribution was applied. For ease of numerical computation the logarithmic form of these expressions was used.

Equation 3.24: Log-Likelihood function for binomial distribution

$$\ln L(y, \theta) = \sum_i N_i \theta_i \ln(y_i) + N_i(1 - \theta_i) \ln(1 - y_i)$$

Here θ is the probability of success in a Bernoulli trial, in this case the given HIV prevalence data-point. N is the sample size of the study from where probability θ comes. N multiplies θ and $(1 - \theta)$ as an expression of the number of successes and failures, respectively. Symbol y is the modelled prevalence.

Numbers of AIDS deaths reported and numbers of people on ART were assumed to follow a *Poisson* distribution. The deviance function for model comparison of *Poisson* outcomes, which contains itself the *Poisson* likelihood function, was used as described below:

Equation 3.25: Log-Likelihood for Poisson distribution

$$\ln \mathcal{L}(y|\theta) = \sum_{i=1}^n (\theta_i \log y_i - y_i - \log \theta_i!)$$

Here, the data-point (θ_i) (e.g. number of AIDS deaths) is being matched against the i_{th} modelled outcome (y_i) . This is assuming that both the number of deaths and numbers on ART are sampled observations of an underlying process.

2.9.3 Posterior weight and Model selection

After assigning a specific posterior probability to each run in step 2, the marginal contribution of each of these parameter-sets to the overall probability estimated for each region was assessed by calculating a Posterior Weight.

Equation 3.26: Weighted posterior

$$W_j = \exp \frac{\text{LogLikelihood}_j}{\max(\text{LogLikelihood})}$$

The posterior probability of each run_j is re-scaled first by dividing over the maximum posterior across all runs, and then taking the antilog to work the weighted values in a positive scale.

A vector of weights W was then sorted in descending order, having as first element of W the equivalent of the best fit simulation in a frequentist approach. Dividing each element of W by the cumulative sum of W allowed us to find the set of parameters that contributed with 95% of the total posterior weight, assembling a credible set of runs that would be posteriorly used for analysis.

2.10 *Analysis plan*

2.10.1 Post-calibration

Calibration results are visualized for each region by plotting the resulting simulations against the available data for each location. Posterior and prior ranges of model parameters are

presented in **Table 5** to understand which parameters were more susceptible to be shaped or informed during the calibration process.

2.10.2 Estimating the impact of ART

Reductions in incidence attributable to ART were estimated by subtracting the cumulative number of HIV infections obtained with the calibrated model(s) for the period 1997 to 2014, from the cumulative number of cases in a counterfactual scenario where no ART was available during the same period.

Equation 3.28: Absolute reduction of HIV infections due to ART during 1997 to 2014

$$C_{diff} = \int_{1994}^{2014} \lambda_0(t)S(t) - \int_{1994}^{2014} \lambda_1(t)S(t)$$

Equation 3.29: Relative reduction of HIV infections with ART during 1997 to 2014

$$C_{Rdiff} = \frac{\int \lambda_0(t)S(t) - \int \lambda_1(t)S(t)}{\int \lambda_0(t)S(t)}$$

The first term, $\lambda_0(t)S(t)$, expresses the number of HIV infections occurring at time t in an alternative scenario of No-ART. The second term of the equation reflects the same outcome but in the current known scenario (*i.e.* the calibrated model).

Similarly, estimations of absolute and relative reductions in incidence stratified by risk group are presented.

To explore the association between the posterior distribution of model parameters and the main outcome of analysis (*i.e.* Cumulative HIV incidence reduction) partial rank correlation coefficients (PRCC) were calculated, as described elsewhere [78]. PRCC values range between 1 and -1, with coefficients of around 1 meaning a very strong positive correlation between the parameter and the outcome, and values near -1 standing for a strong negative correlation. Values around zero show weak correlations.

3 RESULTS

3.1 Calibration results

The calibration procedure -after 1,200,000 initial runs for each region- yielded 785 (North), 107 (Northeast), 219 (Southeast), 184 (South) and 773 (Central-west) eligible parameter sets for further analysis.

The propagation of uncertainty throughout the simulations is a reliable diagnostic of the calibration procedure, and in this case it shows how the availability of data influenced the resulting trends in each region (**Figures 5 to 9**). The Northern region is the one with less information available and that is translated into wide uncertainty bounds.

Across all regions, modelled numbers of people receiving ART showed the greatest uncertainty, especially in the early years of ART scale-up for which no data is available. The initial shape of treatment expansion was highly uncertain in all cases, with various scenarios for ART scale-up -from steep increase to slowly growing shapes- leading to plausible and acceptable model fits. Not having one single trajectory to explain the ART scale-up but a collection of possible trends might reflect a mismatch between the data and the modelled

outcome. The reported number of people on ART each year is not an outcome that emerges naturally from the epidemic dynamics, but a product of the HIV treatment cascade and therefore susceptible to biases. Leaks across the cascade of treatment could have been in place in Brazil's systems which were not adequately captured by this model. Double counting, under-reporting and reporting delays may also be present in the data used for calibration.

Incidence rate projections from the posterior calibrated models suggest that MSM are the driving force behind HIV transmission across regions, with Central-western region displaying the largest incidence rate in this group, which is in line with the fact that the highest HIV prevalence estimates in MSM in later years were found in this location (**Table 4**) (**Figure 10**). However, the lack of prevalence data in the early years in Central West Brazil might be allowing oversized early epidemics to take-off and find an early sharp decline, in contrast to other regions where the presence of early information is constraining an initial epidemic explosion. HIV in FSW has a relevant role in South and Southeast epidemics, and extends to their clients. In general, a consistent decline across groups and regions can be seen in all estimations. Some trajectories find its peak in the late 1980s and early 1990s, plausibly by the effect of natural dynamics (saturation of risk groups) or high levels of condom use in the years after the HIV testing era.

Calibration had a different impact on informing the posterior parameter distribution in relation to the main outcome of the model (i.e. cumulative HIV incidence reduction due to ART) as can be seen in **Table 5**. Parameters with the greatest variation in their posterior distribution from its prior were: the shape parameter for ART scale up (t_{50}), the partner change rate in FSW (c_{fsw}), mortality reporting rate in 1984 ($Mort_{1984}$), the mixing balance coefficient, number of acts per partnership in MSM (α_{msm}) and the factor of mortality reporting ($Mortslope$).

Table 5: Prior and posterior parameter ranges and PRCC analysis for cumulative HIV incidence reduction (1997-2014) due to ART

	Prior Range			North			Northeast			Posterior Range Southeast			South			Central-West		
	Lower	Upper	PRCC	Lower	Upper	PRCC	Lower	Upper	PRCC	Lower	Upper	PRCC	Lower	Upper	PRCC	Lower	Upper	
<i>Seed</i>	1.00E-06	0.0025	-0.2*	1.81E-05	0.0025	-0.2	4.26E-05	0.0025	-0.3*	3.49E-05	0.0025	-0.2	5.06E-05	0.0025	-0.2*	1.64E-05	0.0025	
<i>Cond_{fac}</i>	0	1	-0.1	0.00	1.00	0.0	0.00	0.98	-0.2*	0.01	0.99	0.0	0.01	0.98	-0.1	0.00	1.00	
ρ_4	0.333	10	0.7*	0.362	9.988	0.7*	0.350	9.998	0.7*	0.530	9.940	0.6*	0.342	9.993	0.7*	0.336	9.977	
<i>m</i>	0	1	-0.4*	0.0016	0.9970	-0.2	0.0015	0.9954	-0.5*	0.0022	0.9989	-0.2*	0.0043	0.9951	-0.3*	0.0034	0.9974	
<i>t₅₀</i>	0.01	1	-0.9*	0.0109	0.9459	-0.9*	0.0382	0.8582	-0.9*	0.0104	0.8569	-0.9*	0.0162	0.8104	-0.9*	0.0101	0.8939	
<i>c_{hrw}</i>	2	5	-0.1	2.0	5.0	-0.2	2.0	5.0	0.0	2.0	5.0	0.1	2.04	4.97	0.0	2.00	5.00	
<i>c_{fsw}</i>	52	2000	0.1	129	1998	-0.2	271	1989	0.1	310	1995	0.1	248	1996	0.0	78	1994	
<i>c_{bi}</i>	2	50	-0.1	2.0	49.9	-0.1	2.3	49.8	-0.1	2.2	49.9	0.0	2.1	48.9	0.1	2.2	49.8	
<i>C_{cfsw}</i>	2	50	0.0	2.0	50.0	0.1	2.2	49.7	0.0	2.4	49.8	0.1	2.2	49.8	0.0	2.0	50.0	
<i>e</i>	0	1	0.0	0.00	1.00	0.3*	0.03	1.00	-0.2	0.00	1.00	0.0	0.01	1.00	0.0	0.00	1.00	
β_f	0.0003	0.001	0.0	0.0003	0.0010	-0.1	0.0003	0.0010	0.0	0.0003	0.0010	0.2	0.0003	0.0010	0.0	0.0003	0.0010	
β_m	0.0002	0.0008	0.1*	0.0002	0.0008	0.0	0.0002	0.0008	0.1	0.0002	0.0008	0.1	0.0002	0.0008	0.0	0.0002	0.0008	
β_{msm}	2	20	0.1	2.0	20.0	0.1	2.1	19.6	0.0	2.1	20.0	0.1	2.0	19.5	0.0	2.0	19.9	
$L^{0,l}$	4	18	-0.3*	4.0	18.0	-0.4*	4.1	17.9	-0.4*	4.1	17.8	-0.2	4.1	17.9	-0.3*	4.0	18.0	
$L^{2,l}$	0.04	0.7	-0.7*	0.04	0.70	-0.7*	0.04	0.70	-0.8*	0.04	0.70	-0.7*	0.05	0.70	-0.7*	0.04	0.70	
ς	0.35	0.94	-0.4*	0.35	0.94	-0.3*	0.35	0.93	-0.5*	0.35	0.93	-0.4*	0.35	0.93	-0.3*	0.35	0.94	
<i>F_{fsw}</i>	0.007	0.021	0.0	0.007	0.021	-0.2	0.007	0.021	0.0	0.007	0.021	0.1	0.007	0.021	-0.1	0.007	0.021	
<i>F_{msm}</i>	0.013	0.027	0.0	0.013	0.027	-0.2	0.013	0.027	0.1	0.013	0.027	0.2*	0.013	0.027	0.0	0.013	0.027	
<i>F_{cfsw}</i>	0.067	0.089	-0.1	0.067	0.089	0.0	0.067	0.089	0.0	0.067	0.089	0.2	0.067	0.089	0.1*	0.067	0.089	
<i>c_{msm}</i>	2	50	0.1	2.1	49.9	0.0	2.2	48.9	0.0	2.0	49.8	0.0	2.2	49.7	0.0	2.0	50.0	
θ	0.2	0.9	0.2*	0.20	0.90	0.2	0.21	0.90	0.2*	0.20	0.89	0.2	0.20	0.90	0.2*	0.20	0.90	
<i>Cond_{start}</i>	1985	2000	-0.2*	1985	2000	-0.3	1985	2000	-0.2*	1985	2000	0.0	1985	2000	-0.2*	1985	2000	
<i>Mort₁₉₈₄</i>	0.1	1	0.0	0.1	1.0	0.1	0.1	0.9	0.0	0.1	1.0	0.2	0.1	0.9	0.0	0.1	1.0	
<i>balance</i>	0	1	-0.1	0.0	1.0	0.0	0.0	1.0	0.0	0.0	1.0	-0.1	0.0	0.9	0.0	0.0	1.0	
M_{msm}	0.1	0.9	0.0	0.1	0.9	0.0	0.1	0.9	0.0	0.1	0.9	0.0	0.1	0.9	0.0	0.1	0.9	
α_{msm}	2	30	0.1	2	30	0.0	2	30	0.1	2	28	0.0	2	29	0.1	2	30	
α_{cfsw}	1	2	0.1	1	2	-0.1	1	2	-0.1	1	2	0.1	1	2	0.1	1	2	
<i>Turn_{fsw}</i>	10	20	0.0	10	20	-0.1	10	20	-0.1	10	20	0.2*	10	20	0.0	10	20	
<i>Mortslope</i>	0	1	0.0	0.00	1.00	0.1	0.01	0.96	-0.1	0.00	0.99	0.1	0.00	0.93	0.0	0.00	0.99	

**p* value < 0.01

Brazil, North

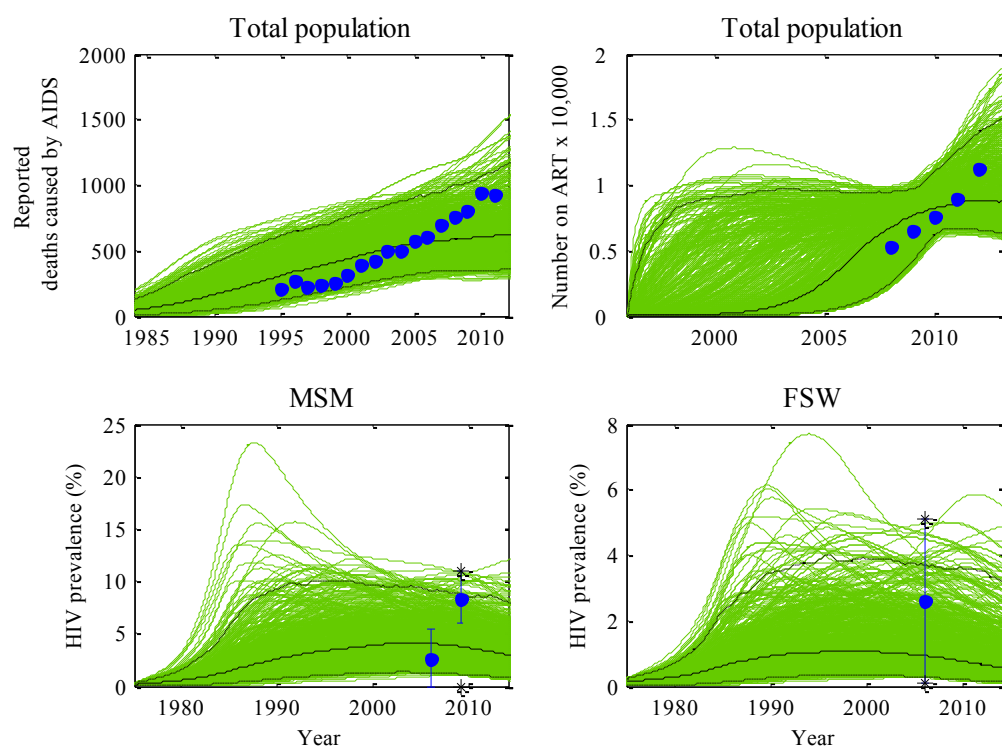


Figure 5 Model comparison to data in Northern region: Top panels show model simulations (green) for reported number of deaths due to AIDS (top-left) and number of people receiving ART (top-right). Blue dots are data points as reported by Brazil DTS and AIDS department. Panels in the bottom show prevalence of HIV in both MSM (left) and FSW (right). Dots and error bars represent point estimations and its 95% confidence intervals. Median values in black solid lines. 95% percentile range is shown within dashed black lines. Black stars are prior limits.

Brazil, Northeast

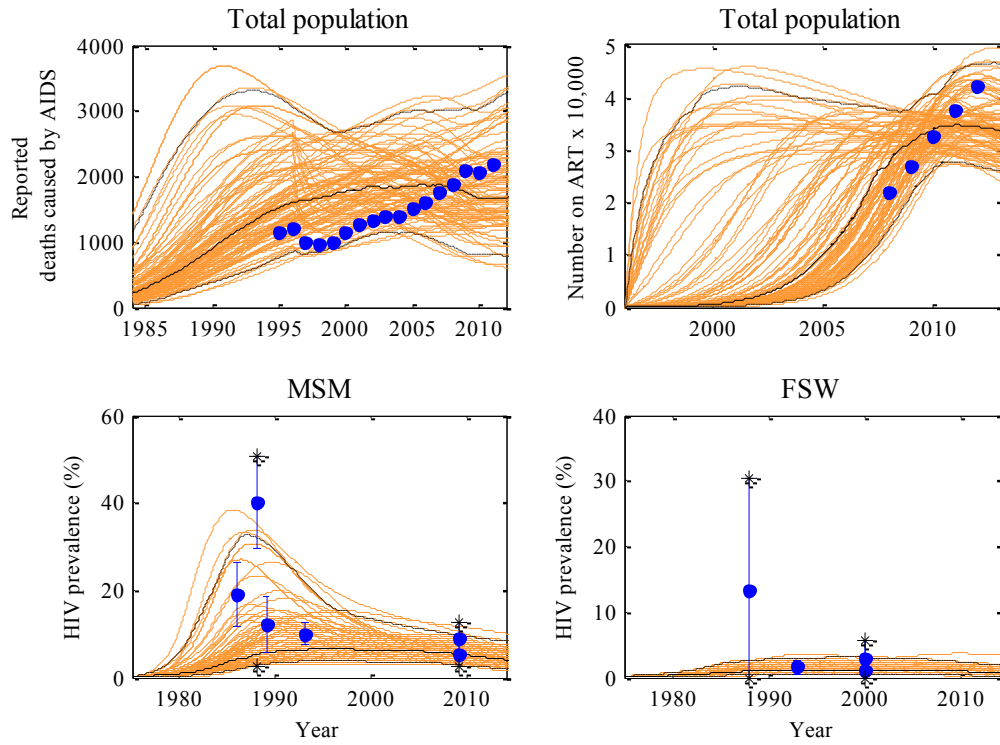


Figure 6 Model comparison to data in North-eastern region: Top panels show model simulations (Orange) for reported number of deaths due to AIDS (top-left) and number of people receiving ART (top-right). Blue dots are data points as reported by Brazil DTS and AIDS department. Panels in the bottom show prevalence of HIV in both MSM (left) and FSW (right). Dots and error bars represent point estimations and its 95% confidence intervals. Median values in black solid lines. 95% percentile range is shown within dashed black lines. Black stars are prior limits.

Brazil, Southeast

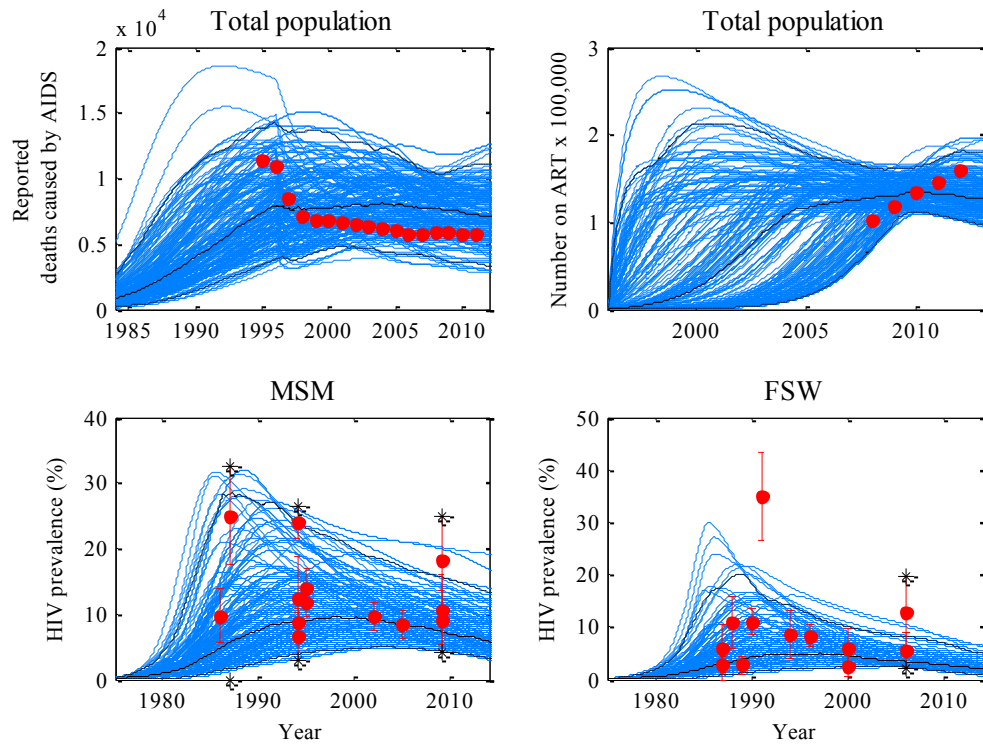


Figure 7 Model comparison to data in South-eastern region: Top panels show model simulations (blue) for reported number of deaths due to AIDS (top-left) and number of people receiving ART (top-right). Red dots are data points as reported by Brazil DTS and AIDS department. Panels in the bottom show prevalence of HIV in both MSM (left) and FSW (right). Dots and error bars represent point estimations and its 95% confidence intervals. Median values in black solid lines. 95% percentile range is shown within dashed black lines. Black stars are prior limits.

Brazil, South

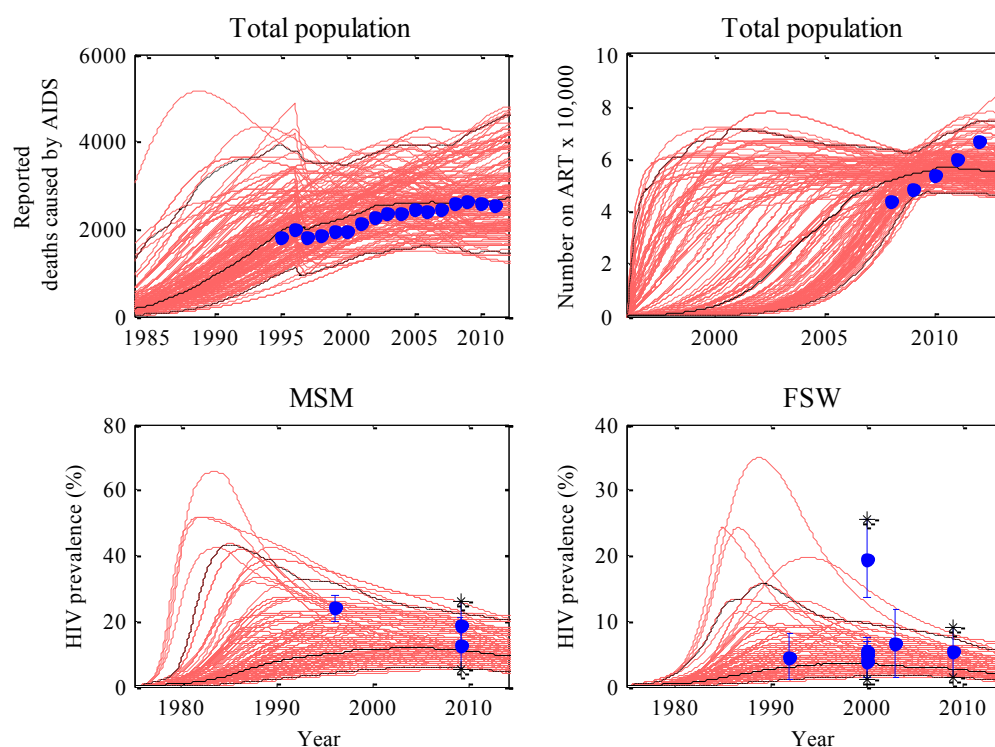


Figure 8 Model comparison to data in Southern region: Top panels show model simulations (pink) for reported number of deaths due to AIDS (top-left) and number of people receiving ART (top-right). Blue dots are data points as reported by Brazil DTS and AIDS department. Panels in the bottom show prevalence of HIV in both MSM (left) and FSW (right). Dots and error bars represent point estimations and its 95% confidence intervals. Median values in black solid lines. 95% percentile range is shown within dashed black lines. Black stars are prior limits.

Brazil, Central-West

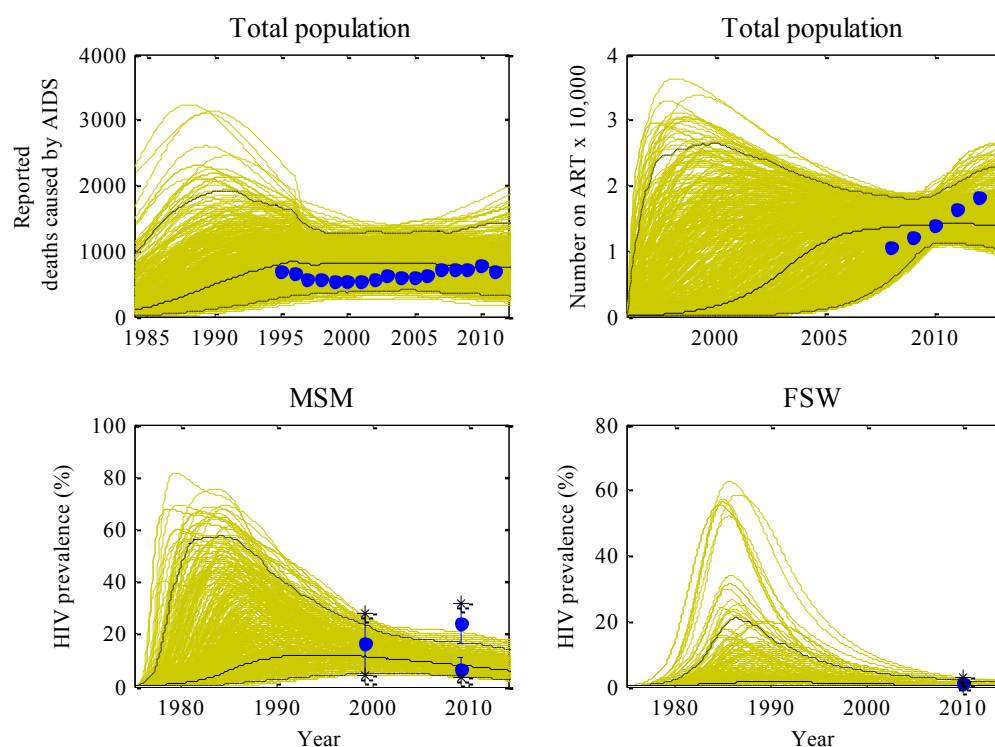


Figure 9 Model comparison to data in Central-western region: Top panels show model simulations (yellow) for reported number of deaths due to AIDS (top-left) and number of people receiving ART (top-right). Blue dots are data points as reported by Brazil DTS and AIDS department. Panels in the bottom show prevalence of HIV in both MSM (left) and FSW (right). Dots and error bars represent point estimations and its 95% confidence intervals. Median values in black solid lines. 95% percentile range is shown within dashed black lines. Black stars are prior limits.

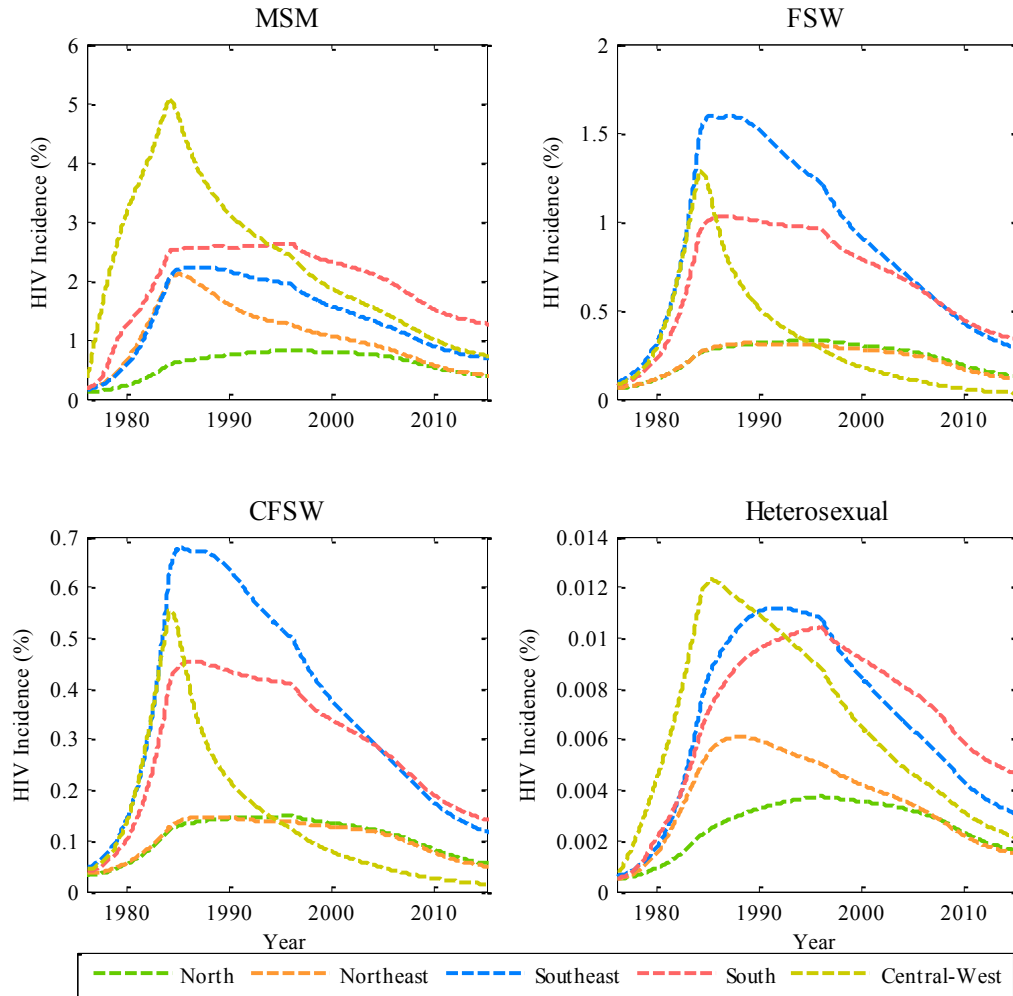


Figure 10 Model projections of HIV incidence rate among MSM, FSW, CFSW and Low and High activity heterosexuals in Brazil: projections reflect the median of the posterior distribution of the calibrated regional models.

3.2 Estimated impact of ART for reducing HIV incidence in Brazil

This model found that the introduction of ART in 1997 could have had a substantial impact in reducing HIV transmission in Brazil. The majority of infections averted come from the southeast region (median $\sim 150,000$), the more populated area and host of the biggest HIV epidemic in Brazil (**Figure 10**). Overall, the aggregated regional estimations tell us that a median 272,000 new HIV infections could have been averted in Brazil between 1997 and 2014 given the introduction of ART. This is in relative terms an average of 30% of HIV

infections averted in that period. Looking closely at the regional level it is evident that the lowest point in relative reduction was found in the Northeast, with a median reduction of 23% (IQR 17%). However, uncertainty bounds are wide around point estimates, showing overlapping ranges, making it difficult to draw conclusions on the regional differences on this regard.

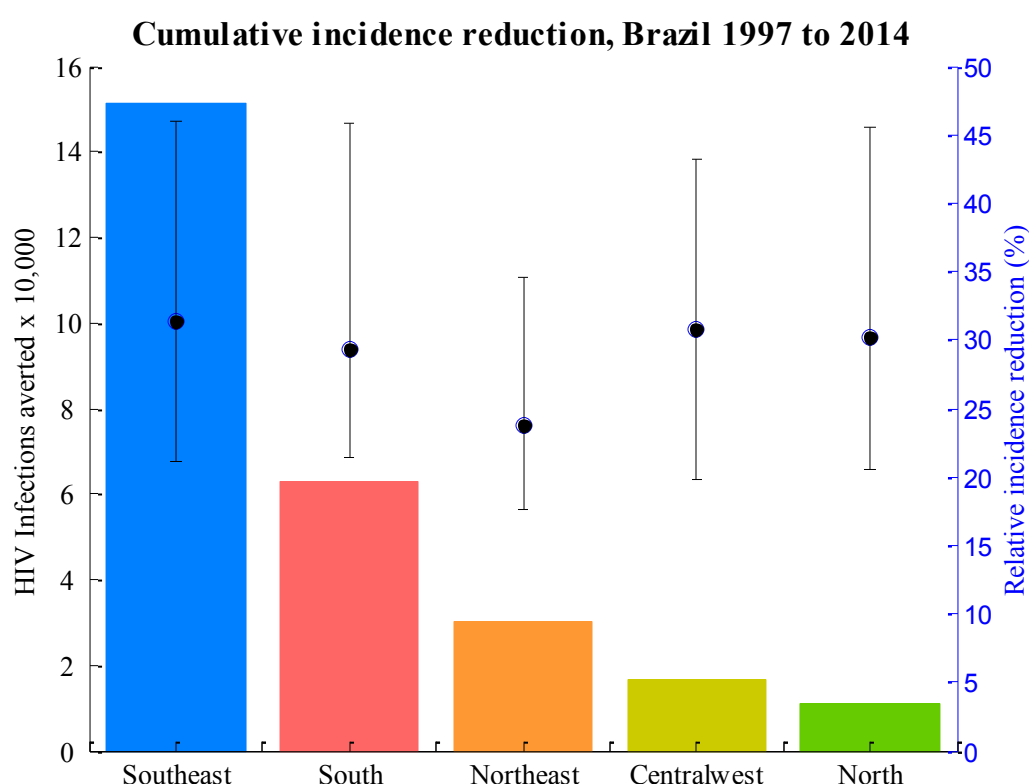


Figure 10 Cumulative absolute and relative HIV incidence reductions from modelling results: Coloured bars for the absolute estimated number of HIV infections averted. Dots and lines are the median relative reduction in each region. Error bars showing interquartile ranges (percentile, 27/75).

Projecting modelling results of HIV incidence and prevalence by region reveals the possible impact that ART has had in shaping the current regional epidemics of Brazil (**Figures 11 and 12**). These simulations show how the local epidemics in the North and South regions would not have found a stable/declining trend without the introduction of ART. In the remaining

areas incidence projections would have found equilibrium by force of natural dynamics and condom use alone.

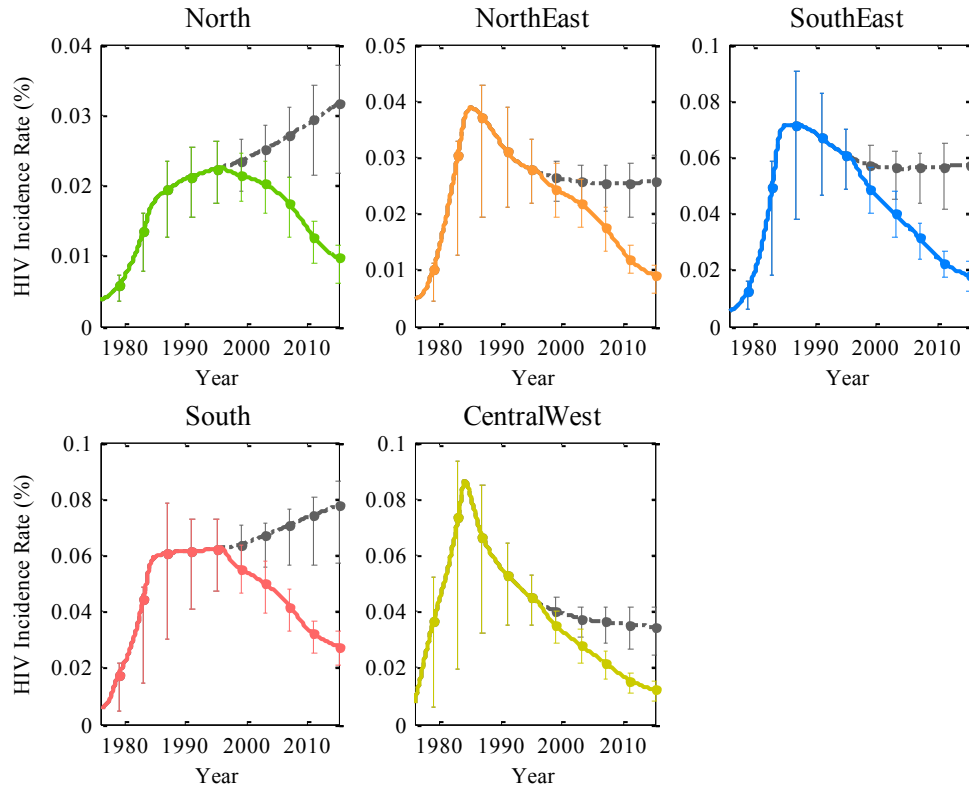


Figure 11 Modelled HIV incidence rate in five regions of Brazil under two scenarios of ART availability: Solid coloured lines are the median of the posterior incidence rate estimated with calibrated model. Dotted line shows the median posterior for a scenario of No ART. Error bars along curves are the interquartile ranges of the posterior model projections.

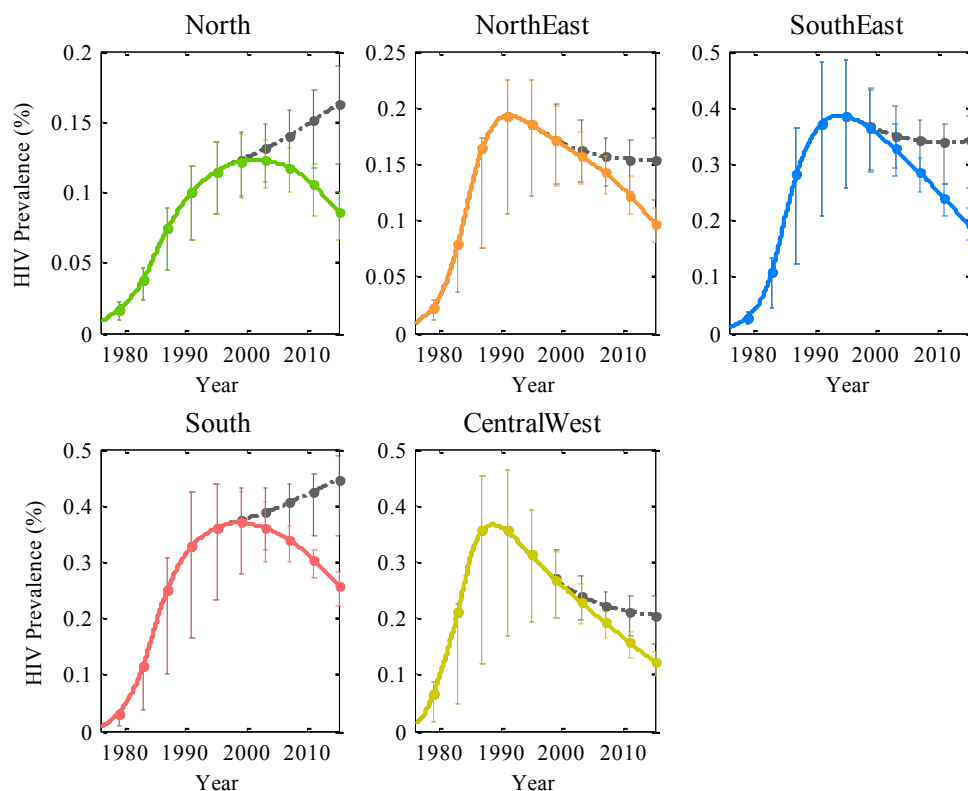


Figure12 Modelled HIV prevalence in five regions of Brazil under two scenarios of ART availability: Solid coloured lines are the median of the posterior prevalence estimated with calibrated model. Dotted line shows the median posterior for a scenario of No-ART. Error bars along curves are the interquartile ranges of the posterior model projections.

ART resulted in a great number of HIV infections averted within MSM over the other risk groups in this model (**Figure 13**).

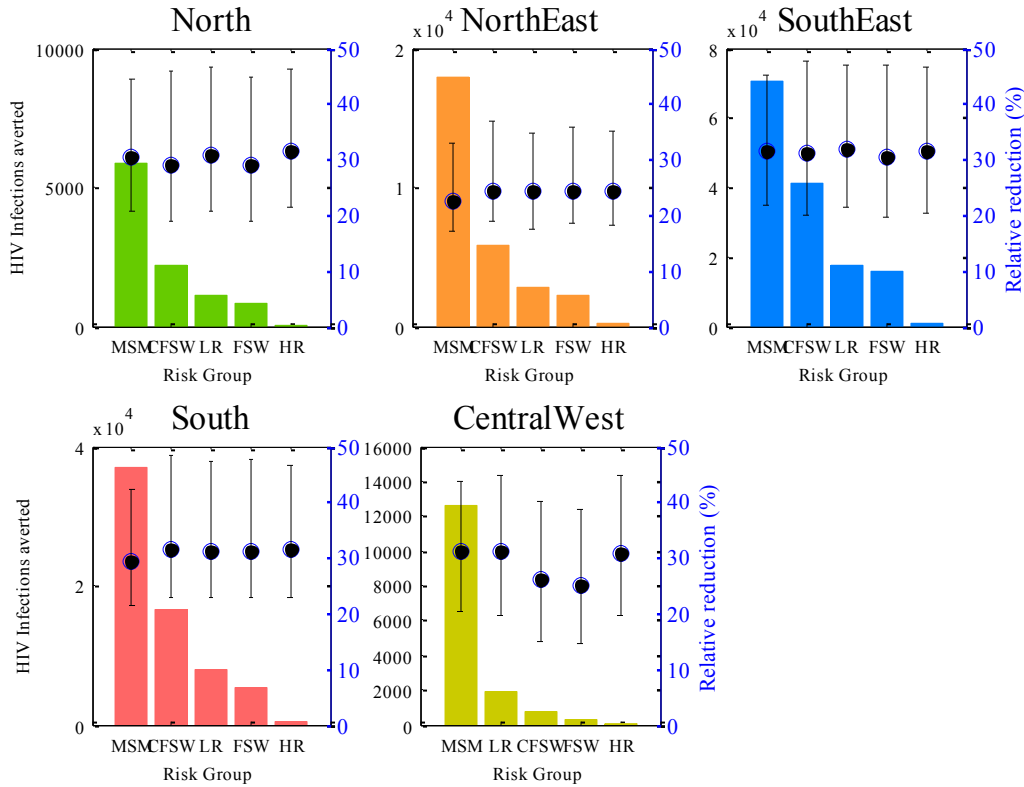


Figure 13 Cumulative absolute and relative HIV incidence reductions from modelling results by risk group and region in Brazil: each panel shows the absolute (bars) vs proportional (dots) incidence reduction by risk group, in descending order. Error bars are interquartile range around the posterior median of model projections.

Correlations between the posterior distribution of parameter values and the decrease in cumulative new HIV infections provides further insights about the model behaviour and the factors determining the estimated impact of ART (**Table 5**). The strongest correlations were observed in those parameters related to ART expansion and effectiveness. This finding was common to all regions. The rate at which individuals with CD4+ count <200 cell/mL move into ART (ρ_4) was positively correlated with the cumulative incidence reduction (PRCC ~ 0.7). This shows that higher recruitment rates during a late stage of disease would actually boost the overall impact of ART for preventing HIV transmission. Similarly, the ART expansion shape-parameter t_{50} was very strongly negatively correlated with the outcome (PRCC ~ -0.9). This parameter sets the turning point of the sigmoidal-like function used here to describe ART scale-up. Small values of t_{50} result in a very steep function, meaning a rapid

increase in the rate of recruitment into ART. On the contrary, large values lead to a smoothly growing shape that result in a lesser number of people being set on ART. Finally, the coefficient for relative reduction of HIV transmission due to ART ($L^{2,i}$) showed a strong negative correlation with cumulative infections averted in all regions. This was expected, since small values of $L^{2,i}$ result in large relative reductions as the parameter is introduced in the model as $(1-L^{2,i})$.

Posterior distributions of this parameter show slightly right-skewed distributions, suggesting a systematic selection of low values of ART effectiveness on transmission during calibration (**Figure 14**).

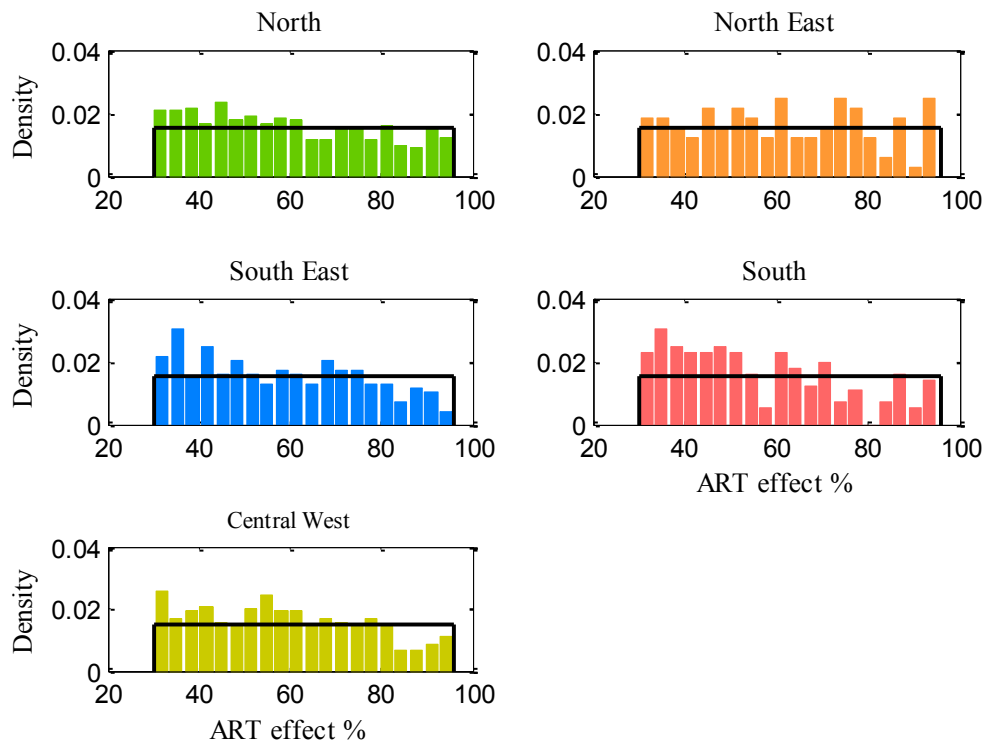


Figure 14 Posterior distribution of ART effectiveness on transmission parameter: frequency histogram by region. Black solid line shows prior distribution density.

4 DISCUSSION

This mathematical modelling analysis of the retrospective impact of ART in Brazil, found that an average 30% (IQR 22%) relative reduction in cumulative new HIV-1 infections was achieved with the introduction of ART across the five major regions of Brazil from 1997 to 2014. HIV incidence in Brazil in 2014 is 63% (IQR 22%) lower than it would be if ART had not been introduced.

For all of the regions, the model was able to reproduce epidemic trends among FSW and MSM while preserving the fit to surveillance data in the general population level. This model behaviour suggests an adequate choice of assumptions and an accurate simulation of the infection dynamics within the risk groups.

Nevertheless, the lack of detail and quantity of information available in some regions increased the uncertainty around estimations, particularly for the cases of North and Central-West regions.

Large absolute reductions of cumulative new HIV infections were estimated for both South and Southeast regions. Relative reduction estimations on the other hand, were similar for all five models, with the North-eastern region displaying the shortest reduction of all (23%, IQR 17% to 34%). This point is of particular interest and adds to a conclusion that can be drawn by simple observation of basic demographic and surveillance data in Brazil: the Northeast is the second most populated region in the country after the Southeast, and is still only third in number of patients receiving HIV treatment (**Tables 2, 3 and 4**). From the surveillance perspective the Northeast holds the smallest epidemic in Brazil [79], that is, based on the rate of cases diagnosed per year. This contrasts not only with our findings, but with other analyses where the size of the epidemic in Brazil has been assessed [80]. We can conclude from a modelling perspective that the Northeast might hold a larger epidemic than it has been

reported, possibly by low levels of detection leading to a relatively low amount of patients receiving treatment. Grangeiro et al, have analysed Brazil's HIV programme data from 2003 to 2006 to establish the rates of late entry into AIDS care (diagnosed at death, AIDS illness or CD4 count < 200cell/mL) for different regions [21]. Their findings support our observations: the Northeast and the North present the biggest proportion of late entry into care among all regions (53.4% and 48.1% respectively) in Brazil.

It is evident from these results that MSM are the driving force behind HIV-1 transmission in Brazil, and as such seem to have benefited the most from the ART preventive effect. The estimated numbers of HIV infections averted are the consequence of simulating very concentrated epidemics in the context of equal access to treatment, that is, proportional effects of ART on incidence according to the contribution of each group to the overall epidemic. Looking closely at the relative reductions of cumulative infections by risk group it is clear that no major differences can be reported across risk groups. The differences observed then correspond to the nature of local epidemics and not to a differential effect by sub-population, since access to ART was modelled as a homogenous rate across risk groups, and was only set to vary over time and CD4 count stages. It can be said though, that those groups whose risk of infection is higher (MSM, FSW, CFSW) obtained the greater benefit of the preventive effects of antiretrovirals, when measured as the absolute number of new HIV-1 infections averted between 1997 and 2014, and under the assumptions of this model. This might oversimplify a more complex reality where vulnerable groups have unequal access to health services or different levels of adherence to treatment. It is possible that allowing all sub-populations to access treatment homogeneously in this model is overestimating the preventive effect of ART. However the lack of consistent data on this point makes it a difficult task to include differential access.

ART has proven its effectiveness for reducing infectiousness in individuals [16] and the evidence supports its population effects [81-83]. Cohen et al, found that the relative hazard reduction was 96%, while cohort studies have found a 92% reduction in the risk of transmission among serodiscordant couples [81]. The 30% reduction estimated with this modelling analysis is by no means contrary to “outside of trial” observations of the impact of preventive effect of antiretrovirals. Tanser et al. analysed a prospective cohort in KwaZulu-Natal finding a reduction of 38% in the risk of HIV acquisition for individuals in communities with high ART coverage (30% to 40% of all PLHA) [84]. Jia et al, have found a 26% reduction of HIV incidence by reconstructing the largest serodiscordant cohort to date, with 38 862 couples followed in China [85]. Other studies have found reduction effects as small as 9% in Uganda [86]. In Brazil, a cohort of 93 serodiscordant couples in Porto Alegre was reconstructed by Melo et al [87]. During the follow-up time, 6 seroconversion events were observed, all in the No-treatment arm. No cases were observed in the ART arm. However, the effect was non-significant, but suggested a large impact of ART in that context. In general, the estimated reductions with this analysis are in line with the argument that it is plausible that bringing ART scale-up programmes outside the trial context might reduce the experimental effect of treatment for stopping transmission. In any case, this model was designed to reproduce retrospectively the impact of ART in Brazil, in a period where halting HIV transmission by the means of antiretrovirals was not in the agenda. It is therefore an unfair comparison for Brazil’s programme. Moreover, the change in epidemiological context is a central factor of the impact of treatment for prevention, as has been described by Dodd et al [88].

One limitation in the population structure of this model is the absence of PWID. This group has played a role in the HIV epidemic of Brazil, particularly in the urban areas of the country (South and Southeast), contributing with a large amount of cases during the 1990s [13]. In

order to maintain comparability across regions and to limit the model complexity, PWID were not included. It is therefore possible that the contribution of the other groups present in the model is over estimated by the absence of PWID, particularly in the first years of the simulation.

As reported by different authors, the use of drugs has changed drastically in Brazil as a function of prices and the availability of new options reducing the frequency of injecting behaviour during the 2000s[12]. This sustained reduction in the number of PWID overlaps in time with ART scale-up increases, which might mean that this population was not widely exposed to ART, thus its absence is not affecting these estimations to a large extent. On the other hand, irrespective of the population size of PWID during ART introduction, these modelling results might be overestimating the marginal impact of ART by risk group due to the assumption of no-PWID.

Another limitation found here, might be one related to oversimplification of the flow inside the treatment programme for a given patient in Brazil: this model allows for one single line of treatment, whose effectiveness is the same from the introduction of ART to the current date, and despite the presence of failure stages, patients return to the same line of treatment if they are re-linked to treatment. It is not possible to predict the effect of this assumption in these results, but a more detailed approach should observe the increasing potency of antiretroviral schemes over time as well as a second and third line treatments. As described before, this analysis is also limited by the level of detail of the programmatic data used for fitting the model outcomes. This is reflected in large amounts of uncertainty around these projections that could be addressed in the future with a better understanding of the collection and construction of these indicators.

Brazil has committed from the beginning of the HAART era to universal access to treatment, and as a programme has been reviewing its own standards to make the most out of its infrastructure and its health system capacity. These estimations shed light over the effect of treatment during the implementation of one of the biggest programmatic efforts in public health history, and might offer new perspectives for planning ahead the future use of antiretrovirals in the era of treatment as prevention.

5 REFERENCES

1. Nunn, A., *The politics and history of AIDS treatment in Brazil*. 2009, New York ; London: Springer.
2. Instituto-Brasileiro-de-Geografia-e-Estatística. [cited 2013 01-10]; Available from: <http://www.ibge.gov.br>.
3. Departamento-de-DST-Aids-e-Hepatites-Virais, *Boletim Epidemiológico*, M.d. Saúde, Editor. 2012, Ministério da Saúde: Brasília DF.
4. Departamento de DST, A.e.H.V., *Aids e DST*, in *Boletim Epidemiológico*, M.d. Saúde, Editor. 2013, Ministério da Saúde: Brasília. p. 1:64.
5. Marins, J.R., et al., *Dramatic improvement in survival among adult Brazilian AIDS patients*. AIDS, 2003. **17**(11): p. 1675-82.
6. Hacker, M.A., et al., *The first ten years: achievements and challenges of the Brazilian program of universal access to HIV/AIDS comprehensive management and care, 1996-2006*. Cad Saude Publica, 2007. **23 Suppl 3**: p. S345-59.
7. Guimarães, M.D., *[Temporal study in AIDS-associated disease in Brazil, 1980-1999]*. Cad Saude Publica, 2000. **16**(## Suppl 1): p. 21-36.
8. Morgado, M.G., et al., *Human immunodeficiency virus/acquired immunodeficiency syndrome and tropical diseases: a Brazilian perspective*. Mem Inst Oswaldo Cruz, 2000. **95 Suppl 1**: p. 145-51.
9. Sampaio, R. and H. Théry, *Orientação metodológica para construção e leitura de mapas temáticos* Confins, 2008(3): p. 1:21.
10. Saúde, M.d., *Boletim Epidemiológico'AIDS*. 1999.
11. Szwarcwald, C.L., et al., *[The spread of the AIDS epidemic in Brazil from 1987 to 1996: a spatial analysis]*. Cad Saude Publica, 2000. **16**(## Suppl 1): p. 7-19.
12. Bastos, F.I., *Structural violence in the context of drug policy and initiatives aiming to reduce drug-related harm in contemporary Brazil: a review*. Subst Use Misuse, 2012. **47**(13-14): p. 1603-10.
13. Mesquita, F., et al., *Trends of HIV infection among injection drug users in Brazil in the 1990s: the impact of changes in patterns of drug use*. J Acquir Immune Defic Syndr, 2001. **28**(3): p. 298-302.

14. Barbosa Junior, A., et al., *[Proposed UNGASS indicators and the monitoring of the AIDS epidemic in Brazil]*. Rev Saude Publica, 2006. **40 Suppl**: p. 94-100.
15. Dourado, I., et al., *Risk factors for human T cell lymphotropic virus type I among injecting drug users in northeast Brazil: possibly greater efficiency of male to female transmission*. Mem Inst Oswaldo Cruz, 1999. **94**(1): p. 13-8.
16. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy*. N Engl J Med, 2011. **365**(6): p. 493-505.
17. Teixeira, T.R., et al., *Social geography of AIDS in Brazil: identifying patterns of regional inequalities*. Cad Saude Publica, 2014. **30**(2): p. 259-71.
18. Szwarcwald, C.L. and E.A. Castilho, *[Estimated number of HIV-infected individuals aged 15-49 years in Brazil, 1998]*. Cad Saude Publica, 2000. **16**(## Suppl 1): p. 135-41.
19. Kerr, L.R., et al., *HIV among MSM in a large middle-income country*. AIDS, 2013. **27**(3): p. 427-35.
20. Fazito, E., et al., *Identifying and quantifying misclassified and under-reported AIDS deaths in Brazil: a retrospective analysis from 1985 to 2009*. Sex Transm Infect, 2012. **88 Suppl 2**: p. i86-94.
21. Grangeiro, A., M.M. Escuder, and J.C. Pereira, *Late entry into HIV care: lessons from Brazil, 2003 to 2006*. BMC Infect Dis, 2012. **12**: p. 99.
22. Lodi, S., et al., *Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm³: assessment of need following changes in treatment guidelines*. Clin Infect Dis, 2011. **53**(8): p. 817-25.
23. Garnett, G.P., et al., *The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey*. Philos Trans R Soc Lond B Biol Sci, 1999. **354**(1384): p. 787-97.
24. Anderson, R.M. and R.M. May, *Infectious diseases of humans : dynamics and control*. Oxford science publications. 1991, Oxford ; New York: Oxford University Press. viii, 757 p.
25. Pinkerton, S.D. and P.R. Abramson, *Occasional Condom Use and HIV Risk Reduction*. Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology, 1996. **13**: p. 13-16.
26. Bezemer, D., et al., *27 years of the HIV epidemic amongst men having sex with men in the Netherlands: An in depth mathematical model-based analysis*. Epidemics, 2010. **2**(2): p. 66-79.
27. Hallett, T.B., et al., *Assessing evidence for behaviour change affecting the course of HIV epidemics: a new mathematical modelling approach and application to data from Zimbabwe*. Epidemics, 2009. **1**(2): p. 108-17.
28. Fernandes, J.R., et al., *[Initiation of antiretroviral therapy in HIV-infected patients with severe immunodeficiency in Belo Horizonte, Minas Gerais State, Brazil]*. Cad Saude Publica, 2009. **25**(6): p. 1369-80.
29. Souza-Jr, P.R., C.L. Szwarcwald, and E.A. Castilho, *Delay in introducing antiretroviral therapy in patients infected by HIV in Brazil, 2003-2006*. Clinics (Sao Paulo), 2007. **62**(5): p. 579-84.
30. Pacheco, A.G., et al., *Estimating the extent of underreporting of mortality among HIV-infected individuals in Rio de Janeiro, Brazil*. AIDS Res Hum Retroviruses, 2011. **27**(1): p. 25-8.
31. Benzaken, A.S., et al., *Field evaluation of the performance and testing costs of a rapid point-of-care test for syphilis in a red-light district of Manaus, Brazil*. Sex Transm Infect, 2008. **84**(4): p. 297-302.
32. Dutra JC and V. F., *Syphilis and HIV prevalence among female sex workers from Manaus, Amazon port zone, using respondent driven sampling - RDS.*, in Research report. 2006, Brazilian National STD/AIDS Program.: Brasília.
33. Ivo-dos-Santos, J., et al., *Prevalence of HIV-1 antibodies in selected groups of a Brazilian city with African sociodemographic characteristics*. J Acquir Immune Defic Syndr, 1991. **4**(4): p. 448-9.

34. Broutet, N., et al., *Prevalence of HIV-1, HIV-2 and HTLV antibody, in Fortaleza, Ceara, Brazil, 1993-1994*. Int J STD AIDS, 1996. **7**(5): p. 365-9.
35. Departamento-de-DST-Aids-e-Hepatites-Virais, *Avaliação da Efetividade das Ações de Prevenção Dirigidas às Profissionais do Sexo, em Três Regiões Brasileiras*, M.-d.-S. 2004, Editor. 2004, Ministério-da-Saúde, 2004: Brasília DF.
36. Rodrigues, L.G. and P. Chequer, *AIDS in Brazil, 1982-1988*. Bull Pan Am Health Organ, 1989. **23**(1-2): p. 30-4.
37. Cortes, E., et al., *HIV-1, HIV-2, and HTLV-I infection in high-risk groups in Brazil*. N Engl J Med, 1989. **320**(15): p. 953-8.
38. Granato, C., W. Johnson, and C. Brites, *Retrovirus Infection in Prostitutes in Brazil*, in *VI International Conference on AIDS*. 1990: San Francisco.
39. Aoki, F.H., L.J. N., and W.B. Abreu, *HIV Infection among Prostitutes and Transvestites in Brazil*, in *V International Conference on AIDS* 1989: Montreal.
40. Lurie, P., et al., *Socioeconomic status and risk of HIV-1, syphilis and hepatitis B infection among sex workers in Sao Paulo State, Brazil*. Instituto Adolfo Lutz Study Group. Aids, 1995. **9 Suppl 1**: p. S31-7.
41. Bueno, R.C., G. L. Paes, and F. C. Mesquita, *A Comparison of IVDU and Heterosexual Transmission in Sex Workers of Low Social-Economics Situation in Santos, Brasil*, in *VIII International Conference on AIDS*. 1992: Amsterdam
42. Pires, I.C.P. and A.E.B. Miranda, *Prevalência e fatores correlatos de infecção pelo hiv e sífilis em prostitutas atendidas em centro de referência DST/AIDS*. Revista Brasileira de Ginecologia e Obstetrícia, 1998. **20**: p. 151-154.
43. Szwarcwald, C.L., et al., *The relationship of illicit drug use to HIV-infection among commercial sex workers in the city of Santos, São Paulo, Brazil*. The International journal on drug policy, 1998. **9**(6): p. 427-436.
44. Barroso, P.F., et al., *Barriers to recruit female commercial sex workers for HIV vaccine trials: the Rio de Janeiro experience*. J Acquir Immune Defic Syndr, 2009. **50**(1): p. 116-7.
45. Lacerda, R., et al., *Respondent Driving Sampling (RDS): An effective methodology to estimate HIV transmission vulnerability among sex workers from Santos*. , in *Research report*. 2006, Brazilian National STD/AIDS Program.: Brasília.
46. Andrade-Neto, J.L., *Female Sex Work in Brazil: Risk and Prevalence*, in *Tenth International Conference on AIDS*. 1994: Yokohama, Japan.
47. Froes, A., *Prevencao de DST/AIDS Associada ao Reconhecimento e Exercicio da Cidadania de Mulheres Profissionais do Sexo em Porto Alegre/RS*, in *I Forum e II Conferencia de Cooperacao Tecnica Horizontal da America Latina e do Caribe em HIV/AIDS e DST*. 2000: Rio de Janeiro, Brasil.
48. Trevisol, F.S. and M.V. Silva, *HIV frequency among female sex workers in Imbituba, Santa Catarina, Brazil*. Braz J Infect Dis, 2005. **9**(6): p. 500-5.
49. Schuelter-Trevisol, F., et al., *HIV genotyping among female sex workers in the State of Santa Catarina*. Rev Soc Bras Med Trop, 2007. **40**(3): p. 259-63.
50. Fernandes, F.R., et al., *HIV seroprevalence and high-risk sexual behavior among female sex workers in Central Brazil*. AIDS Care, 2014. **26**(9): p. 1095-9.
51. Mott, L., et al., *Impact of condom use to prevent HIV transmission among male homosexuals in Bahia, Brazil[abstract]* in *Sixth International Conference on AIDS*. 1989; : San Francisco, California, USA.
52. Ribeiro, T.T., et al., *Serologic validation of HIV infection in a tropical area*. J Acquir Immune Defic Syndr, 1993. **6**(3): p. 319-22.
53. de Lima e Costa, M.F., et al., *Factors associated with AIDS and AIDS-like syndrome among homosexual and bisexual men in Minas Gerais, Brazil*. Int J Epidemiol, 1990. **19**(2): p. 429-34.

54. Suttmoller, F., et al., *Human immunodeficiency virus incidence and risk behavior in the 'Projeto Rio': results of the first 5 years of the Rio de Janeiro open cohort of homosexual and bisexual men, 1994-98*. Int J Infect Dis, 2002. **6**(4): p. 259-65.
55. Saúde., M.d., *Bela Vista e Horizonte: estudos comportamentais e sorológicos entre homens que fazem sexo com homens*. 2000, Ministério da Saúde.: Brasília.
56. Greco, D.B., J.R. Carneiro, and F. Suttmoller, *Feasibility of Clinical Trials with Candidate HIV/AIDS Vaccines in Brazil*, in 12th World AIDS Conference. 1998: Geneva, Switzerland.
57. Viana, L.G., A.C. Toledo, and C.M. Antunes, *Laboratory Status of Homo/Bisexual Men from a Cohort Study in Belo Horizonte, Brazil.*, in XI International Conference on AIDS. 1996: Vancouver, Canada.
58. Friedman, R.K., J. Rodrigues, and L.F. Fraga, *Prevalence of Markers for Sexually Transmitted Diseases in a Male Population at High Risk for HIV Infection*, in 12th World AIDS Conference. 1998: Geneva, Switzerland.
59. Luna, E.J.A., G.M. Figueiredo, and L.Y.L. Mirim, *Sexually Transmitted Diseases (STD) and HIV Infection Incidence among Men Who Have Sex with Men (MSM)*. , in XI International Conference on AIDS. 1996: Vancouver, Canada.
60. Utsch, M.J.D., M.A.P. Greco, and Silva, *Acompanhamento de Homo/Bissexuais Masculinos em Belo Horizonte Para Avaliação da Incidência da Infecção Pelo HIV e Futuros*, in 2nd Forum on HIV/AIDS/STD in Latin American and the Caribbean. 2003: La Havana, Cuba.
61. Tun, W., et al., *Sexual risk behaviours and HIV seroprevalence among male sex workers who have sex with men and non-sex workers in Campinas, Brazil*. Sex Transm Infect, 2008. **84**(6): p. 455-7.
62. Barcellos, N.T., S.C. Fuchs, and F.D. Fuchs, *Prevalence of and risk factors for HIV infection in individuals testing for HIV at counseling centers in Brazil*. Sex Transm Dis, 2003. **30**(2): p. 166-73.
63. Pereira, G.A., et al., *Human immunodeficiency virus type 1 and hepatitis C virus co-infection and viral subtypes at an HIV testing center in Brazil*. J Med Virol, 2006. **78**(6): p. 719-23.
64. Wood, E., et al., *Vienna Declaration: a call for evidence-based drug policies*. Lancet, 2010. **376**(9738): p. 310-2.
65. Departamento-de-DST-Aids-e-Hepatites-Virais, *Pesquisa de Conhecimentos, Atitudes e Práticas na População Brasileira de 15 a 64 anos 2008 (PCAP 2008)*, M.d. Saúde, Editor. 2011, Ministério da Saúde: Brasília DF.
66. Fazito, E., et al., *Analysis of duration of risk behaviour for key populations: a literature review*. Sex Transm Infect, 2012. **88 Suppl 2**: p. i24-32.
67. Departamento-de-DST-Aids-e-Hepatites-Virais, *Pesquisa de Conhecimento Atitudes e Práticas na População Brasileira de 15 a 54 anos, 2004*. Ministério da Saúde, 2005.: Brasília DF.
68. Kerr-Pontes, L.R., et al., *Self-reported sexual behaviour and HIV risk taking among men who have sex with men in Fortaleza, Brazil*. Aids, 1999. **13**(6): p. 709-17.
69. de Mello, M., et al., *Assessment of risk factors for HIV infection among men who have sex with men in the metropolitan area of Campinas city, Brazil, using respondent-driven sampling*. Horizons Final Report. 2008, Washington DC.: Population Council.
70. Stover, J., J.T. Bertrand, and J.D. Shelton, *Empirically Based Conversion Factors for Calculating Couple-Years of Protection*. Evaluation Review, 2000. **24**(1): p. 3-46.
71. Berquo, E., R.M. Barbosa, and L.P. Lima, *Trends in condom use: Brazil 1998 and 2005*. Rev Saude Publica, 2008. **42 Suppl 1**: p. 34-44.
72. Boily, M.C., et al., *Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies*. Lancet Infect Dis, 2009. **9**(2): p. 118-29.
73. Baggaley, R.F., R.G. White, and M.C. Boily, *HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention*. Int J Epidemiol, 2010. **39**(4): p. 1048-63.

74. Hollingsworth, T.D., R.M. Anderson, and C. Fraser, *HIV-1 transmission, by stage of infection*. J Infect Dis, 2008. **198**(5): p. 687-93.
75. Weller, S. and K. Davis, *Condom effectiveness in reducing heterosexual HIV transmission*. Cochrane Database Syst Rev, 2002(1): p. Cd003255.
76. Cesar, C., et al., *Rates and reasons for early change of first HAART in HIV-1-infected patients in 7 sites throughout the Caribbean and Latin America*. PLoS One, 2010. **5**(6): p. e10490.
77. Vo, T.T., et al., *Durability and outcome of initial antiretroviral treatments received during 2000--2005 by patients in the Swiss HIV Cohort Study*. J Infect Dis, 2008. **197**(12): p. 1685-94.
78. Blower, S.M. and H. Dowlatabadi, *Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV Model, as an Example*. International Statistical Review, 1994. **62**(2): p. 13.
79. Saúde, M.d., *Brazilian Policy on addressing AIDS: results, progress and perspectives*, A.a.V.H. Department of STD, Editor. 2012: Brasilia.
80. Grangeiro, A., M.M. Escuder, and E.A. Castilho, *Magnitude and trend of the AIDS epidemic in Brazilian cities, from 2002 to 2006*. Rev Saude Publica, 2010. **44**(3): p. 430-40.
81. Donnell, D., et al., *Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis*. Lancet, 2010. **375**(9731): p. 2092-8.
82. Das, M., et al., *Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco*. PLoS One, 2010. **5**(6): p. e11068.
83. Montaner, J.S., et al., *Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study*. Lancet, 2010. **376**(9740): p. 532-9.
84. Tanser, F., et al., *High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa*. Science, 2013. **339**(6122): p. 966-71.
85. Jia, Z., et al., *Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study*. Lancet, 2012.
86. Anglemeyer, A., et al., *Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples*. Cochrane Database Syst Rev, 2013. **4**: p. Cd009153.
87. Melo, M.G., et al., *Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil*. Sex Transm Dis, 2008. **35**(11): p. 912-5.
88. Dodd, P.J., G.P. Garnett, and T.B. Hallett, *Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings*. AIDS, 2010. **24**(5): p. 729-35.

Chapter 4: Estimating HIV Incidence from Case-report

Data: Method and an Application in Colombia

1 INTRODUCTION

In any setting, one of the most important pieces of information in responding to an HIV epidemic, evaluating past efforts, and planning for the future, is the time-course of the HIV incidence rate.

Direct observation of new infections, whether through cohort studies or via the use of incidence assays and algorithms (1), is not feasible in most national settings. Mathematical modelling provides an alternative mean to infer incidence using other more readily available data. Currently, UNAIDS estimates of HIV incidence trends in generalised epidemics are derived through fitting a simple model to HIV prevalence measurement among pregnant women and prevalence measurements in national household surveys (2, 3). This approach has been less effective in settings with concentrated epidemics, due to a combination of factors: inconsistencies in the measurements of prevalence over time, scarce prevalence measurements among hard-to-reach groups, and lack of robust estimates on the size of these groups. For this reason, it is important to explore other means of estimating HIV incidence in these settings, which would not exclusively rely on estimates of HIV prevalence and size estimates of key populations.

Other sources of available data, which could potentially be combined with models to draw inference on incidence in concentrated epidemics, include time-series data on AIDS deaths and reported cases. Here, the focus is on the use of reported cases.

In many settings, especially in Latin America and Europe, systems are in place to centrally record the number of persons newly diagnosed with HIV. In many settings, it is believed that the coverage of this system (the proportion of newly diagnosed cases that are counted) could be as high as 80% (4, 5). However, the interval between an infection and a diagnosis is not known and may change over time and this would confound all estimates of incidence unless

further information could be included on the interval between testing and diagnosis. Possible candidates to inform the interval between infection and diagnosis are the clinical stage and CD4 cell count (6). Further, in the future, measurement of a well characterized biomarker of recent infection may also be available (7).

This method builds on prior work (8, 9) to develop a modelling framework that can be used to estimate HIV incidence drawing primarily on HIV case report data. Synthetic data is used to test the performance in recovering a wide range of possible incidence trajectories. Finally, the model is applied to Colombia to derive HIV incidence estimates, which are then compared to other estimates available for Colombia.

2 METHODS

2.1 *Mathematical Model*

The proposed model consists of a deterministic mathematical model to simulate the process of HIV infection and disease progression, death and diagnosis (Figure 1).

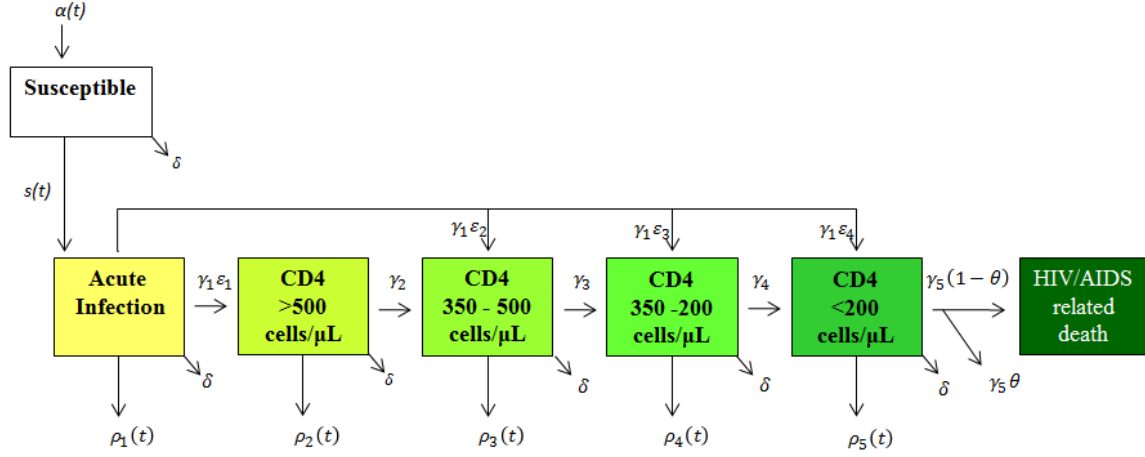


Figure 1 Model of HIV infection and progression: Parameter values and prior distributions for calibration can be found in table 1.

This structure is expressed through a set of six ordinary differential equations as follows:

$$\frac{dU(t)}{dt} = \alpha(t) - U(t)(s(t) + \delta); \text{ Eq.1: Susceptible}$$

$$\frac{dI_1(t)}{dt} = s(t)U(t) - I_1(\delta + \gamma_1 + \rho_1(t)); \text{ Eq.2: Acute infection}$$

$$\frac{dI_2(t)}{dt} = I_1\gamma_1\epsilon_2 - I_2(\delta + \gamma_2 + \rho_2(t)); \text{ Eq.3: CD4+ count } >500 \text{ cell}/\mu\text{L}$$

$$\frac{dI_3(t)}{dt} = I_1\gamma_1\epsilon_3 + I_2\gamma_2 - I_3(\delta + \gamma_3 + \rho_3(t)); \text{ Eq.4: CD4+ count } 350\text{-}500 \text{ cell}/\mu\text{L}$$

$$\frac{dI_4(t)}{dt} = I_1\gamma_1\epsilon_4 + I_3\gamma_3 - I_4(\delta + \gamma_4 + \rho_4(t)); \text{ Eq.5: CD4+ count } 200\text{-}350 \text{ cell}/\mu\text{L}$$

$$\frac{dI_5(t)}{dt} = I_1\gamma_1\epsilon_5 + I_4\gamma_4 - I_5(\delta + \gamma_5 + \rho_5(t)); \text{ Eq.6: CD4+ count } <200 \text{ cell}/\mu\text{L}$$

Where $U(t)$ is the number of persons HIV susceptible at time t ; $I_1(t)$ is the number of infected individuals in acute infection at time t ; $I_j(t)$ ($j=2, \dots, 5$) is the number of infected individuals in CD4+ count category j at time t ; and $s(t)$ is the time-varying rate at which the population of infected individuals transmits HIV to susceptible persons. The rate at which

new infections occur in this population is given by $s(t)U(t)$. All symbols and parameters are described in Table 1.

At infection, individuals pass through a stage of acute infection following which individuals enter one of four CD4 cell count categories (<200, 200-350, 350-500, 500+ cell/ μ L). Thereafter, individuals progress to lower CD4 cell counts at rates which have previously been estimated from European data (10). Individuals with CD4 cell count below 200 cell/ μ L die of AIDS. The overall median survival time is 10.4 years, consistent with estimates from low and middle-income countries (11). In the model framework, these parameters describing the progression of HIV infections are considered to be known perfectly.

At all times after infection, individuals can be diagnosed with HIV. At that point they transition into a ‘diagnosed’ category. The number of HIV-infected persons that transition to the diagnosed category in a given year in the model is compared with the data on the number of reported cases.

2.2 Model parameterization

2.2.1 HIV infection rate

Following Hogan *et al.* (2), the instantaneous hazard of infection for susceptible individuals $s(t)$ is specified as a B-spline function of time. The B-spline is parameterised by a vector of coefficients $(\beta_{1,...,n})$, where $n-3$ is the number of knots of the spline which were evenly spaced on the time interval 1975 to 2015. This flexible functional form allows many credible incidence trajectories whilst constraining the trajectory to evolve smoothly with respect to time. This does not attempt to provide a mechanistic description of HIV transmission. Note that in other formulations, the spline describes a force of infection (which gives incidence when multiplied with the product of $U(t)$ and all infected individuals) rather than a hazard of

infection but this is not possible here as, for parsimony, the entire infected population is not modelled.

It was set $\beta_1 = \beta_2 = \beta_3 = 0$, to anchor the incidence trajectory at zero before 1975, while β_4 to β_6 were independently specified with uniform priors: $\beta_4 \sim U(0,5)$, $\beta_5 \sim U(-5,5)$, and $\beta_6 \sim U(-5,5)$. Penalties were imposed (12) on the spline, in order to limit over-fitting to potentially noisy data and to represent our prior assumption that rapid large oscillations in the HIV incidence rate are unlikely. The second degree difference penalties (12) used are expressed as:

$$\beta_i = 2\beta_{i-1} - \beta_{i-2} + \mu_i, \dots, \text{ for } i > 6$$

where the error μ_i is the amount of deviance from the trajectory defined by the two previous coefficients.

The prior for μ_i is normally distributed with parameters $N(0, \tau^2)$, where τ^2 is a hyper-parameter controlling the overall smoothness of the function; small values of τ^2 result in little deviance from the previous trajectory and large values in contrast produce more flexible curves.

2.2.2. HIV detection rates

The rate at which HIV-infected individuals are diagnosed is $\rho_j(t)$, and is allowed to vary by CD4 cell count category j and calendar time t :

$$\rho_j(t) = \left((m\omega)T_j + \rho_5(0) \right) \sigma(t)$$

where T_j is the average time (years) to reach CD4+ count category <200 cell/ μ L ($j=5$) for those in CD4 cell count category $j=1, \dots, 4$ ($T_1=8.17$; $T_2=7.93$; $T_3=6.74$; $T_4=3.74$; $T_5=0$).

This parameterization sets the rate of detection to vary linearly as the time to reach CD4 <200 cell/ μ L decreases. The slope of this line is specified by parameter ω , which allows the linear relationship to be either positive or negative. With $\omega>0$, individuals with high CD4 counts are more likely to be detected, which is plausible scenario if exposure to HIV is suspected or symptoms of acute infection drive testing; with $\omega<0$, individuals with low CD4 counts are more likely to be detected, which may be true if HIV testing is prompted by increasing experience of illness. The prior on ω reflects that both of these possibilities are equally likely: $\omega \sim U(-1,1)$. Parameter m is a constant scaling parameter which ensures that the diagnosis rate is greater than zero for all CD4 categories, irrespective of the value of ω .

Rate of testing for those in CD4 cell count category <200 cell/ μ L (ρ_5) has a prior distribution such that the average interval from infection to diagnosis is uniformly distributed between 0.5 and 10 years: $\sim U\left(\frac{1}{10}, \frac{1}{0.5}\right)$.

$\sigma(t)$ describes the change in the rates of diagnosis over time. Here it is assumed that this change can be represented by the logistic function: $\sigma(t) = \frac{1}{1+e^{-r(t-t_{50})}}$, where r is the rate of increase, and t_{50} is the time to reach half the upper limit rate. Parameter r is set at 0.003 and a prior was placed on t_{50} that allows a wide range in shapes in $\sigma(t)$ from a stable trend over time

($t_{50}=1$) to a sharp increase in the rate of diagnosis from close to zero at the start of the epidemic ($t_{50}=0.1$): $t_{50} \sim U(0.1,1)$.

2.3 Model validation and calibration procedures

The inference on the HIV incidence rate is done in a Bayesian framework. The likelihood is given by the probability of observing the number of HIV cases without AIDS reported in a year, the number of HIV cases with AIDS reported in a year (i.e. symptomatic illness or CD4+ count <200 cell/ μ L), and the number of persons diagnosed with HIV after death in a given year, each modelled as *Poisson* process. The Metropolis Hastings algorithm was used with component-wise updating to sample from the posterior distribution of the model. Also, an adaptive proposal density variance was used in order to achieve an acceptance rate of approximately 30%. Three chains were run in parallel for 500,000 iterations after which chains were visually inspected for convergence and 50% of the initial runs were discarded.

Models are estimated that use B-spline functions with number of knots $n=7, 8, 10$, and with hyper-prior for τ^2 variously given as $\sim U(0.001,0.1)$, $\sim U(0.1,0.5)$, $\sim U(0.5,1.0)$, $\sim U(1.0,1.5)$ or $\sim U(1.5, 2.5)$, giving a total of 15 models runs for each estimation problem. Among these, a model is chosen that has the greatest agreement to data, given its number of effective parameters, as measured by the model with smallest Deviance Information Criterion (DIC) (13). For that chosen model, a sample from the joint posterior distribution is formed by randomly sampling 1000 iterations across all its chains. Medians and 95% credible intervals are reported for the posterior samples.

Table 1: Model parameters

Symbol	Description	Value/Prior Distribution	Reference
$\alpha(t)$	Birth Rate	$N(t)E + (\delta) \left(\sum_i I_j(t) + U(t) \right) + I_5(t)\gamma_5$	
$N(t)$	Total population at any time t	$U(t) + \sum_j I_j$, for $j = 1, \dots, 4$	-
E	Average population growth per year	2.7%	(14)
δ	Background mortality rate	1/72 years	(14)
θ	Fraction of AIDS related deaths detected <i>post mortem</i>	$\sim U(0,1)$	Assumption
γ_j	Progression rates (1/years) from CD4+ count stage k to the subsequent inferior CD4+ count category	$\frac{1}{\text{yrs}}$ $\gamma_1 = \frac{1}{0.24}$ $\gamma_2 = \frac{1}{2}$ $\gamma_3 = \frac{1}{3}$ $\gamma_4 = \frac{1}{3}$ $\gamma_5 = \frac{1}{2.4}$	(10, 15)
ε_j	Proportion moving to each CD4+ stage after acute infection	$\varepsilon_2 = 0.58$ $\varepsilon_3 = 0.23$ $\varepsilon_4 = 0.16$ $\varepsilon_5 = 0.03$	(10, 16)
ρ_5	Diagnostic rate at CD4+ <200cell/ μ L	$\rho_5 \sim U\left(\frac{1}{10}, \frac{1}{0.5}\right)$	Assumption
m	Slope scaling parameter. Is the slope for the line crossing (0, ρ_5) and (0, ρ_1)	$m = \frac{0 - \rho_5(0)}{8.17 - 0}$	Assumption
ω	Relative slope variation factor.	$\omega \sim U(-1,1)$	Assumption
$\sigma(t)$	Function for the variation of HIV detection over time	$\sigma(t) = \frac{1}{1 + e^{-r(t-t_{50})}}$, for $r=0.003$	Assumption
t_{50}	Shape parameter in function $\sigma(t)$	$t_{50} \sim U(0.1,1)$	Assumption
β_i	Basis coefficients for spline function $s(t)$	$\beta_i = 0$, for $i=1, \dots, 3$ $\beta_i \sim U(0,5)$, $i=4$ $\beta_i \sim U(-5,5)$, $i=5,6$ $\beta_i = 2\beta_{i-1} - \beta_{i-2} + \mu_i$, For $i=7, \dots, n$	
μ_i	Deviance of the i th β from the former two coefficients β_{i-1} and β_{i-2} , for $i=7, \dots, 10$.	$\mu_i \sim N(0, \tau^2)$ $\tau^2 \sim U(0,2)$	Assumption

2.4 Assessment of Model Performance Using Synthetic Data

The performance of model in recovering the ‘correct’ incidence trajectory from sets of synthetic data was assessed. One major concern was that the specification of this estimation method would render it unable to correctly discern all possible trajectories with different amounts of variation over time or timing of inflections. For this reason, three “challenge datasets” were created using the same assumptions as the estimation model about natural history but varying the number in the spline function that generates that incidence rate ($n=7, 8, 10$). Synthetic data were generated under the assumption of constant rates of diagnosis over time and CD4 cell count.

2.5 Application of the Model to Colombia

Between 1983 and 2010 Colombia reported 78,999 cases of HIV and AIDS, the vast majority coming from urban areas and major cities (17). Overall prevalence was estimated at 0.22% in 2009 in the adult population overall (18), but HIV prevalence appears to be substantially concentrated among men-who-have-sex-with-men (MSM), among whom prevalence has been estimated to be between 5.6% and 24.1% in different cross-sectional studies in 2010 (19). In this method it is assumed equivalence between an AIDS diagnosis in the data and a diagnosis for a patient with a CD4 cell count below 200 in the model.

There have been official records of the number of deaths that were classified as AIDS deaths among persons who had not previously been recorded as HIV-infected (i.e. *post mortem* HIV diagnosis) since 1985 (20). No reporting bias or misclassification in this is assumed.

Data was used on the total number of HIV tests reported to have been performed in Colombia to centre the prior on the trend in the rate of diagnosis over time (21). This trend can be broadly described as a sigmoid increase with a turning point in 1996 and a plateau in the more recent years.

These data were used in the method outlined above to estimate incidence over time. The results were compared with reported estimates of incidence from UNAIDS (22), which are based on fitting a model to prevalence data and population size estimates for key populations (3).

3 RESULTS

3.1 Assessment of Model Performance Using Synthetic Data

Three challenge datasets with different epidemic trajectories were proposed and the current method was able to successfully recover each of them (Figure 2). A part of the method is to estimate multiple models and then select that model with the lowest DIC; as expected, the model that was favoured in each these tests was the model which has the same number of knots as that used to generate the synthetic data. Also as expected, uncertainty becomes greater in more recent years as the data on case reports are less informative on current incidence rates. Uncertainty for estimates in the recent years is especially great when the data indicate that trend in incidence has changed.

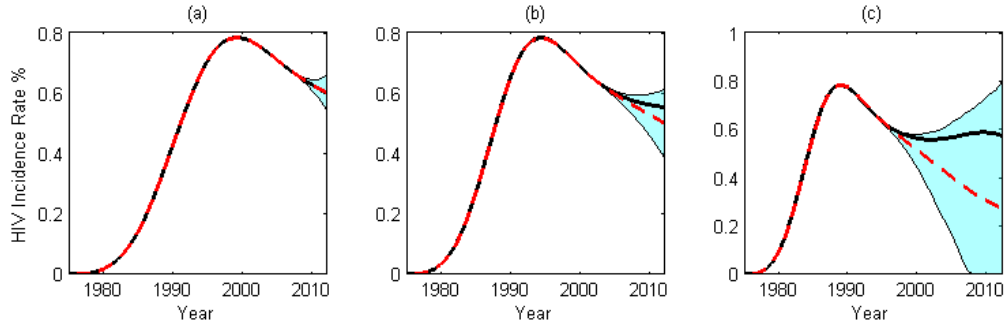


Figure 2 Incidence estimation with three configurations of the spline function: In each panel, the black solid line is the true simulated incidence trend; the dashed red is the incidence estimation using the proposed method (median of the posterior distribution); the shaded blue region gives a 95% credible interval for incidence using the proposed method. The synthetic data was created using a model with 7 knots (a), 8 knots (b) or 10 knots (c).

3.2 Estimating HIV Incidence in Colombia

The model was applied to Colombian data using the proposed method. Model estimates and data on HIV cases, AIDS cases and *post mortem* detection are presented in Figure 3(a-c) and resultant estimates of HIV incidence are presented in Figure 3(d). For Colombia, the model formulation with the lowest DIC was one with 8 knots and hyper-prior $\tau^2 \sim U(1, 1.5)$.

The model has a good fit with the observed data (Figure 3(a-c)) in the early years, while uncertainty is widely propagated in the recent years as noted in the experiments with synthetic data. The data for post mortem detected cases and AIDS cases exhibit complex patterns which the model is forced to reconcile with the clear monotonic increase in reported HIV cases and with the *a priori* belief that the incidence trajectory should vary smoothly over time.

The resulting estimate of HIV incidence (Figure 3(d)), describes an early peak in new infections in 1990 and resurgence in the epidemic since 2000. The period with the highest incidence rate is estimated to be 2008-2009.

These incidence estimates can be compared with those previously presented by UNAIDS and which are based on an entirely different methodology whereby models are fitted to observed prevalence data and estimated sizes of key population (Figure 4). In recent years, the estimates derived through the proposed method and the UNAIDS methods are in very close agreement. However, the UNAIDS estimated historical trajectory of incidence suggests very high peak incidence during 1995, of 0.3 per 100 person-years at risk (pyar) whereas the proposed method suggests an incidence rate much lower, at 0.03 per 100 pyar.

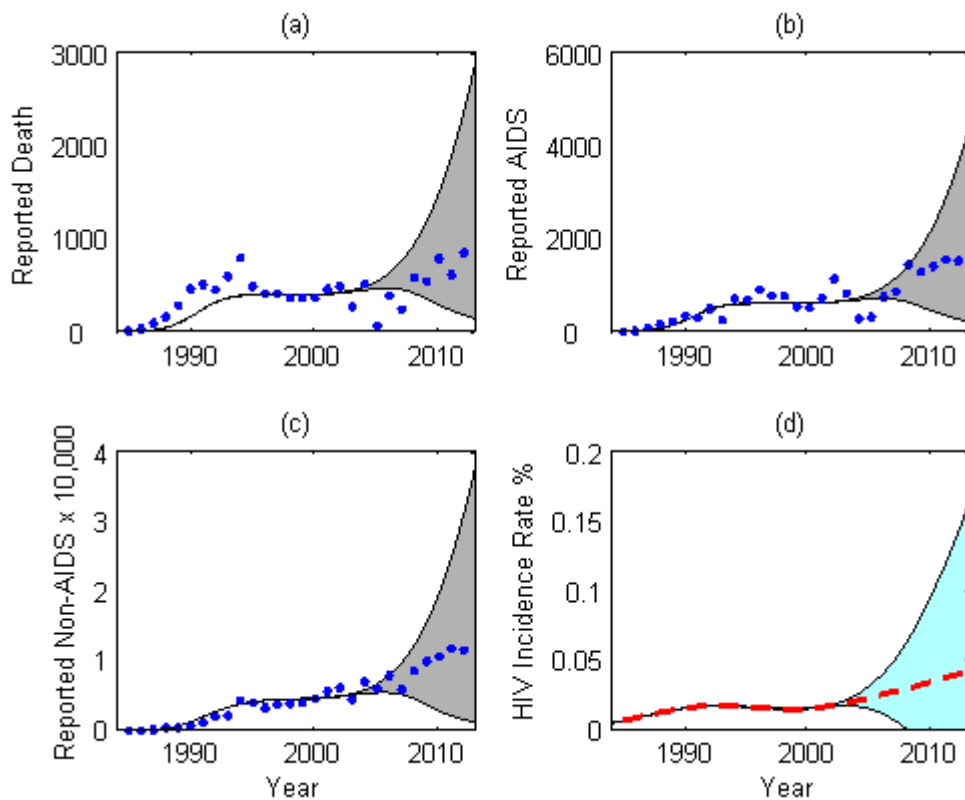


Figure 3 Model fit to data in Colombia: Panels with data points (blue dots) as reported on a yearly basis by Colombian surveillance system, in three categories: cases previously undiagnosed and only detected after death (a); cases detected during AIDS stage (b); and cases detected and classified as non-AIDS at the time of diagnosis (c). In a-c, the coloured lines are the posterior estimation from the model chosen for Colombia. (d) The resulting HIV incidence trajectory in Colombia from the proposed method (red dashed line) with 95% credible interval (shaded area).

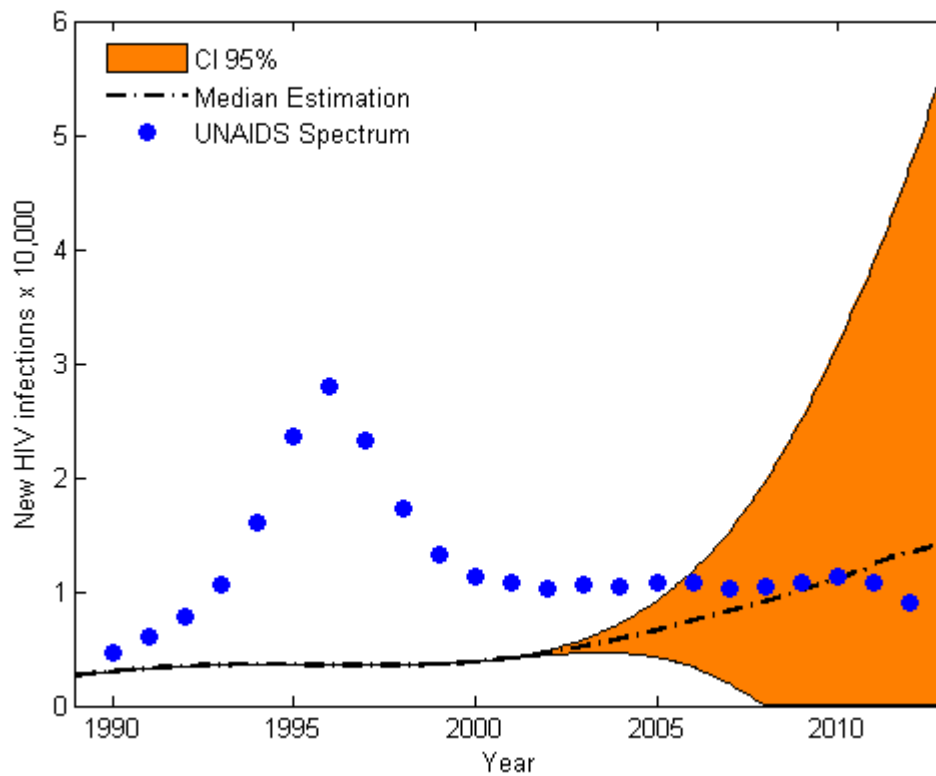


Figure 4 Estimated number of new HIV infections in Colombia: from the proposed method (black dashed lines) and current UNAIDS methods (blue dots). The orange shaded area shows the 95% credible interval of the estimates of the proposed method. Note that UNAIDS does compute uncertainty intervals for most of its statistics but intervals were not retrievable from online data sources for this statistic (22).

4 DISCUSSION

Here a method for estimating HIV incidence from case-report data was examined. It has been shown that it is capable of correctly recovering a wide range of possible incidence trajectories and has been applied to data from Colombia to give complementary estimates of incidence to that derived from other methods.

Whilst it is promising that this method can broadly identify a wide range of incidence trajectories, some small inconsistencies remained. It is possible these will be due to the setting of the fixed placement of the knots and the rigid ordering of unconstrained and

constrained knots. It will be possible to determine whether the evaluation of a wider range of models that incorporate these differences and model selection based on DIC is sufficient to overcome these challenges. This would inevitably increase the computational demands of the estimation procedure and so alternative methods for estimating the model will also be explored.

It will also be useful to examine how this method works under different conditions of data availability. In the challenges with synthetic data, it was assumed that all required data were present and unbiased. Whilst this may be a reasonable assumption for some settings, it will not be universally the case and small errors in early estimates of number of cases may propagate to large errors in the inferred incidence trajectory. The same assumption for the natural history of HIV was used (survival rates and CD4 progression) in the method that generated the synthetic data as in the estimation model, which will inevitably flatter the performance of the model. A further step would be to examine the impact of the survival rates used to generate the synthetic data departing from those assumed in the estimation model, as well as propagating uncertainty in the assumptions about natural history in the estimation procedure. Finally, here the impact of the use of inappropriate assumptions on the trend in diagnosis rates over time was not assessed.

This method give uncertain results especially in recent years and this is because there remains confounding by potential changes in the interval between infection and death and because numbers of cases and deaths are informative of incidence rates sometime in the past rather than current incidence. Therefore, in the current form this method cannot be expected to reliably detect recent changes in incidence, which would be very important in monitoring a national epidemic. We can expect, however, that it would be highly advantageous for this method to draw on further data. It will be possible to extend this method to incorporate data and/or estimates on deaths and numbers on ART, which should contribute to discriminating

the earlier part of incidence trajectory in particular. Although it is not commonly used at present, the addition of measurement of biomarkers that relate to recency of infection at diagnosis could also help discriminate current incidence levels, although this would depend on the characteristics of the biomarker and how well they are known (Bao et al. unpublished).

Estimates of HIV incidence for Colombia must be interpreted with a high degree of caution and in light of this method's assumptions and present limitations. Of particular note, the estimates from the proposed model suggest that incidence was historically much lower than the levels the previous UNAIDS estimate indicate. This could stem from the assumption of complete case reporting and no misclassification of AIDS deaths: if, in fact, some diagnoses go unreported and some true AIDS deaths are misclassified, then these estimates will be too low. Nevertheless, it seems unlikely that these biases would fully explain the discrepancy and it is also noteworthy that, as reported elsewhere (Sabin et al., unpublished), the total all-cause deaths implied in the UNAIDS estimates are substantially greater than estimated all-cause death rate by IHME (23). For that reason, future incidence estimates by UNAIDS will be scaled such that this discrepancy is minimised, and that may bring a closer agreement between UNAIDS estimates and those derived using the method proposed here.

In conclusion, this method is promising technique for estimating HIV incidence trends that does not rely on using prevalence data and size estimates of key populations, and which leverages high quality routinely collected data. Future work should focus on updating the model structure to allow other forms of surveillance data, such as AIDS deaths and people on ART and further scrutiny of model performance under circumstances of missing or biased availability of data.

5 REFERENCES

1. Group IACPW. More and better information to tackle HIV epidemics: towards improved HIV incidence assays. *PLoS Med.* 2011;8(6):e1001045.
2. Hogan DR, Zaslavsky AM, Hammitt JK, Salomon JA. Flexible epidemiological model for estimates and short-term projections in generalised HIV/AIDS epidemics. *Sex Transm Infect.* 2010;86 Suppl 2:ii84-92.
3. Brown T, Bao L, Raftery AE, Salomon JA, Baggaley RF, Stover J, et al. Modelling HIV epidemics in the antiretroviral era: the UNAIDS Estimation and Projection package 2009. *Sex Transm Infect.* 2010;86 Suppl 2:ii3-10.
4. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2011. . Centers for Disease Control and Prevention, 2013.
5. Health Protection Agency. HIV in the United Kingdom: 2011 Report. London: 2011.
6. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, et al. HIV incidence in men who have sex with men in England and Wales 2001-10: a nationwide population study. *Lancet Infect Dis.* 2013;13(4):313-8.
7. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, et al. Estimation of HIV incidence in the United States. *JAMA.* 2008;300(5):520-9.
8. Sweeting MJ, De Angelis D, Aalen OO. Bayesian back-calculation using a multi-state model with application to HIV. *Stat Med.* 2005;24(24):3991-4007.
9. van Sighem A, Nakagawa F, Bezemer D, De Angelis D, Op de Coul E, Egger M, et al. Estimating the Size of the Undiagnosed HIV Population in the Netherlands by Disease Stage Conference on Retroviruses and Opportunistic Infections 2014; March 3 to March 6; Boston, Massachusetts.
10. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiébaud R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm³: assessment of need following changes in treatment guidelines. *Clin Infect Dis.* 2011;53(8):817-25.
11. Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. *AIDS.* 2007;21 Suppl 6:S55-63.
12. Eilers PHC, Marx B. Flexible Smoothing with B-splines and Penalties Statistical Science. 1996;11(2):89-121.
13. Spiegelhalter DJ, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society.* 2002;Series B,(64):583–640.
14. DANE. Estadísticas Vitales [cited 10 Nov 2012]. Available from: http://www.dane.gov.co/index.php?option=com_content&view=article&id=73&Itemid=119.
15. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis.* 2008;198(5):687-93.
16. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. *PLoS One.* 2014;9(1):e84511.
17. UNFPA. Panorama del VIH/sida en Colombia 1983-2010 Bogota2012 [6 February 2013]. Available from:

<http://www.unfpa.org.co/uploadUNFPA/file/PANORAMA%20VIH%20SIDA%20COLOMBIA%201983-2010.pdf>.

18. Castro J. VII Estudio nacional centinela de VIH en gestantes. Instituto Nacional de Salud, 2009.
19. MPS/UNFPA. Comportamiento sexual y prevalencia de VIH en hombres que tienen relaciones sexuales con hombres en siete ciudades de Colombia. Bogota: 2012.
20. Garcia-Bernal R, Klaskala W, Castro J, Zhang G, Baum M. HIV/AIDS surveillance in Colombia: regional differences in epidemic trends. *AIDS*. 1997;11(10):1297-8.
21. Observatorio-Nacional-de-VIH-sida. Informe de indicadores de atención integral por departamento y periodo. Bogota: Ministerio de la Protección Social, 2012.
22. UNAIDS. AIDSinfo Online Database. Available from: <http://aidsinfoonline.org/devinfo/libraries/aspx/Home.aspx>.
23. (IHME) IfHMaE. Available from: <http://www.healthdata.org/>.

Chapter 5: Discussion

HIV spread in Latin America is largely constrained by transmission within vulnerable sub-groups of the population. This is different to the generalized epidemics seen in other parts of the world like sub-Saharan Africa. The pattern of concentrated transmission has been extensively documented in most Latin American countries through surveillance and population surveys. These have shown the disproportionate burden that HIV has had on vulnerable groups, especially among MSMs, when compared to the general population [1-4]. This has led transmission to occur within restricted networks and means that the epidemic has not found the appropriate conditions to sustain its spread on a larger scale in the general population. How much of that containment is due to natural transmission dynamics and to what extent it is the reflection of interventions, is a question that this research has sought to answer for the cases of Brazil and Bogota. Interventions for HIV prevention have taken place in both countries, with ART delivery and medical care being prioritized over other forms of prevention. Extended delivery of condoms, and, to a lesser extent, behaviour change strategies, have also been applied in these settings [5-9]. In both Brazil and Colombia, ART introduction and the subsequent periodical update of guidelines for an earlier delivery of ART has allowed these countries to reach the same level of treatment coverage as in most industrialized countries. Brazil has gone even further and is now attempting to be the first and largest case-study of TasP - fully funded by the government and implemented at a national level [10]. Determined policy-making and a strong infrastructure for further ART expansion have meant that ART interventions have been rolled-out as real life programmes as opposed to carefully tailored trials. In contexts like these, where no intervention is available for comparison, mathematical modelling provides a central part of programme evaluation. Two chapters of this thesis have carried out a retrospective evaluation of HIV interventions and have revealed the distinction between the differential effects attributable to ART, and to behaviour change and that which has been observed by epidemic dynamics.

In Brazil and Colombia, programmatic and surveillance data prevail over behavioural data and other estimations obtained through cross-sectional studies. This is partly due to surveillance systems and health programmes in place and also to the concentrated nature of the epidemic. Disproportions in risk of acquiring HIV in these settings are mirroring disproportions in vulnerability and social marginalization, making key populations hard to reach through behaviour and seroprevalence surveys [11-13]. These data are essential pieces of information for most of the current methods for estimating HIV incidence. At the same time, incidence is crucial for evaluating the effect of interventions. With this in mind, a method for estimating incidence, that relies exclusively in case reporting data, has been proposed, validated, and applied to the case of Colombia in chapter four.

This Discussion chapter discusses the main findings of the thesis, its limitations and reflects about its implications and future development.

8 SUMMARY OF MAIN FINDINGS

Deterministic mathematical models were designed, calibrated and analysed for the contexts of Bogota, Colombia, and five macro-regions of Brazil. HIV transmission was simulated considering the risk heterogeneity of each population and interventions were introduced for further estimations of their effect on HIV incidence. To the latest knowledge of the author, these are the first analysis of this kind to be conducted in any of the settings studied in this thesis.

ART had a role in containing further HIV incidence in Brazil and Bogota when compared against counterfactual scenarios where ART had been removed. A summary of modelling results can be seen in **Table 1**. The effect of interventions (ART and condoms) in at least two regions of Brazil (North and South) was necessary for bringing HIV incidence to declining or

equilibrium patterns. In Bogota, ART had a lesser role while condoms were crucial for bringing the epidemic to stable levels. Absolute reductions in HIV infections were larger among MSM in Bogota studies and, across all regions modelled in Brazil. Relative reductions of incidence were similar when seen by risk group (MSM and FSW) in Brazil. In Bogota, a substantial difference was observed between these two groups.

A novel approach to HIV incidence estimation from case-report time series was able to retrieve different incidence trajectories generated for validation. Application of the method to real data from Colombia showed that some inconsistencies remain producing wide ranges of uncertainty particularly for the most recent years.

Table 1 Summary table of modelling results of the impact of ART on HIV Incidence

Outcome	Population	Bogota	North	North East	Brazil South East	South	Central West
Median Cumulative HIV Infections Averted 1997 -2014 Due to ART	Total population	53,178	10,822	30,153	151,230	62,893	16,693
Relative HIV infections averted 1997 -2014 due to ART , % (IQR)*	Total population	17% (12)	30.2%(24)	23.7%(17)	31.4%(24)	29.2%(22)	30.7%(23)
	MSM	16%(6.7)	30.2%(23)	22.4%(16)	31.5%(23)	29%(20)	31%(23)
	FSW	2%(3.5)	29%(25)	24%(17)	30%(27)	31%(25)	26%(24)

*Relative to a counterfactual scenario of no interventions for the same period.

9 THE ROLE OF MODEL ASSUMPTIONS IN THE IMPACT OF INTERVENTIONS

9.1 *The impact of ART in the presence of behaviour changes*

ART needs to be understood in a framework of combination interventions if prevention outcomes want to be maximized [14-17]. Even in the context of a large ART-scale up programme like Brazil, condoms alone had a bigger impact in averting HIV infections in the modelling results of this thesis (**Table 1**). This needs to be interpreted as a result of factors stemming from the transmission mechanics of the model and the assumptions regarding behaviour change. Evidence has been put forward about the re-emergence of MSM epidemics in contexts of high coverage of ART and prevention interventions like The Netherlands [18] and the UK[19]. These increases seem to be related to further increases in risk behaviours after the introduction of ART as a form of risk compensation. These behaviours are expressed by Bezemer et al. [18] in terms of increment in the reproduction number $R_{(t)}$, and explained by Phillips and others [19] as a result of changes in the reported condom-less anal sex in more recent years. This evidence shows a pattern that might be taking place in other MSM epidemics like those in Latin America. The models in the present thesis incorporated condom use as the only form of behaviour change. A single window for wide variations in condom-use was allowed from 1984 to ~1999 in the simulation and survey data informed the trends for the rest of years. This approach could be restrictive and over-relying in self-report data about condom use, which ultimately results in an overestimation of the preventive benefit of condoms. It is well documented that self-report data is susceptible to recall and several forms of motivational biases that could lead to an over-report of protective behaviours in risk populations [20, 21]. Furthermore, a simplistic approach was taken regarding the rate of change in partners by fixing the values for the duration of the simulation. Partner change rates were calibrated but not allowed to change over time. This necessarily imposes a heavy burden on condom-use to represent preventive effects on incidence, which could result at the

end in overestimation of its overall effect. However, if partner change rates declined in MSM or FSW over time is not certain for these settings.

9.2 *Different approaches to modelling ART in key populations*

Modelling results in this thesis have shown that interventions had a role in controlling HIV transmission. ART had a greater effect in preventing new infections in Brazil than in Bogota. This seems feasible, and the higher levels of ART coverage in Brazil are possibly reflected in greater preventive benefit. More precisely, UNAIDS have estimated that 46% of people living with HIV/AIDS (PLHA) in Brazil were receiving ART in 2013, while in Colombia the same indicator was 29% [22]. Nevertheless, the two models incorporated ART in different manners and these assumptions need to be stated clearly for a proper interpretation of the results. In Bogota, ART uptake was interpreted as a function of differential rates of HIV testing in risk groups, and variations in detection rates by CD4+ stage. This information was assembled and interpolated over an exponential function. This explains the differentiated effect of treatment on HIV incidence in MSM contrasted with a very small (2%) effect among FSW. HIV testing rates are playing their part here by generating differential rates of access to ART by risk group. In Brazil, a more flexible approach was adopted, allowing variation in ART-enrolling rates by stage of disease and generating a wide range of ART expansion trends by calibrating the shape parameter of a sigmoidal function (i.e. allowing from vertical increase and saturation to slow growth and exponential rise). This approach (i.e. the one in Brazil) did not consider any variability over risk group, which means that access to ART was equally likely for any individual regardless of their risk category. The first approach, used in the model for Bogota, might be a more realistic assumption when model parameters are calibrated (like in this case) against data on reported numbers of people on ART, and there are no further details about the risk condition of those receiving the

treatment. On the other hand, the presence of detailed data about the risk status of reported people on ART could favour a more flexible calibration procedure like the one used in the model for Brazil.

9.3 *HIV Prevention effect in concentrated epidemics*

Important insights about the characteristics of the epidemics and its relation to the effect of interventions can be drawn from this modelling analysis. PAF estimations as the one performed for the case of Bogota, reveals the potential impact of targeting interventions in gay and bisexual men in this context. The attributable fraction of cumulative incidence, as estimated by mathematical models, offers a good indicator of the direct and indirect effect of a single transmission group within its community. As such, its estimation is a proxy of the prevention potential if a complete halt of HIV transmission is achieved. PAF and intervention effects as reported in chapter two revealed that the gross effect of any of the interventions in the model was achieved by reducing transmission among MSM. The analysis by source of infection confirms this. This is to say that through these two simple calculations it was possible to infer what was subsequently observed in the impact evaluation. These measures are important tools for epidemic appraisal and provide a better understanding of the drivers behind than other more commonly used measures like short-term distribution of new HIV infections [23, 24].

The complexity and nuances in sexual behaviour makes risk categorization a difficult task. The risk heterogeneity proposed in this work is arguably far from describing in detail MSM and sex-work behaviours in Brazil or Colombia. This configuration of sub-populations proved to be sufficient to sustain a concentrated epidemic among MSM and replicate real trends of HIV prevalence among this group. However, the added value of more heterogeneity within MSM and FSW could have been reflected in better incidence projections. Some of the

natural dynamics missing in some projections of this work can be related to the lack of the effects of core-groups saturation which is naturally achievable by increasing with-in group heterogeneity: subdividing MSM in smaller fractions of risk (e.g. Trans, male sex workers, stable MSM couples) let smaller groups of susceptible to be rapidly infected (saturated) which leads to incidence trends finding its peak naturally and decay slowly as the lower risk groups start absorbing that number of infections “spilling-over” from the high-risk sub-groups. From the health policy perspective, a detailed depiction of group heterogeneity allows for a better identification of nuances in behaviour that in practice can be targeted in the field. A good example of detailed representation of MSM behaviour in a similar setting was done by Gomez and colleagues [25]. This approach demands larger amounts of information and for the purpose of this thesis was hardly reproducible, particularly for broader geographical locations like the macro-regions of Brazil.

9.4 HIV prevention effect and the stage of infection

Acutely infected individuals are more likely to pass the virus to their partners as has been demonstrated [26], but the contribution of acutely infected individuals to the epidemic is debated. The fraction of the total transmission that can be attributed to individuals in the early stage of infection has been estimated from data and also through modelling and the results are still inconclusive ranging from 5% to 50% [27-29]. This piece of information has become more important recently as it has been suggested that a greater proportion of cases arising from early transmitters would hamper the overall effect of TasP [29]. The argument behind this, basically, says that individuals in the early stage of infection are less likely to be detected and therefore treated, thus the greater the proportion of infections arising from them, the lesser the impact of ART for reducing HIV incidence. However, new modelling evidence from Eaton and Hallett [30] suggests that it might not be that straight forward. Their

modelling analysis of the generalized epidemic of South Africa shows that other complexities play an important role when assessing early infection and its impact on ART interventions, such as behaviour changes, assortativeness in mixing and the rate at which individuals move from high to low risk groups. More importantly, they concluded that while early infection might be important in the short term evaluation of ART programmes, in the long term might be counterbalanced by other factors that can be reducing R_0 in the long run.

The model for Bogota found that cumulatively, by 2014, ~30% of all HIV infections in the overall epidemic had its source in individuals at the acute-stage. Similar values were found in the epidemic of Lilongwe, where 38% of cases came from this stage of infection [31]. The implications of this finding might have an important effect in the models described in this work. Both models recreate stages of increased infectiousness during the first 3-5 months of infection, and both models assume that no testing or recruitment into care is happening at this stage. As stated before in chapter two, this means that the maximum preventive potential that could be achieved is 70% by any intervention. This assumption could be relaxed in the future to explore the programmatic impact of strategies reaching this group.

10 MORE AND BETTER DATA FOR BETTER ESTIMATIONS

A barrier found in the design of detailed transmission models in Chapters two and three, was the scarcity of data and in particular that related to sexual behaviours. The absence of appropriate sources to inform all the required parameters of sexual mixing and transmission resulted in great uncertainty around the estimations. The computational cost of the simulations was also increased since large parameter spaces needed to be explored during the calibration algorithms.

But scarcity of information about behavioural parameters is not the only source of uncertainty in these of models. The quality and frequency of the data used for model fitting is in close relation with the accuracy of model projections, and here a notorious gap divides the modelling of HIV in Latin America and contexts like sub-Saharan Africa. In many African settings behavioural data and HIV prevalence estimations are routinely collected even at national level through the demographic health surveys guaranteeing consistency or at least representativeness of the statistical sample across the surveys. This, of course, is possible given the widespread epidemic found in such settings, where HIV+ individuals are not necessarily hard to reach. This consistency in the data makes simulations robust when fitted accurately. On the contrary, HIV prevalence data from risk groups such as FSW, MSM or PWID are not routinely collected and almost never comes from the same population sample. This observation is shared by others and has been previously discussed elsewhere [32]. A hint of this was previously exposed in **Table 1** of Chapter 3, where prevalence studies among MSM and FSW in Brazil are listed. There, striking differences in size, quality and estimations can be seen. Survey data in many locations of South America is robust and sufficient enough to designed detailed transmission models. However, the task of producing national-level estimations can be a limited by the absence of consistent behavioural and serological data. In response, the proposed method as described in Chapter four moved in a complementary direction towards the rest of the work carried out in this thesis, with a common motivation of elucidating accurately how HIV transmission has occurred in these concentrated epidemics settings. It proposed a flexible system to simulate transmission without making any behavioural assumptions and it relied exclusively on case report data. When put through different challenges, the system was successful in revealing different incidence shapes from “challenging” datasets. The method was applied to Colombia, producing estimations with a great amount of uncertainty in more recent years and somehow

missing that flexibility in the early years of the epidemic to reproduce more natural epidemic forms. An interesting insight comes from the greatest limitation of this method: case-report data is not informative enough in the context of a highly uncertain method as the one used here. Methodological inconsistencies are still to be clarified regarding the appropriate configuration of the spline function, but from a broader perspective it was made clear that more or more detailed information was required. Having precise information about the clinical stage at the time of report could bring more precise estimations. Expanding the model structure to allow ART could as well improve the estimations. Another possibility to be explored in the future is the use of mortality data. Since the uncertainty resides in the amount of information that is fed to the model to interpret the time between an incident infection and the observed event (case-report, death), mortality could add to inform this gap.

Conclusions can be drawn as well as recommendations from this research regarding the data needs in the region. First, the strengthening of surveillance information is central since it is a rich source of information in Latin America. Greater effort must be made to introduce a greater level of detail to data recorded routinely, especially regarding modes of transmission and sexual orientation, as a handle to understand the distribution of new cases in the population. This data currently is not reliable and does not reflect the trends of transmission. Also, systematic biases and sources of underreporting need to be assessed in these contexts. Equally important is the systematic recording of the clinical stage and CD4+ count at the time of reporting. This information is usually collected in clinical settings but a systematic linkage of official reports and clinical data does not exist or is not completely implemented. In this line of thinking, the possibility of introducing algorithms for estimation the recency of infection (RITA) needs to be explored.

Strengthening surveillance systems however will not suffice to gather the necessary information for understanding the factors behind transmission in concentrated epidemics.

More behavioural surveys are urgently needed in Latin America particularly addressing the more vulnerable populations. Vulnerable populations, their behaviours and seroprevalence must be placed higher in the national health agendas of Latin American countries for an effective response to HIV. The current vehicles for data consecution (i.e. national health surveys) should attempt to explore further in sexual behaviour and sexual trends, involve men more strongly in their samples and make an effort to take advantage of MSM and FSW subsamples. Moreover, independent surveys in MSM, clients of FSW, FSW, male sex workers and PWID should be carried out more frequently. Sampling hard-to-reach population is not an easy task, but the constant developments in this research field are producing more robust and consistent estimations and should be applied in the region [33].

11 INSIGHTS FROM THE METHODOLOGICAL APPROACH

The methodological exploration in this thesis offers the possibility of contrasting different methods often used in mathematical epidemiology, but rarely found together in a single piece of research. This thesis explored sampling and calibration procedures across a spectrum from frequentist to a fully Bayesian approach. However, this should not be seen as a statement about the quality or appropriateness of any of the methods, but as an opportunity to draw useful conclusions for future work.

Latin Hypercube Sampling (LHS) and Maximum Likelihood Estimation were used in the case of Bogota, while a mixed methodological approach and pure Bayesian methods were used subsequently for Brazil and the incidence estimation model respectively. LHS proved to be a very efficient method for parameter sampling. Its algorithm is moderately easy to code and its application was easy. LHS also exploits the computational power of parallel computing, since it works with completely independent parameter sets, after an initial randomization. LHS appears as an ideal method for very large parameter spaces when

computational power and time are limited. However, this complete independence of model runs exposes its weakness at assimilating parameter correlations and an over-reliance on the assumptions made about the prior parameter distributions.

On the other hand, the Markov Chain Monte-Carlo (MCMC) method offers a heuristic process capable of exploring “wisely” the parameter space as it constantly improves the probability of the parameter values for explaining the data. The Metropolis-Hastings was the algorithm of choice in Chapter 4, and although its application is not extremely difficult, it poses many more challenges for understanding the mechanics of the process. It also demands a careful exploration of the sampling settings, and tuning-up procedures are strongly recommended. Moreover, when dealing with asymmetrical parameter distributions, the corrections required during the process can be cumbersome.

MCMC is a very thorough and informative method which goes way beyond merely sampling parameter values. If done properly, it not only produces very robust results but also enriches the knowledge about the model behaviour and the connection between parameters and the outcome. It is however very demanding in terms of time and computation and its intertwined nature of events makes it difficult to parallelize (*i.e.* a single MCMC chain). For these reasons MCMC should be the method of choice when the time and resources are available, and if a thorough exploration of parameters is required. For large parameter spaces and when a good prior knowledge about the nature of the parameters is at hand, LHS offers a very efficient and reliable option.

A different sort of challenge was found in the incidence estimation model presented in Chapter 4. Establishing the right amount of flexibility allowed in the spline-function parameterisation was a challenging task. It was clear from these results that tuning the location and number of knots in the function seem to be one of the keys to produce more

accurate estimates with this method. Sampling and calibration of the components of the spline function is something that requires further exploration. The global parameter (hyperparameter) controlling the overall flexibility of the function requires fine-tuning and this appeared very difficult to control during the calibration process, resulting in the uncertainty propagation seen in the model projections. Alternative approaches should be explored to make the most of this flexible and promising method.

12 THE SCOPE OF RESEARCH AND A HEALTH POLICY PERSPECTIVE

Two specific areas of South America were studied throughout this thesis. Generalizability of this work varies across the region and depends on the scope of analysis. In the case of Bogota, an urban setting with high HIV prevalence in MSM and moderate coverage of ART, the results might be informative for other urban areas even outside the country which hold the same type of epidemic. Health infrastructures and overall capacity for prevention delivery is similar across the region, which makes the results generalizable. The case of Brazil is more particular given the unprecedented approach to ART expansion that took place in the country. However, the lessons learned in terms of possible impact of such programmes could be highly valued by other settings that intend to follow a similar path in prevention.

Prevention programmes implemented at a large scale are a valuable source of evidence. Its results are a faithful reflection of “real-life” effectiveness and if evaluated properly they could bring not only solid estimations of an intervention’s effect but also a rich source of experience for future policy implementation. Limitations of this approach include the lack of generalizability, less systematic recording of outcomes and limited dimensions for analysis. Generalizability of results in health programmes of this kind can be limited by the fact that all the estimations obtained are hard to disentangle from confounding factors and the competing effect of parallel interventions. Also, a poor or inconsistent recording of primary and

secondary outcomes can reduce the level and dimensions in which the intervention can be analysed. On the other hand, more scientific approaches to evaluation (e.g. RCTs, C-RCTs, observational cohorts) reduce those limitations at the expense of the “real life” effectiveness factor that health programmes can provide. Health programmes should be planned with the aim of being evaluated. Better engagement of the scientific community during the planning and implementation could reduce future costs by preventing the loss of valuable resources.

The specific case of current TasP expansion in Brazil leaves room for a reflection about what was mentioned before: irrespective of the assumption we make about the real world effectiveness of treatment as prevention, the positive externalities provided by ART at the population level are undeniable. Having the chance to exploit this effectiveness in a setting where transmission is mainly circumscribed to one group of people is a one-off opportunity that should be grasped before is too late. It is also true that the challenges of targeting prevention could overwhelm any sensible policy maker, but the infrastructure and the know-how are already in place. Reaching out for vulnerable populations requires an effort and a strong bond between policy makers, researchers and activists, this is, the will, the method and the way. Political will, not only as a mere whim, but as the capacity of understanding the benefits of such approach and being able to translate it into action. The method is what research provides by establishing the priorities and the evidence. Finally the way is the experience that brings scientific theory to life.

13 FUTURE WORK

With its strengths and limitations, this work opens the doors for many possible directions for future exploration. This thesis may contribute to different areas: from the epidemic appraisal point of view it has provided fresh and distinct estimations of the past and present of HIV

epidemics in South America, and it has also contributed to the development of new modelling methods for estimating HIV incidence from surveillance data.

A more thorough exploration of the assumptions regarding behaviour change in the impact evaluation case-studies of Bogota and Brazil is a priority in the development of these chapters. A sensitivity analysis to see the impact of other forms of behaviour change over time (i.e. apart from condoms) and how these variations might impact the estimated impact of condoms and ART on HIV incidence is necessary to understand better the reach of the results.

Assessing the role of people who inject drugs (PWID) in the overall epidemic of Brazil was a limitation of this work and should be addressed in future research. Similarly, the implications of modelling such vast areas in Brazil should be investigated. Narrowing the scope of the modelling analysis might open the possibility to use more detailed clinical and programmatic data for more accurate results.

The model for HIV incidence estimation was a first and important effort on which future research can be built. As mentioned before, many technical details may be addressed in future versions of this model. Using other dimensions of surveillance data like people receiving ART and AIDS mortality might be the missing link to informing the time variations in incidence.

Modelling results unveiled in some way the urgent need to explore the potential of targeted interventions in these settings. HIV incidence reductions among MSM represented the largest fraction of infections averted in the two study cases, suggesting that a re-assessment of how the resources are being deployed is a top priority in the HIV response. In the same line of thinking, a thorough assessment of the added value of having surveillance data by group of exposure is urgently needed in the region. Given that surveillance is one of the strengths of

Latin America, more efforts must be made to improve the level of detail and start making these data work for the benefit of the countries.

14 REFERENCES

1. Cáceres, C.F., *HIV among gay and other men who have sex with men in Latin America and the Caribbean: a hidden epidemic?* AIDS, 2002. **16 Suppl 3**: p. S23-33.
2. Montano, S.M., et al., *Prevalences, genotypes, and risk factors for HIV transmission in South America*. J Acquir Immune Defic Syndr, 2005. **40**(1): p. 57-64.
3. Kerr, L.R., et al., *HIV among MSM in a large middle-income country*. AIDS, 2013. **27**(3): p. 427-35.
4. MPS/UNFPA, *Comportamiento sexual y prevalencia de VIH en hombres que tienen relaciones sexuales con hombres en siete ciudades de Colombia*, Ministerio-de-la-protección-social/UNFPA, Editor. 2012: Bogota.
5. Mott, L., et al., *Impact of condom use to prevent HIV transmission among male homosexuals in Bahia, Brazil*[abstract] in *Sixth International Conference on AIDS*. 1989; : San Francisco, California, USA.
6. Rodrigues, L.G. and P. Chequer, *AIDS in Brazil, 1982-1988*. Bull Pan Am Health Organ, 1989. **23**(1-2): p. 30-4.
7. Filgueiras, A., *Taking health promotion on to the streets*. AIDS Action, 1992(17): p. 7.
8. Departamento-de-DST-Aids-e-Hepatitis-Virais, *Avaliação da Efetividade das Ações de Prevenção Dirigidas às Profissionais do Sexo, em Três Regiões Brasileiras*, M.-d.-S. 2004, Editor. 2004, Ministério-da-Saúde, 2004: Brasília DF.
9. UNFPA. *Panorama del VIH/sida en Colombia 1983-2010*. 2012 6 February 2013]; Available from: <http://www.unfpa.org.co/uploadUNFPA/file/PANORAMA%20VIH%20SIDA%20COLOMBIA%201983-2010.pdf>.
10. Departamento de DST, A.e.H.V., *Aids e DST*, in *Boletim Epidemiológico*, M.d. Saúde, Editor. 2013, Ministério da Saúde: Brasília. p. 1:64.
11. Cáceres, C.F., *HIV among gay and other men who have sex with men in Latin America and the Caribbean: a hidden epidemic?* AIDS (London, England), 2002. **16 Suppl 3**: p. S23-33.
12. RecolviH/UNAIDS, *Voces Positivas: resultados del índice de estigma en personas que viven con VIH en Colombia*. 2011.
13. Magnani, R., et al., *Review of sampling hard-to-reach and hidden populations for HIV surveillance*. AIDS, 2005. **19 Suppl 2**: p. S67-72.
14. 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.
15. Boily, M.C., et al., *HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention*. PLoS Med, 2012. **9**(7): p. e1001250.
16. Kurth, A.E., et al., *Combination HIV prevention: significance, challenges, and opportunities*. Curr HIV/AIDS Rep, 2011. **8**(1): p. 62-72.
17. Padian, N.S., et al., *Evaluation of large-scale combination HIV prevention programs: essential issues*. J Acquir Immune Defic Syndr, 2011. **58**(2): p. e23-8.
18. Bezemer, D., et al., *A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy*. Aids, 2008. **22**(9): p. 1071-7.

19. Phillips, A.N., et al., *Increased HIV Incidence in Men Who Have Sex with Men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic*. PLoS ONE, 2013. **8**(2): p. e55312.
20. Weinhardt, L.S., et al., *Reliability and validity of self-report measures of HIV-related sexual behavior: progress since 1990 and recommendations for research and practice*. Arch Sex Behav, 1998. **27**(2): p. 155-80.
21. Schroder, K.E., M.P. Carey, and P.A. Venable, *Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports*. Ann Behav Med, 2003. **26**(2): p. 104-23.
22. UNAIDS. *AIDSinfo Online Database*. [cited 2014 1 July]; Available from: <http://aidsinfoonline.org/devinfo/libraries.aspx/Home.aspx>.
23. Mishra, S., et al., *Distinguishing sources of HIV transmission from the distribution of newly acquired HIV infections: why is it important for HIV prevention planning?* Sex Transm Infect, 2014. **90**(1): p. 19-25.
24. Mishra, S., et al., *HIV epidemic appraisals for assisting in the design of effective prevention programmes: shifting the paradigm back to basics*. PLoS One, 2012. **7**(3): p. e32324.
25. Gomez, G.B., et al., *The potential impact of pre-exposure prophylaxis for HIV prevention among men who have sex with men and transwomen in Lima, Peru: a mathematical modelling study*. PLoS Med, 2012. **9**(10): p. e1001323.
26. Hollingsworth, T.D., R.M. Anderson, and C. Fraser, *HIV-1 transmission, by stage of infection*. J Infect Dis, 2008. **198**(5): p. 687-93.
27. Cohen, M.S., et al., *Acute HIV-1 Infection*. N Engl J Med, 2011. **364**(20): p. 1943-54.
28. Miller, W.C., et al., *Role of acute and early HIV infection in the sexual transmission of HIV*. Curr Opin HIV AIDS, 2010. **5**(4): p. 277-82.
29. Cohen, M.S., et al., *HIV treatment as prevention: debate and commentary--will early infection compromise treatment-as-prevention strategies?* PLoS Med, 2012. **9**(7): p. e1001232.
30. Eaton, J.W. and T.B. Hallett, *Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence*. Proc Natl Acad Sci U S A, 2014.
31. Powers, K.a., et al., *The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study*. Lancet, 2011. **378**: p. 256-68.
32. Garcia Calleja, J.M., et al., *Has the quality of serosurveillance in low- and middle-income countries improved since the last HIV estimates round in 2007? Status and trends through 2009*. Sex Transm Infect, 2010. **86 Suppl 2**: p. ii35-42.
33. Sabin, K.M. and L.G. Johnston, *Epidemiological challenges to the assessment of HIV burdens among key populations: respondent-driven sampling, time-location sampling and demographic and health surveys*. Curr Opin HIV AIDS, 2014. **9**(2): p. 101-6.

APPENDIX TO CHAPTER 2

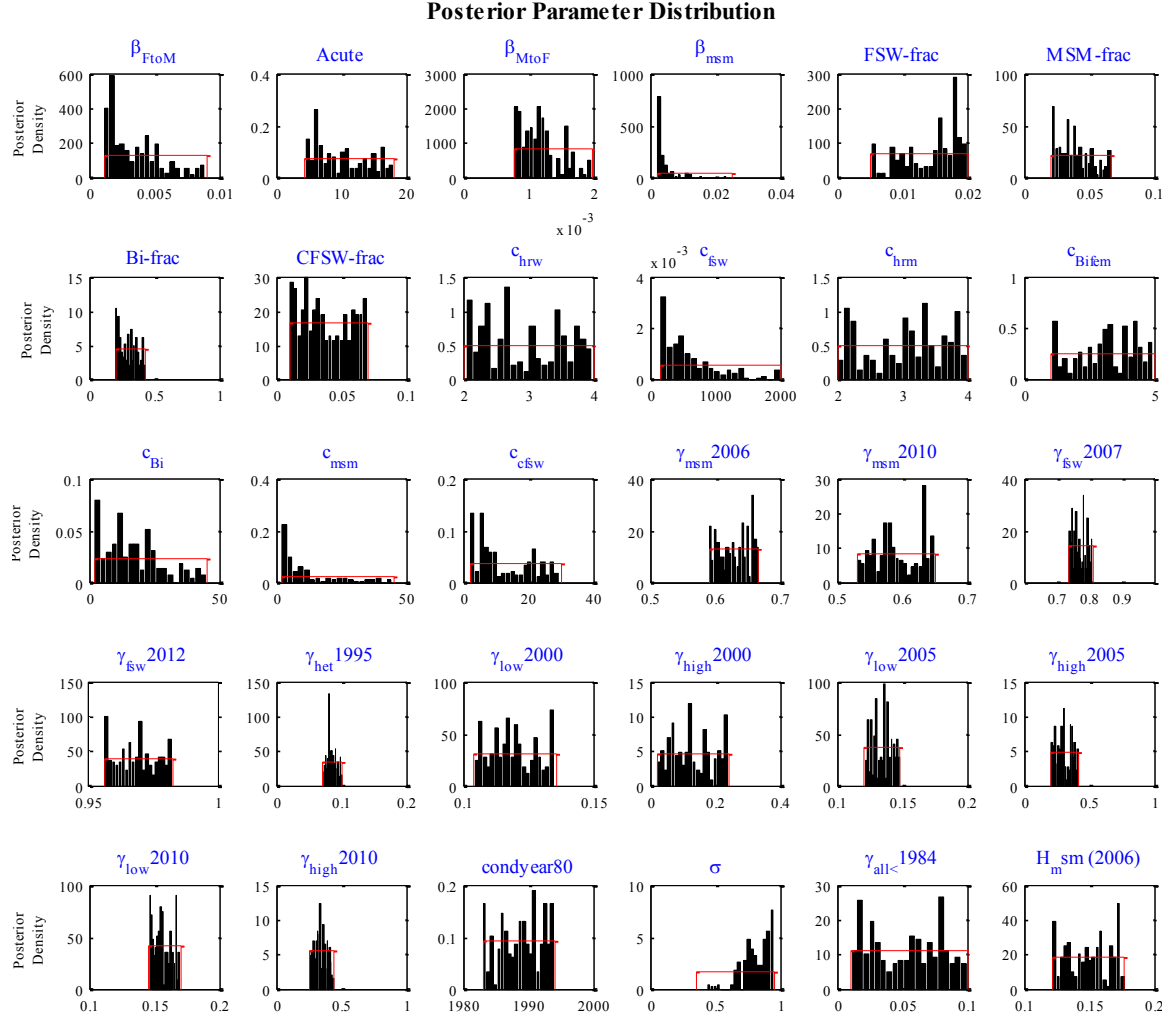


Figure A1.1 Prior (red line) and posterior (black bars) distribution histogram of model parameters 1 to 30.

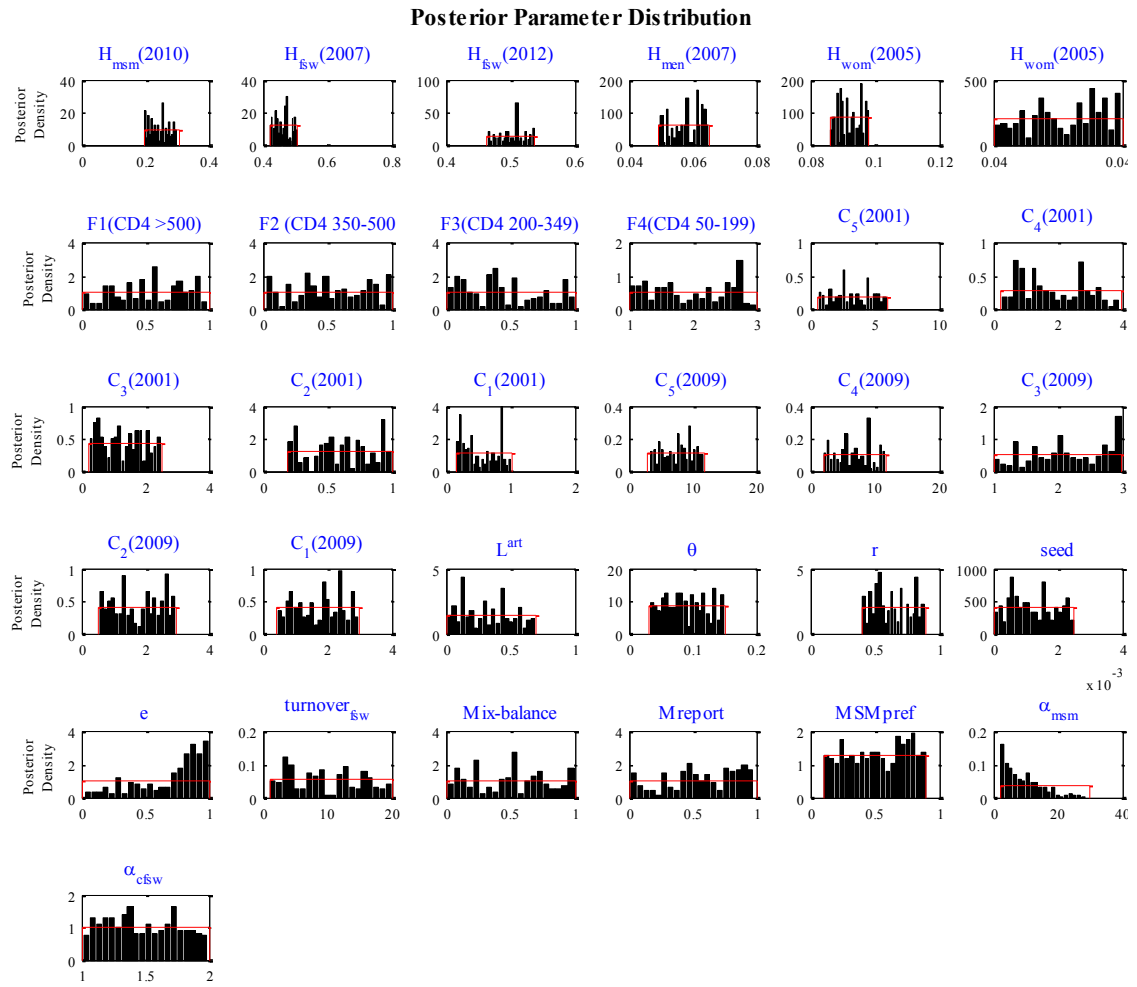


Figure A1.22 Prior (red line) and posterior (black bars) distribution histogram of model parameters 30 to 61.

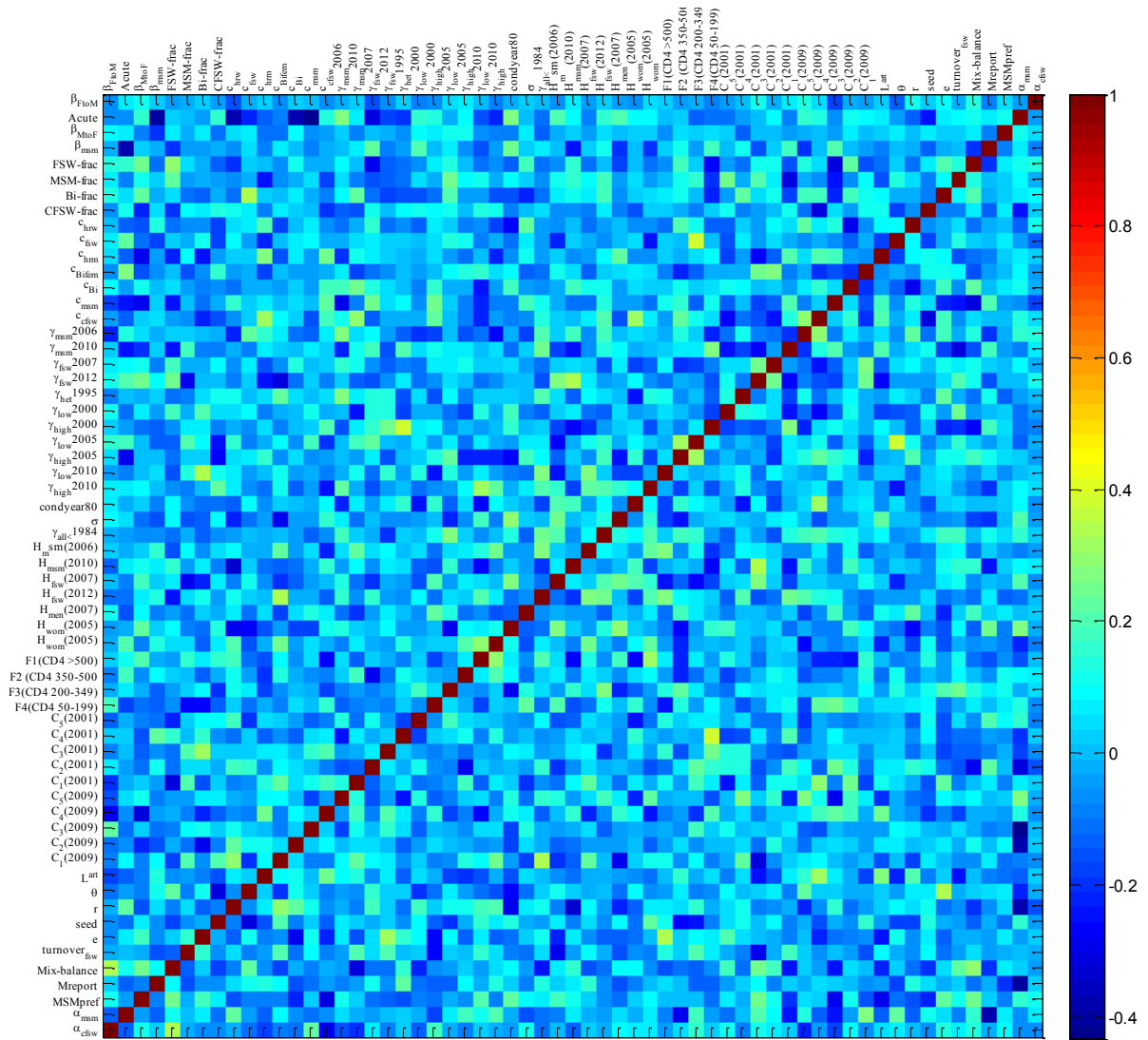


Figure A1.3 Correlation matrix of posterior parameter values.

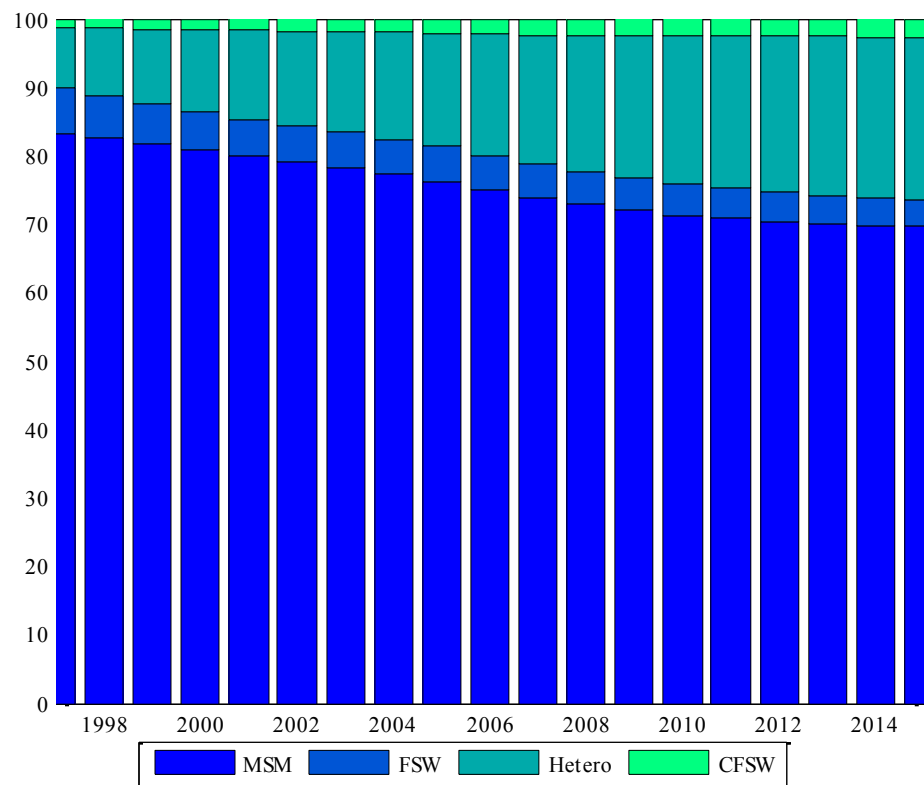


Figure A1.4 Distribution of people receiving ART in the model for Bogotá by group of exposure, 1997-2014

APPENDIX TO CHAPTER 4

OPEN

Estimating HIV incidence from case-report data: method and an application in Colombia

Juan Fernando Vesga^a, Anne Cori^a, Ard van Sighem^b and Timothy B. Hallett^a

Objective: Quantifying HIV incidence is essential for tracking epidemics but doing this in concentrated epidemic can be a particular challenge because of limited consistent high-quality data about the size, behaviour and prevalence of HIV among key populations. Here, we examine a method for estimating HIV incidence from routinely collected case-reporting data.

Methods: A flexible model of HIV infection, diagnosis and survival is constructed and fit to time-series data on the number of reported cases in a Bayesian framework. The time trend in the hazard of infection is specified by a penalized B-spline. We examine the performance of the model by applying it to synthetic data and determining whether the method is capable of recovering the input incidence trend. We then apply the method to real data from Colombia and compare our estimates of incidence with those that have been derived using alternative methods.

Results: The method can feasibly be applied and it successfully recovered a range of incidence trajectories in synthetic data experiments. However, estimates for incidence in the recent past are highly uncertain. When applied to data from Colombia, a credible trajectory of incidence is generated which indicates a much lower historic level of HIV incidence than has previously been estimated using other methods.

Conclusion: It is feasible, though not satisfactory, to estimate incidence using case-report data in settings with good data availability. Future work should examine the impact on missing or biased data, the utility of alternative formulations of flexible functions specifying incidence trends, and the benefit of also including data on deaths and programme indicators such as the numbers receiving antiretroviral therapy.

© 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

AIDS 2014, **28** (Suppl 4):S489–S496

Keywords: case-reporting data, HIV, HIV incidence rate, mathematical modelling, spline function

Introduction

In any setting, one of the most important pieces of information in responding to an HIV epidemic, evaluating past efforts, and planning for the future is the time-course of the HIV incidence rate.

Direct observation of new infections, whether through cohort studies or via the use of incidence assays and algorithms [1], is unfeasible in most national settings.

Mathematical modelling provides an alternative mean to infer incidence using other more readily available data. Currently, UNAIDS estimates of HIV incidence trends in generalized epidemics are derived through fitting a simple model to HIV prevalence measurement among pregnant women and prevalence measurements in national household surveys [2,3]. This approach has been less satisfying in settings with concentrated epidemics because of a combination of factors: inconsistencies in the measurements of prevalence over

^aDepartment of Infectious Disease Epidemiology, Imperial College London, London, UK, and ^bStichting HIV Monitoring, Amsterdam, the Netherlands.

Correspondence to Dr Juan Fernando Vesga, Department of Infectious Diseases Epidemiology, St. Mary's Campus, Norfolk Place, Imperial College London, London W2 1PG, UK.

E-mail: j.vesga10@imperial.ac.uk

Received: 21 August 2014; revised: 21 August 2014; accepted: 21 August 2014.

DOI:10.1097/QAD.0000000000000466

ISSN 0269-9370 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

time, scarce prevalence measurements among hard-to-reach groups and lack of robust estimates on the size of these groups. For this reason, it is important to explore other means of estimating HIV incidence in these settings, which would not exclusively rely on estimates of HIV prevalence and size estimates of key populations.

Other sources of available data, which could potentially be combined with models to draw inference on incidence in concentrated epidemics, include time-series data on AIDS deaths and reported cases. The use of estimated death time series is investigated in another article in this collection (Stover *et al.* in this supplement). Here, we focus on the use of reported cases.

In many settings, especially in Latin America and Europe, systems are in place to centrally record the number of persons newly diagnosed with HIV. In many settings, it is believed that the coverage of this system (the proportion of newly diagnosed cases that are counted) could be as high as 80% [4,5]. However, the interval between an infection and a diagnosis is not known and may change over time, and this would confound all estimates of incidence unless further information could be included on the interval between testing and diagnosis. Possible candidates to inform the interval between infection and diagnosis are the clinical stage and CD4⁺ cell count [6]. Further, in the future, measurement of a well characterized biomarker of recent infection may also be available [7].

In this study, we build on prior work [8,9] to develop a modelling framework that can be used to estimate HIV incidence drawing primarily on HIV case-report data. We then use synthetic data to test the performance in recovering a wide range of possible incidence trajectories. Finally, we apply the model to Colombia to derive HIV incidence estimates, which are then compared with other estimates available for Colombia.

Methods

Mathematical model

The proposed model consists of a deterministic mathematical model to simulate the process of HIV infection and disease progression, death and diagnosis (Fig. 1).

This structure is expressed through a set of six ordinary differential equations as follows:

$$\frac{dU(t)}{dt} = \alpha(t) - U(t)(s(t) + \delta); \text{ Eq. 1 : Susceptible}$$

$$\frac{dI_1(t)}{dt} = S(t)U(t) - I_1(\delta + \gamma_1 + \rho_1(t)); \text{ Eq. 2}$$

: Acute infection

$$\frac{dI_2(t)}{dt} = I_1\gamma_1e_2 - I_2(\delta + \gamma_2 + \rho_2(t)); \text{ Eq. 3}$$

: CD4+ count > 500 cell/ml

$$\frac{dI_3(t)}{dt} = I_1\gamma_1e_3 + I_2\gamma_2 - I_3(\delta + \gamma_3 + \rho_3(t)); \text{ Eq. 4}$$

: CD4+ count 350 – 500 cell/ml

$$\frac{dI_4(t)}{dt} = I_1\gamma_1e_4 + I_3\gamma_3 - I_4(\delta + \gamma_4 + \rho_4(t)); \text{ Eq. 5}$$

: CD4 + count 200 – 350 cell/ml

$$\frac{dI_5(t)}{dt} = I_1\gamma_1e_5 + I_4\gamma_4 - I_5(\delta + \gamma_5 + \rho_5(t)); \text{ Eq. 6}$$

: CD4+ count < 200 cell/ml

Where $U(t)$ is the number of persons HIV susceptible at time t ; $I_1(t)$ is the number of infected individuals in acute infection at time t ; $I_j(t)$ ($j = 2, \dots, 5$) is the number of infected individuals in CD4⁺ cell count category j at time

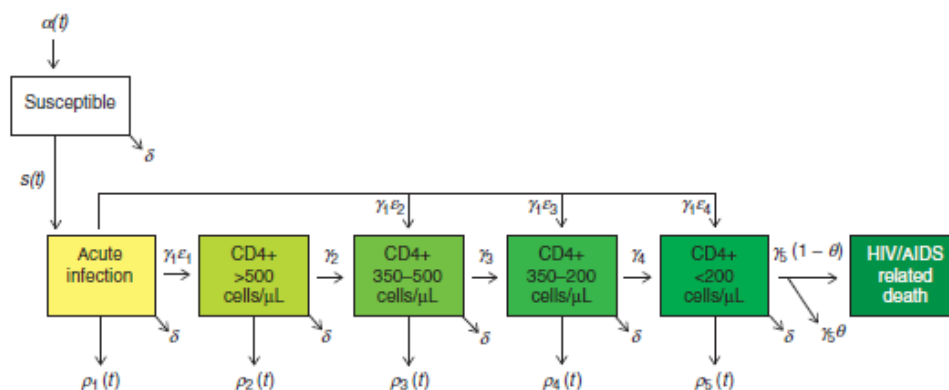


Fig. 1. Model of HIV infection and progression. Parameter values and prior distributions for calibration can be found in Table 1.

t and $s(t)$ is the time-varying rate at which the population of infected individuals transmits HIV to susceptible persons. The rate at which new infections occur in this population is given by $s(t)U(t)$. All symbols and parameters are described in Table 1.

At infection, individuals pass through a stage of acute infection following which individuals enter one of four CD4⁺ cell count categories (<200, 200–350, 350–500, 500+ cell/μl). Thereafter, individuals progress to lower CD4⁺ cell counts at rates which have previously been estimated from European data [10]. Death due to AIDS in the model is assumed to occur at a fixed rate only among individuals with CD4⁺ cell count below 200 cell/μl. The overall median survival time is 10.4 years, consistent with estimates from low-income and middle-income countries [11]. In the model framework, these parameters describing the progression of HIV infections are considered to be known perfectly.

At all times after infection, individuals can be diagnosed with HIV. At that point they transition into a 'diagnosed' category. The number of HIV-infected persons that transition to the diagnosed category in a given year in the model is compared with the data on the number of reported cases.

Model parameterization

HIV infection rate

Following Hogan et al. [2], the instantaneous hazard of infection for susceptible individuals $s(t)$ is specified as a B-spline function of time. The B-spline is parameterized by a vector of coefficients $\beta_1, \dots, \beta_n$, where $n-3$ is the number of knots of the spline which were evenly spaced on the time interval 1975–2015. This flexible functional form allows many credible incidence trajectories while constraining the trajectory to evolve smoothly with respect to time. This does not attempt to provide a mechanistic description of HIV transmission. Note that in other formulations, the spline describes a force of infection (which gives incidence when multiplied with the product of $U(t)$ and all infected individuals) rather than a hazard of infection, but this is not possible here as, for parsimony, we do not model the entire infected population.

We set $\beta_1 = \beta_2 = \beta_3 = 0$ to anchor the incidence trajectory at zero before 1975, whereas β_4 to β_6 were independently specified with uniform priors: $\beta_4 \sim U(0, 5)$, $\beta_5 \sim U(-5, 5)$ and $\beta_6 \sim U(-5, 5)$. We impose penalties [12] on the spline, in order to limit over-fitting to potentially noisy data and to represent our prior assumption that rapid large oscillations in the

Table 1. Model parameters.

Symbol	Description	Value/prior distribution	Reference
$\alpha(t)$	Birth rate	$N(t)E + (\delta)(\sum_j I_j(t) + U(t)) + I_5(t)\gamma_5$	
$N(t)$	Total population at any time t	$U(t) + \sum_j I_j$, for $j = 1, \dots, 4$	–
E	Average population growth per year	2.7%	[14]
δ	Background mortality rate	1/72 years	[14]
θ	Fraction of AIDS-related deaths detected <i>post mortem</i>	$\sim U(0, 1)$	Assumption
γ_j	Progression rates (1/years) from CD4 ⁺ cell count stage k to the subsequent inferior CD4 ⁺ cell count category	(1/yr) $\gamma_1 = \frac{1}{0.24}$ $\gamma_2 = \frac{1}{1}$ $\gamma_3 = \frac{1}{1}$ $\gamma_4 = \frac{1}{1}$ $\gamma_5 = \frac{1}{24}$	[10,15]
e_j	Proportion moving to each CD4 ⁺ stage after acute infection	$e_1 = 0.58$ $e_3 = 0.23$ $e_4 = 0.16$ $e_5 = 0.03$	[10,16]
ρ_5	Diagnostic rate at CD4 ⁺ <200 cell/μL	$\rho_5 \sim U(\frac{1}{10}, \frac{1}{0.5})$	Assumption
m	Slope scaling parameter. Is the slope for the line crossing (0, ρ_5) and (0, ρ_1)	$m = \frac{0 - \rho_5(0)}{0.17 - 0}$	Assumption
ω	Relative slope variation factor.	$\omega \sim U(-1, 1)$	Assumption
$\sigma(t)$	Function for the variation of HIV detection over time	$\sigma(t) = \frac{1}{1 + e^{-\omega(t - t_{50})}}$, for $r = 0.003$	Assumption
t_{50}	Shape parameter in function $\sigma(t)$	$t_{50} \sim U(0.1, 1)$	Assumption
β_i	Basis coefficients for spline function $s(t)$	$\beta_i = 0$, for $i = 1, \dots, 3$ $\beta_i \sim U(0, 5)$, $i = 4$ $\beta_i \sim U(-5, 5)$, $i = 5, 6$ $\beta_i = 2\beta_{i-1} - \beta_{i-2} + \mu_i$, For $i = 7, \dots, n$	
μ_i		$\mu_i \sim N(0, \tau^2)$ $\tau^2 \sim U(0, 2)$	Assumption

HIV incidence rate are unlikely. We use second-degree difference penalties [12] expressed as:

$$\beta_i = 2\beta_{i-1} - \beta_{i-2} + \mu_i, \dots, \text{for } i > 6$$

where the error μ_i is the amount of deviance from the trajectory defined by the two previous coefficients.

The prior for μ_i is normally distributed with parameters $N(0, \tau^2)$, where τ^2 is a hyper-parameter controlling the overall smoothness of the function; small values of τ^2 result in little deviance from the previous trajectory and large values in contrast produce more flexible curves.

HIV detection rates

The rate at which HIV-infected individuals are diagnosed is $\rho_j(t)$, and is allowed to vary by CD4⁺ cell count category j and calendar time t :

$$\rho_j(t) = (m\omega T_j + \rho_j(0))\sigma(t)$$

where T_j is the average time (years) to reach CD4⁺ cell count category below 200 cell/ μ L ($j=5$) for those in CD4⁺ cell count category $j=1, \dots, 4$ ($T_1=8.17$; $T_2=7.93$; $T_3=6.74$; $T_4=3.74$; $T_5=0$).

This parameterization sets the rate of detection to vary linearly as the time to reach CD4⁺ <200 cell/ μ L decreases. The slope of this line is specified by parameter ω , which allows the linear relationship to be either positive or negative. With $\omega > 0$, individuals with high CD4⁺ cell counts are more likely to be detected, which is plausible scenario if exposure to HIV is suspected or symptoms of acute infection drive testing; with $\omega < 0$, individuals with low CD4⁺ cell counts are more likely to be detected, which may be true if HIV testing is prompted by increasing experience of illness. The prior on ω reflects that both of these possibilities are equally likely: $\omega \sim U(-1, 1)$. Parameter m is a constant scaling parameter which ensures that the diagnosis rate is greater than zero for all CD4⁺ categories, irrespective of the value of ω .

Rate of testing for those in CD4⁺ cell count category below 200 cell/ μ L (ρ_5) has a prior distribution such that the average interval from infection to diagnosis is uniformly distributed between 0.5 and 10 years: $\sim U(\frac{1}{10}, \frac{1}{0.5})$.

$\sigma(t)$ describes the change in the rates of diagnosis over time. Here we assume that this change can be represented by the logistic function: $\sigma(t) = \frac{1}{1 + e^{-r(t-t_{50})}}$, where r is the rate of increase, and t_{50} is the time to reach half the upper limit rate. Parameter r is set at 0.003 and a prior was placed on t_{50} that allows a wide range in shapes in $\sigma(t)$ from a

stable trend over time ($t_{50}=1$) to a sharp increase in the rate of diagnosis from close to zero at the start of the epidemic ($t_{50}=0.1$): $t_{50} \sim U(0.1, 1)$.

Model validation and calibration procedures

The inference on the HIV incidence rate is done in a Bayesian framework. The likelihood is given by the probability of observing the number of HIV cases without AIDS reported in a year, the number of HIV cases with AIDS reported in a year (i.e. symptomatic illness or CD4⁺ cell count <200 cell/ μ L) and the number of persons diagnosed with HIV after death in a given year, each modelled as Poisson process. We used the Metropolis Hastings algorithm with component-wise updating to sample from the posterior distribution of the model. We used an adaptive proposal density variance in order to achieve an acceptance rate of approximately 30%. Three chains were run in parallel for 500 000 iterations after which chains were visually inspected for convergence and 50% of the initial runs were discarded.

Models are estimated that use B-spline functions with number of knots $n=7, 8, 10$, and with hyper-prior for τ^2 variously given as $\sim U(0.001, 0.1)$, $\sim U(0.1, 0.5)$, $\sim U(0.5, 1.0)$, $\sim U(1.0, 1.5)$ or $\sim U(1.5, 2.5)$, giving a total of 20 models runs for each estimation problem. Among these, a model is chosen that has the greatest agreement to data, given its number of effective parameters, as measured by the model with smallest deviance information criterion (DIC) [13]. For that chosen model, a sample from the joint posterior distribution is formed by randomly sampling 1000 iterations across all its chains. Medians and 95% credible intervals are reported for the posterior samples.

Assessment of model performance using synthetic data

The performance of model in recovering the 'correct' incidence trajectory from sets of synthetic data was assessed. One major concern was that the specification of this estimation method would render it unable to correctly discern all possible trajectories with different amounts of variation over time or timing of inflections. For this reason, we created three 'challenge datasets' using the same assumptions as the estimation model about natural history but varying the number in the spline function that generates that incidence rate ($n=7, 8, 10$). Synthetic data were generated under the assumption of constant rates of diagnosis over time and CD4⁺ cell count.

Application of the model to Colombia

Between 1983 and 2010, Colombia reported 78 999 HIV/AIDS patients, the vast majority coming from urban areas and major cities [17]. Overall prevalence was estimated at 0.22% in 2009 in the adult population [18], but HIV prevalence appears to be substantially concentrated among MSM, among whom prevalence has been

estimated to be between 5.6 and 24.1% in different cross-sectional studies in 2010 [19]. In our method, we assumed equivalence between an AIDS diagnosis in the data and a diagnosis for a patient with a $CD4^+$ cell count below 200 in the model.

There have been official records of the number of deaths that were classified as AIDS deaths among persons who had not previously been recorded as HIV-infected (i.e. post-mortem HIV diagnosis) since 1985 [20]. No reporting bias or misclassification in this is assumed.

We used data on the total number of HIV tests reported to have been performed in Colombia to centre the prior on the trend in the rate of diagnosis over time [21]. This trend can be broadly described as a sigmoid increase with a turning point in 1996 and a plateau in the more recent years.

These data were used in the method outlined above to estimate incidence over time. The results were compared with reported estimates of incidence from UNAIDS [22], which are based on fitting a model to prevalence data and population size estimates for key populations [3].

Results

Assessment of model performance using synthetic data

We created three challenge datasets with different epidemic trajectories and the proposed method was able to successfully recover each of them (Fig. 2). A part of the method is to estimate multiple models and then select that model with the lowest DIC; as expected, the model that was favoured in each of these tests was the model which has the same number of knots as that used to generate the synthetic data. Also as expected, uncertainty becomes

greater in more recent years as the data on case reports are less informative on current incidence rates. Uncertainty for estimates in the recent years is especially great when the data indicate that trend in incidence has changed.

Estimating HIV incidence in Colombia

The model was applied to Colombian data using the proposed method. Model estimates and data on HIV cases, AIDS cases and post-mortem detection are presented in Fig. 3a–c and resultant estimates of HIV incidence are presented in Fig. 3d. For Colombia, the model formulation with the lowest DIC was one with eight knots and hyper-prior $\tau^2 \sim U(1, 1.5)$.

The model has a good fit with the observed data (Fig. 3a–c) in the early years, whereas uncertainty is widely propagated in the recent years as noted in the experiments with synthetic data. The data for post-mortem-detected cases and AIDS cases exhibit complex patterns which the model is forced to reconcile with the clear monotonic increase in reported HIV cases and with our a priori belief that the incidence trajectory should vary smoothly over time.

The resulting estimate of HIV incidence (Fig. 3d), describes an early peak in new infections in 1990 and resurgence in the epidemic since 2000. The period with the highest incidence rate is estimated to be 2008–2009.

These incidence estimates can be compared with those previously presented by UNAIDS and which are based on an entirely different methodology whereby models are fitted to observed prevalence data and estimated sizes of key population (Fig. 4). In recent years, the estimates derived through the proposed method and the UNAIDS methods are in very close agreement. However, the UNAIDS-estimated historical trajectory of incidence suggests very high-peak incidence during 1995, of 0.3 per

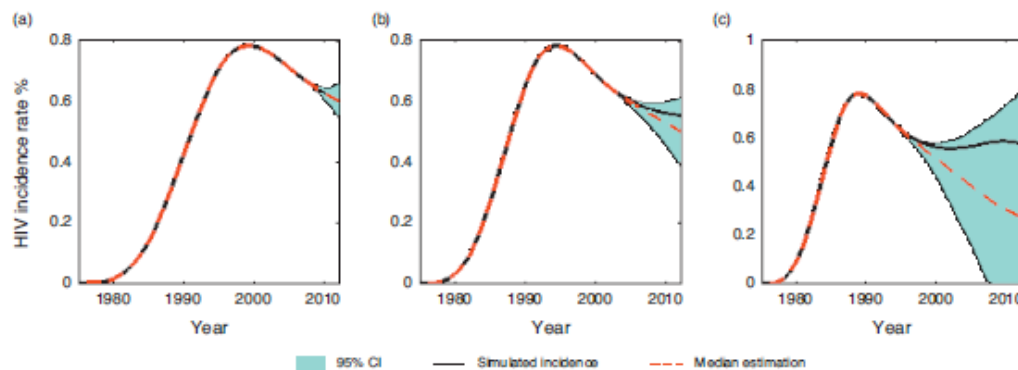


Fig. 2. Incidence estimation with four configurations of the spline function. In each panel, the black solid line is the true simulated incidence trend; the dashed red is the incidence estimation using the proposed method (median of the posterior distribution); the shaded blue region gives a 95% credible interval for incidence using the proposed method. The synthetic data were created using a model with (a) 7 knots, (b) 8 knots or (c) 10 knots.

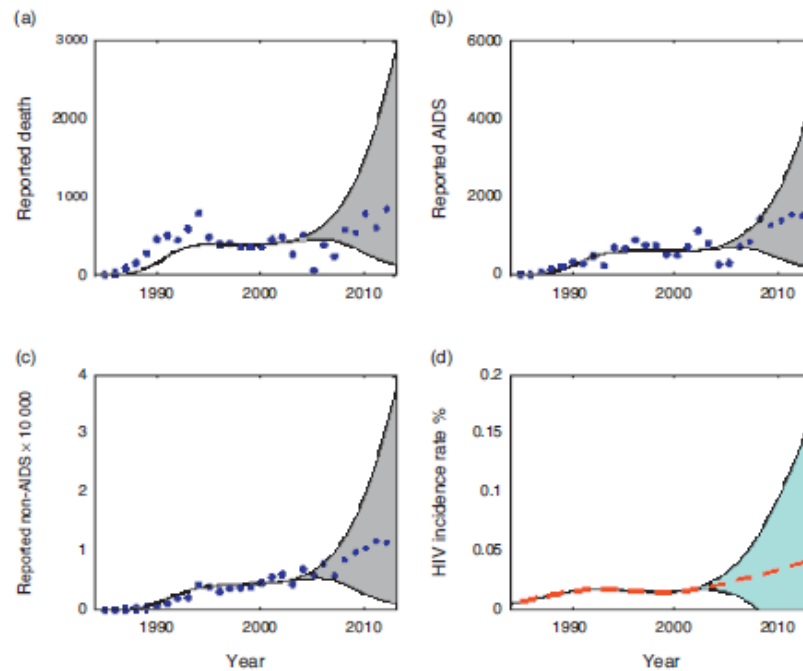


Fig. 3. Model fit to data in Colombia. Panels with data points (blue dots) as reported on a yearly basis by Colombian surveillance system, in three categories: (a) cases previously undiagnosed and only detected after death, (b) cases detected during AIDS stage and (c) cases detected and classified as non-AIDS at the time of diagnosis. In a–c, the coloured lines are the posterior estimation from the model chosen for Colombia. (d) The resulting HIV incidence trajectory in Colombia from the proposed method (red dashed line) with 95% credible interval (shaded area).

100 person-years at risk (pyar), whereas the proposed method suggests an incidence rate much lower, at 0.03 per 100 pyar.

Discussion

We examined a method for estimating HIV incidence from case-report data. We have shown that it is capable of correctly recovering a wide range of possible incidence trajectories and have applied to data from Colombia to give complementary estimates of incidence to that derived from other methods. The present formulation gives highly uncertain estimated for most recent years, limiting its usefulness.

Although it is promising that our method can broadly identify a wide range of incidence trajectories, some small inconsistencies remained. We believe these will be because of the setting of the fixed placement of the knots and the rigid ordering of unconstrained and constrained knots. It will be possible to determine whether the evaluation of a wider range of models that incorporate these differences and model selection based

on DIC is sufficient to overcome these challenges. This would inevitably increase the computational demands of the estimation procedure and so alternative methods for estimating the model will also be explored.

It will also be useful to examine how this method works under different conditions of data availability. In the challenges with synthetic data, we assumed that all required data were present and unbiased. Although this may be a reasonable assumption for some settings, it will not be universally the case and small errors in early estimates of number of cases may propagate to large errors in the inferred incidence trajectory. We also used the same assumption for the natural history of HIV (survival rates and CD4⁺ progression) in the method that generated the synthetic data as in the estimation model, which will inevitably flatter the performance of the model. It will be crucial to test the performance of the model when alternative assumptions are made and the model cannot be considered to have been fully tested until this step is done. A further step would be to examine the impact of the survival rates used to generate the synthetic data departing from those assumed in the estimation model, as well as propagating uncertainty in the assumptions about natural history in the estimation procedure. Finally, we did not

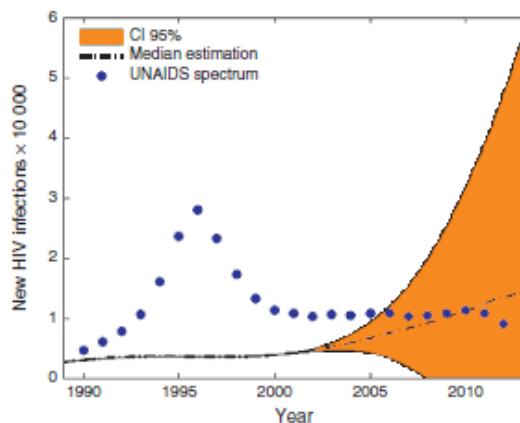


Fig. 4. Estimated number of new HIV infections in Colombia from the proposed method (red dashed lines) and current UNAIDS methods (blue dots). The orange shaded area shows the 95% credible interval of the estimates of the proposed method. Note that UNAIDS does compute uncertainty intervals for most of its statistics but intervals were not retrievable from online data sources for this statistic [22].

assess the impact of the use of inappropriate assumptions on the trend in diagnosis rates over time.

Here, we allowed HIV detection rates to vary by different CD4⁺ cell count stage, according to a prior which reflects a wide spectrum of detection scenarios. It is possible that unlikely detection configurations are allowed within this approach, but the absence of evidence to support a more restrictive parameterization led us to opt for the more flexible assumption. Ideally, in a model-aggregation framework specific detection rates by group of transmission and stage of disease would be modelled separately, but this will only be feasible for those contexts with highly detailed case-report data and evidence of differential HIV detection and linkage to care.

This method gives uncertain results, especially in recent years, because there remains confounding by potential changes in the interval between infection and death and because numbers of cases and deaths are informative of incidence rates sometime in the past rather than current incidence. Therefore, in the current form, this method cannot be expected to reliably detect recent changes in incidence, which would be very important in monitoring a national epidemic. We expect, however, that it would be highly advantageous for this method to draw on further data. It will be possible to extend this method to incorporate data and/or estimates on deaths and numbers on antiretroviral therapy (ART), which should contribute to discriminating the earlier part of incidence trajectory in particular. Although it is not commonly used at present, the addition of measurement of biomarkers that relate to recency of infection at diagnosis

could also help discriminate current incidence levels, though this would depend on the characteristics of the biomarker and how well they are known (Bao *et al.* in this collection).

Our estimates of HIV incidence for Colombia must be interpreted with a high degree of caution and in light of our method's assumptions and present limitations. Of particular note, the estimates from the proposed model suggest that incidence was historically much lower than the levels the previous UNAIDS estimate indicate. This could stem from our assumption of complete case reporting and no misclassification of AIDS deaths: if, in fact, some diagnoses go unreported and some true AIDS deaths are misclassified, then our estimates will be too low. Nevertheless, it seems unlikely that these biases would fully explain the discrepancy. Added to this, we note that the level of incidence estimated here is in closer agreement with that recently reported by Murray *et al.* [23].

In conclusion, this method is promising technique for estimating HIV incidence trends that does not rely on using prevalence data and size estimates of key populations, and which leverages high quality routinely collected data. Future work should focus on updating the model structure to allow other forms of surveillance data, such as AIDS deaths and people on ART, and further scrutiny of model performance under circumstances of missing or biased availability of data.

Acknowledgements

T.B.H. thanks UNAIDS, The World Bank, The Rush Foundation and the Bill & Melinda Gates Foundation for funding support. A.C. thanks the NIH for funding through the NIAID cooperative agreement UM1 AI068619.

Conflicts of interest

There are no conflicts of interest.

References

1. Incidence Assay Critical Path Working Group. **More and better information to tackle HIV epidemics: towards improved HIV incidence assays.** *PLoS Med* 2011; 8:e1001045.
2. Hogan DR, Zaslavsky AM, Hammit JK, Salomon JA. **Flexible epidemiological model for estimates and short-term projections in generalised HIV/AIDS epidemics.** *Sex Transm Infect* 2010; 86 (Suppl 2):i184–i192.
3. Brown T, Bao L, Raftery AE, Salomon JA, Baggaley RF, Stover J, *et al.* **Modelling HIV epidemics in the antiretroviral era: the UNAIDS Estimation and Projection package 2009.** *Sex Transm Infect* 2010; 86 (Suppl 2):ii3–ii10.
4. Centers for Disease Control and Prevention. **Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2011.** Centers for Disease Control and Prevention; 2013.
5. Health Protection Agency. **HIV in the United Kingdom: 2011 Report.** London: Health Protection Agency; 2011.

6. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, et al. HIV incidence in men who have sex with men in England and Wales 2001-10: a nationwide population study. *Lancet Infect Dis* 2013; **13**:313-318.
7. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, et al. Estimation of HIV incidence in the United States. *JAMA* 2008; **300**:520-529.
8. Sweeting MJ, De Angelis D, Aalen OO. Bayesian back-calculation using a multistate model with application to HIV. *Stat Med* 2005; **24**:3991-4007.
9. van Sighem A, Nakagawa F, Bezemer D, De Angelis D, Op de Coul E, Egger M, et al. Estimating the Size of the Undiagnosed HIV Population in the Netherlands by Disease Stage [CROI abstract 975]. *Top Antivir Med* 2014; **22** (e-1):512-513.
10. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiébaud R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm³: assessment of need following changes in treatment guidelines. *Clin Infect Dis* 2011; **53**:817-825.
11. Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. *AIDS* 2007; **21** (Suppl 6):S55-S63.
12. Eilers PHC, Marx B. Flexible smoothing with B-splines and penalties. *Stat Sci* 1996; **11**:89-121.
13. Spiegelhalter DJ, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc* 2002; **64**:583-640.
14. DANE. Estadísticas Vitales. http://www.dane.gov.co/index.php?option=com_content&view=article&id=73&Itemid=119. [Accessed 7 August 2014].
15. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis* 2008; **198**:687-693.
16. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): a cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: mathematical model. *PLoS One* 2014; **9**:e84511.
17. UNFPA. Panorama del VIH/sida en Colombia 1983-2010. Bogotá; 2012. <http://www.unfpa.org.co/uploadUNFPA/file/PANORAMA%20VIH%20SIDA%20COLOMBIA%201983-2010.pdf>. [Accessed 7 August 2014].
18. Castro J. VII Estudio nacional centinela de VIH en gestantes. Bogotá: Instituto Nacional de Salud, December 2009;1-79.
19. MPS/UNFPA. Comportamiento sexual y prevalencia de VIH en hombres que tienen relaciones sexuales con hombres en siete ciudades de Colombia. Bogotá: MPS/UNFPA; 2012.
20. García-Bernal R, Klaskala W, Castro J, Zhang C, Baum M. HIV/AIDS surveillance in Colombia: regional differences in epidemic trends. *AIDS* 1997; **11**:1297-1298.
21. Observatorio-Nacional-de-VIH-sida. Informe de indicadores de atención integral por departamento y periodo. Bogotá: Ministerio de la Protección Social; 2012.
22. UNAIDS. AIDSinfo Online Database. <http://aidsinfoonline.org/devinfo/libraries/aspx/Home.aspx>. [Accessed 1 July 2014].
23. Evaluation IHMa. Data Visualization Tool 2014. <http://vizhub.healthdata.org/mdg/>. [Accessed 7 August 2014].