Modelling HIV transmission and control among men who have sex with men in the United Kingdom

Narat Punyacharoensin

Department of Infectious Disease and Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine

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In loving memory of my father, Sununt Punyacharoensin,
and my sister, Panjapak Punyacharoensin (Mew)

Forever in my heart

DECLARATION OF OWN WORK

I, Narat Punyacharoensin, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

I have read and understood the School's definition and policy on the use of third parties (either paid or unpaid) who have contributed to the preparation of this thesis by providing copy editing and, or, proof reading services. I declare that no changes to the intellectual content or substance of this thesis were made as a result of this advice, and, that I have fully acknowledged all such contributions.

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Narat Punyacharoensin, 211356

(April 15, 2015)

ACKNOWLEDGEMENTS

I accidentally started this PhD in January 2009 and it took me more than six years to finish. When I went back to the School to have my viva in March 2015, I could barely remember anyone there as most of my friends had already finished their PhD a while ago. It is probably accurate to say that I am the last of the students who started PhD in 2009 and actually completed it. A record truly worth remembering.

I lost my father about a year and my older sister about a month before my viva. For me, the losses were overwhelming. It was like my soul was torn apart, almost completely, even at this very moment. I kept on fighting, however, because of the belief that at the end I will be able to use all the knowledge and experiences obtained here to help my home country, Thailand. I did not concern at all about publications, giving talks in conferences, or being famous, although I can understand very well why most people took it so seriously. All the credit should go to my mother who taught me repeatedly the value of living a happy life by helping others, which works exceptionally well in the world that full of greed and selfishness. She has also been the co-sponsor of this PhD since before day one. Without her there will be absolutely nothing. Thanks Mum, and also Dad and Mew, my sister. Miss you both so much.

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My co-supervisors, John Edmunds and Daniela De Angelis are also the two great people that deserve a standing ovation. I am particularly thankful to them both for sharing expertise and invaluable guidance to me. Thanks so much John and Dani, I could have not done it without you two.

I also wish to express my sincere gratitude to the advisory panel for their support and advice, to the Public Health England for the funding and providing access to the UK HIV/AIDS databases, to all co-authors of the papers included in this PhD for their contributions, and finally, to one and all who have lent their hand in this project. Thank you all, including you my love.

ABSTRACT

Background and objectives

Men who have sex with men (MSM) remain one of the groups with the highest HIV prevalence in the UK. The goal of this study is to help inform appropriate health policy by investigating the contribution to HIV transmission of various MSM subgroups and estimating the impacts of alternative HIV control measures. The future course of the epidemic is also projected.

Methods

Research questions were addressed through the use of rigorous data analysis and a partnership-based HIV transmission model that takes into account key MSM and HIV heterogeneities and intervention effects. The model was fitted and validated against the observed data and reported estimates of various types. Sensitivity analyses were conducted throughout the study to assess the effects of parameter uncertainty.

Results

Without additional interventions, the estimated 44,000 UK MSM living with HIV in 2013 could increase to around 52,000 men by the end of the decade, with around 2,400 new infections each year. The key group sustaining HIV transmission was the higher-sexual activity MSM aged below 35 years living with undiagnosed asymptomatic HIV. Pre-exposure prophylaxis (PrEP) with 44% efficacy and 100% coverage would prevent approximately 10,000 cases (59% of total incidence) over 2014–2020. Simultaneously offering PrEP, expanding HIV testing, and initiating a test-and-treat programme in 25% of different target populations could save around 7,400 UK MSM from HIV. An extreme increase in unsafe sex and number of sexual partners would greatly reduce the incidence reduction but is unlikely to completely negate the prevention benefit.

Conclusion

Increasing HIV testing uptake should remain the core of the national HIV/AIDS strategy, but a combination of HIV prevention interventions are also necessary to enhance the overall performance of HIV control measures. Combining a program to expand HIV testing with other novel interventions, such as test-and-treat and PrEP, has a great potential to save thousands of UK MSM from HIV and become the key HIV prevention initiatives in the UK.

PROJECT SUMMARY

Primary goal	Develop a mathematical model to evaluate a range of interventions for HIV transmission control among men who have sex with men (MSM) and help inform HIV/AIDS prevention policy in the UK
Research questions:	1. What are the current levels of HIV incidence and prevalence among MSM in the UK? 2. What proportion of current HIV incidence among UK MSM is contributed by various subpopulation groups, e.g. diagnosed MSM with or without antiretroviral treatment (ART), and infections from different disease stages? 3. What will be the potential future impact of implementing the various interventions to control HIV transmission among MSM in the UK? 4. What is likely to be the most effective combination of feasible interventions to reduce HIV transmission among MSM in the UK?
Methodology:	Literature review, data analysis, and HIV transmission mathematical model
Researcher:	Narat Punyacharoensin, IDE
Supervisor:	Richard White, IDE
Co-supervisors:	John Edmunds, IDE Daniela De Angelis, Public Health England and MRC Biostatistics Unit, Cambridge
Advisory committee:	Ken Eames, IDE Graham Hart, Centre for Sexual Health and HIV Research, University College London Noel Gill, HIV and STI Department, Public Health England

ABBREVIATIONS AND DEFINITIONS

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
GUM	Genitourinary medicine
HIV	Human immunodeficiency virus
MSM	Men who have sex with men
MPES	Multi-parameter Evidence Synthesis
PHE	Public Health England (previously known as HPA: Health Protection Agency)
PrEP	Pre-exposure prophylaxis
STI	Sexually transmitted infection
STD	Sexually transmitted disease
UAI	Unprotected anal intercourse
UIAI	Unprotected insertive anal intercourse
URAI	Unprotected receptive anal intercourse
UROI	Unprotected receptive oral intercourse
UK	United Kingdom
US	United States of America

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Chapter 1

Introduction

In this chapter:

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1.1. Rationale and justification

Sex between men continues to represent one of the most common routes of HIV transmission in the UK. A total of almost 11,000 deaths among men who have sex with men (MSM) caused by HIV infection has been reported [1] (Table 1-1). In 2007, there were an estimated 32,000 MSM living with HIV in the UK, and of these around a quarter were unaware of their HIV infection. Given that an estimated 420,000 MSM aged 15-44 were living in the UK, HIV prevalence among this group was estimated to be 5.3% [2]. The 2009 national HIV report confirms that MSM remain one of the groups with the highest HIV prevalence [3]. HIV transmission through sex between men is still a major public health problem in the UK.

Recent surveillance information shows that the number of new diagnosed infected MSM increased between 1998 and 2005 and may have reached approximately 2,500 cases since then. During 2007, around 11% of MSM have tested for HIV at a genitourinary medicine (GUM) clinic [2]. The uptake of HIV testing in GUM clinics has continued to rise but, still, around 35% of infected MSM left clinics without knowing that they are infected with HIV. Moreover, a community-based survey in 2005 reported that only 48% of MSM were offered a HIV test during their last visit to a GUM clinic [4]. The average CD4 cell count at diagnosis among MSM has continued to increase from 334 in 1999 to 416 in 2008 [5]; however, around 43% were diagnosed with a CD4 cell count less than the threshold at which treatment should begin (350 cells/µL) and 20% were diagnosed during the late disease stage (CD4 cell count less than 200 cells/µL) which is associated with a significant increase in mortality within a year of diagnosis compared with those diagnosed earlier [3].

Table 1-1: Summary of current HIV epidemic among MSM in the UK

Indicators	Number
Incidence and prevalence	
Number of MSM aged 15-44 in 2007[a]	415,700
HIV prevalence among MSM aged 15-44 in 2007[a]	5.3%
HIV prevalence among London MSM aged 15-44 in 2007[a]	8.5%
Annual HIV incidence among MSM in 2007[a]	1.8%
Proportion of MSM who get infected from abroad in 2008[b,*]	17%
Diagnoses and deaths	
Annual HIV diagnoses among MSM in 2008[c]	2,433
Cumulative HIV diagnoses among MSM up to the end of June 2009[c]	45,947
Annual AIDS diagnoses among MSM in 2008[c]	160
Cumulative AIDS diagnoses among MSM up to the end of June 2009[c]	13,825
Annual AIDS deaths among MSM in 2008[c]	180
Cumulative AIDS deaths among MSM up to the end of June 2009[c]	10,990
Number of MSM living with diagnosed HIV in 2007[a]	24,000
Number of MSM living with undiagnosed HIV in 2007[a]	8,000
HIV testing	
Number of MSM offered HIV test in 2007[a]	45,748
Proportion of MSM accepting HIV test in 2007[a]	86%
Proportion of MSM leaving GUM clinic undiagnosed in 2007[a,**]	35%
Number of MSM accessing HIV-related care in 2007[a]	23,990
Average CD4 cell count at diagnosis in 2008 (cells/µL)[d]	416
Proportion of MSM diagnosed at CD4 < 200 cells/µL in 2008[b]	20%
Proportion of MSM diagnosed at CD4 < 350 cells/µL in 2008[b]	43%

GUM: Genitourinary medicine

[a] Sexually transmitted infections and men who have sex with men in the UK: 2008 report [2], [b] HIV in the United Kingdom: 2009 report [3], [c] Men who have sex with men: United Kingdom HIV new diagnoses to end of June 2009 [1], [d] New HIV diagnoses show burden continuing in gay men [5], * calculated by dividing the number of HIV-infected MSM diagnosed in 2008 who get infected from abroad (=480) by the total number of HIV-infected MSM diagnosed in 2008 (=2,760), ** calculated by dividing the number of MSM who left the clinic undiagnosed in 2007 (=121) by the total number of MSM who were unaware of their infection before visiting the clinic in 2007 (=349).

An increase in unprotected anal intercourse (UAI) was also reported in the 2005 sexual health survey of MSM attending community venues in London with approximately 25% reported UAI with partners of unknown or discordant HIV status [4] which presented a risk of both HIV transmission to an uninfected individual and cross-infection by drug-resistant strains for HIV-positive men [6]. Results from this survey also showed that HIV-positive men, particularly those who were unaware of their infection, were more likely to practice UAI, have casual partners, and have serodiscordant partnerships. These data and findings highlight the importance of evaluating and improving the HIV control interventions which is in line the recommendations made recently by Public Health England [2,3].

A transmission model that is parameterised using the latest biological, behavioural and surveillance data collected in the UK can be used to explore a range of interventions in terms of their prevention effectiveness to inform best practice. Such a model needs to be flexible enough to include the important biological and behavioural factors and the HIV testing patterns. This has the additional benefit of allowing an investigation into the effects of promoting different testing policies as well as policies aimed to change sexual behaviours. Conventional compartmental models have traditionally been employed to evaluate the effects of such interventions, and yet this type of model does not fully allow important heterogeneities (e.g. partnership duration, partnership concurrency) to be incorporated and, more importantly, provides a very simplistic representation of the role of partnerships and contact network in disease evolution. Moreover, there may be more than one factor that is driving the ongoing transmission among MSM. The contribution of these factors to net infections cannot be inferred easily from behavioural surveys and surveillance data because of their complex interactions and unknown underlying mechanism of HIV transmission. Using mathematical models that are informed by rigorous data analysis to gain a clear picture of the actual epidemic situation is, thus, necessary.

The main objective of this study is, therefore, to develop alternative modelling approaches that include important heterogeneities and make a better use of available

data than has been attempted to date to evaluate a wide range of the current and potential future interventions for the control of HIV transmission in UK MSM. This should help inform appropriate HIV/AIDS policy and contribute towards an ultimate goal of providing information that leads to reduced HIV transmission among MSM in the UK.

1.2. Primary research questions

Through the use of the mathematical model, this study aims to answer the following questions:

1. What are the current levels of HIV incidence and prevalence among MSM in the UK?
2. What proportion of the current HIV incidence among UK MSM is contributed to by the following MSM sub-groups?
    a. HIV-undiagnosed MSM, diagnosed MSM who are not on antiretroviral therapy (ART), diagnosed MSM who are on ART
    b. MSM by HIV infection stage (primary, asymptomatic, and symptomatic stages)
    c. MSM by age group and sexual activity level
3. What will be the potential future impact of implementing the following interventions to control HIV transmission among MSM in the UK?
    a. Changing the current HIV testing strategy, e.g. testing more frequently
    b. Changing the current ART strategy, e.g. treating infected MSM earlier in their disease
    c. Implementing behavioural change intervention to reduce number of partners and unsafe sex
    d. Introducing pre-exposure prophylaxis
4. What is likely to be the most effective combination of feasible interventions to reduce HIV transmission among MSM in the UK?

1.3. Scope of the study

The scope of this study is described in Table 1-2.

Table 1-2: Summary of scope of the study

Index	Description
Population	Men who have sex with men aged 15 to 64 excluding those at risk of infection from sharing injection equipment. Men who have sex with both men and women are included but the transmission route will be limited only to sex between men.
Disease	HIV/AIDS. Effects of other sexually transmitted infections (STIs) are not included.
Geographic area	The entirety of the United Kingdom without geographic categorisation
Epidemic timeframe	Year 2000-2020
Economic evaluation	There is no economic evaluation of HIV prevention interventions.

1.4. Ethical approval

Only frequency, proportion and count data will be used in this study. There is no linked or traceable personal information of any kind involved, and thus, no ethical approval was required.

1.5. Thesis overview

The thesis is comprised of seven chapters. The flow diagram in Figure 1-1 describes the processes undertaken in this study.

Chapter 2 reviews the mathematical modelling methodology, the development and use of modelling to simulate HIV transmission among MSM, and the HIV control strategy

suggested by modelling studies. The review also identifies important heterogeneities that have been used for designing the model in Chapter 3.

Chapter 3 presents the design of the HIV transmission model and the detailed description of model development based on the literature review from Chapter 2. The resulting model illustrates the proposed input parameters that are estimated in the next chapter.

Chapter 4 initiates the process of parameter estimation by exploring model parameters and various aspects of the required data from multiple sources in details including characteristics, completeness, and bias. The parameter values obtained from data analysis are used in the model, which then fitted to observed data in Chapter 5.

Chapter 5 describes the fitting of the developed model. The reported HIV surveillance data and estimates are used to estimate unknown parameters. The final model with complete parameter values are then used to investigate the current HIV epidemic among MSM in the UK and project its future course. The primary research questions 1 and 2 are answered in this chapter.

Chapter 6 assesses the potential impact of a range of interventions in preventing HIV transmission UK MSM. The primary research questions 3 and 4 are addressed in this chapter.

Chapter 7 summarises the main findings from this study as well as the limitations and implications for HIV prevention among MSM in the UK.

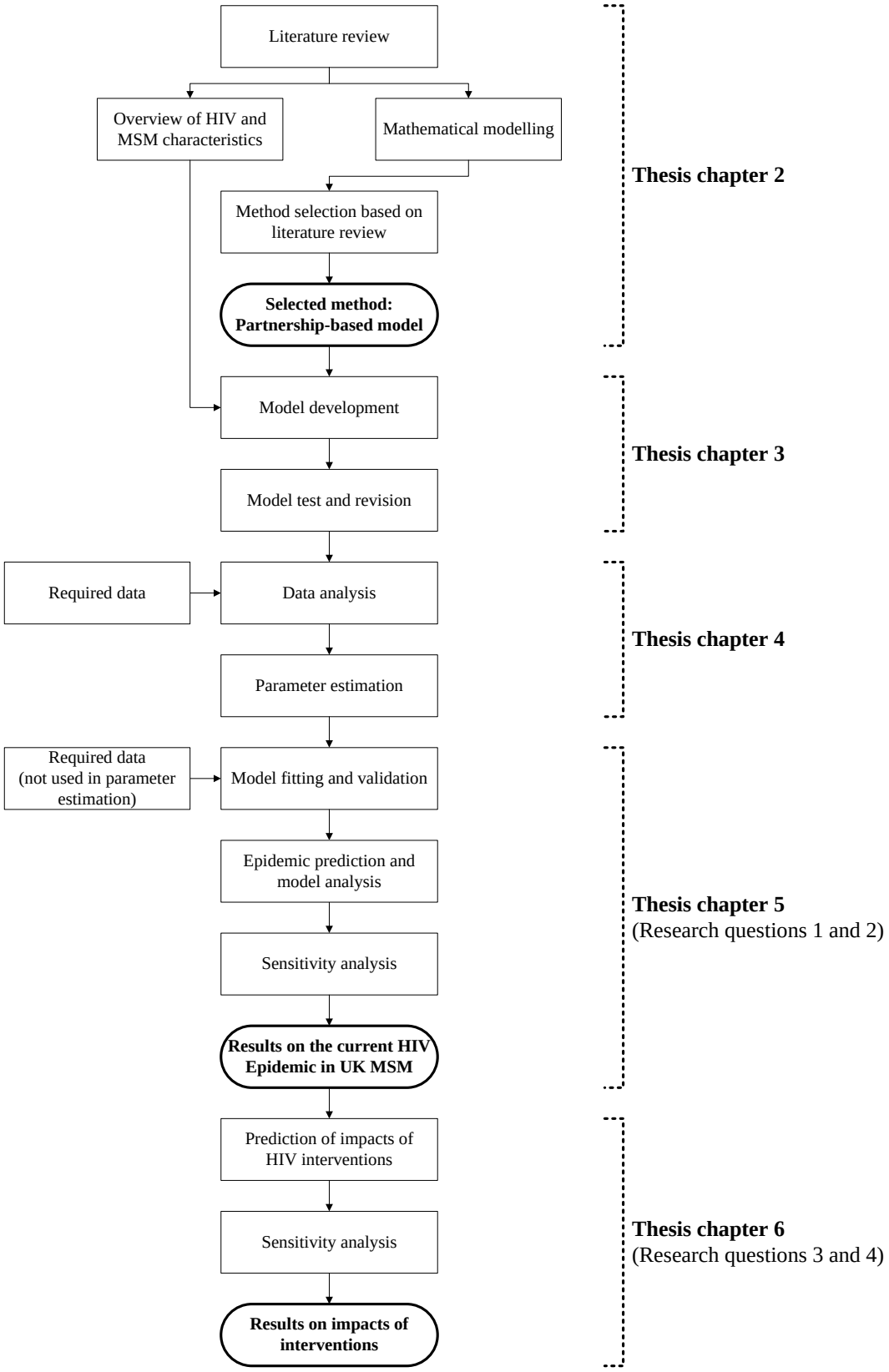

Figure 1-1: Flow process diagram of the study

Chapter 2

Literature review

In this chapter:

The review of modelling methodology for HIV transmission

Modelling approach evaluation and selection

Publication:

'Mathematical models for the study of HIV spread and control amongst men who have sex with men'

European Journal of Epidemiology (2011)

2.1. Introduction

The introductory chapter presented the motivation for this PhD and outlined the use of HIV transmission model to address key research questions. This chapter reviews relevant aspects of HIV/AIDS and men who have sex with men (MSM) characteristics that are important for designing HIV transmission model. The previous modelling works for HIV transmission in MSM since the early epidemic are also reviewed to help inform appropriate modelling sequences and important population heterogeneities.

2.2. HIV/AIDS

Human immunodeficiency virus (HIV) is a retrovirus that primarily infects CD4 cells and subsequently leads to the failure of human immune system and the acquired immunodeficiency syndrome (AIDS) in the late stage of infection [7]. HIV was first discovered in 1983 and variously named including “lymphadenopathy-associated virus (LAV)” [8] and “HTLV-III” [9] before all were found to be the same type of virus and renamed HIV in 1986 [7]. The first recognised AIDS cases were reported in 1981 [10] before AIDS was initially defined by the US Centers for Disease Control and Prevention in 1982 as “a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease. Such diseases include Kaposi's sarcoma, Pneumocystis carinii pneumonia, and serious opportunistic infections [11]. The new AIDS-defining clinical symptoms and conditions were subsequently added due to updated evidence on epidemiology of HIV/AIDS. The current definition of an AIDS case could vary across regions but commonly based either on a very low CD4 cell counts within HIV-positive individuals, usually less than 200 cells/µL, or one or more symptomatic conditions that occur during the infection [12,13]. In most European countries including the UK, an AIDS case was defined according to the 1993 European AIDS Surveillance Case Definition which has not included CD4 counts in the definition [14].

HIV is transmitted mainly through exchange of body fluids during sexual intercourse which has accounted for with the majority of global HIV infections since the start of the epidemic [15]. HIV transmission through an exposure to contaminated blood or blood products, and from an HIV-positive mother to child during pregnancy are also among the main routes. A few days after HIV enters the body and successfully bonds to CD4 cells, the virus replicates rapidly and causes great damage to the host immune system, which results in a very high viral load in the bloodstream [16]. The host body then starts to seroconvert and recover CD4 cells in an attempt to fight the virus, whereas the viral load continues to decrease until the setpoint is reached. The viral load remains relatively stable at this level accompanied with a gradual decline in CD4 cell counts for a period of approximately 8-10 years depending partly on the viral load setpoint [17]. No HIV-related symptoms are observed during this so-called asymptomatic HIV infection. The HIV-infected persons subsequently progress to the symptomatic stage of HIV infection where one or more opportunistic infections can initially be observed. Without appropriate and urgent treatment, the disease will progress rapidly towards AIDS with a greater frequency and severity of opportunistic infections that eventually leads to death [18,19]. In the absence of treatment, the median time from HIV seroconversion to AIDS and death is, respectively, around 10 and 11 years in developed countries [20], and 9 and 10 years in Africa [21].

Two major types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), have been identified. HIV-1 is related to viruses isolated from the chimpanzee [22], and responsible for the vast majority of global HIV pandemic [15]. HIV-2 is related to viruses isolated from the sooty mangabey [22], and spreads mainly in West Africa but an increasing number of cases have been found in other parts of the world [23,24]. The severity of HIV-1 infection exceeds that of HIV-2 in many aspects. A direct comparison study suggested that HIV-1 patients have significant lower median CD4 cell count at AIDS diagnosis and shorter survival time after AIDS than HIV-2 patients [25]. The excess mortality rate and mother-to-child transmission rate are also higher in HIV-1-infected individuals [23]. Since HIV-1 is the predominant HIV type in the UK, the instances of ‘HIV’ refer to HIV-1 unless otherwise stated.

2.3. HIV and men who have sex with men

The term ‘men who have sex with men’, abbreviated ‘MSM’, is defined according to the UNAIDS Action Framework as males who have sex with other males, regardless of whether or not they have sex with women or have a personal or social identity associated with that behaviour, such as being ‘gay’ or ‘bisexual’ [26]. MSM did not always identify themselves as gay [27]. Therefore, using the term ‘MSM’ to clearly distinguish between the self-defined gender identity and actual sexual behaviours of persons is of high importance for the epidemiological study of the spread of HIV and other sexually transmitted diseases.

MSM are at increased risk of HIV infection mainly because of the unprotected receptive anal intercourse (URAI) that is common among this population. A thin layer of mucous membrane lining the anus and rectum has a physically delicate structure, and contains several types of living cells including CD4 that are the main targets for HIV [28,29]. Irritating the rectum by an act of URAI can cause damage to the lining tissues and allows HIV from ejaculatory fluid to enter the body and infects the surrounding cells [28]. Even without ejaculating, HIV found in the pre-ejaculatory fluid of HIV-positive men still poses a risk for HIV infection [30,31]. The long length of the rectum and colon also facilitates HIV infection from URAI [32]. HIV can be transmitted through the unprotected insertive anal intercourse (UIAI) as well, but at a much lower rate than the URAI [33].

The 2013 UNAIDS report estimated that 7-19% of MSM are infected with HIV worldwide, depending on the region [15]. In many developed countries, the HIV epidemic among MSM is not declining despite the fact that antiretroviral treatment (ART) has been widely used in these countries [34]. In the UK, MSM account for an increasingly large proportion of new HIV diagnoses, from around 30% in 2002 to almost 50% in 2011 [35].

2.4. HIV transmission model

In order to model the dynamics of the HIV epidemic, two main approaches have been used. First, epidemic forecasts have been derived through two statistical methods: extrapolation and backcalculation. The extrapolation is based on fitting a statistical model to the AIDS incidence observed up to a particular time and using the fitted model to predict future AIDS incidence. The backcalculation method combines the knowledge about incubation period distribution and the observed AIDS incidence data to reconstruct the HIV incidence curve in the past and forecast the AIDS incidence in the near future. A common limitation of statistical models is that the mechanism of disease transmission and dynamics of the epidemic is ignored [36-39]. Epidemic projections without taking into account changes over time in the number of infected individuals can be misleading [40]. Moreover, the temporal effects of behaviour change and interventions cannot be directly incorporated, making an evaluation of HIV/AIDS strategies not feasible through this approach [41].

Another approach is through transmission (or mechanistic) models which have been developed to explicitly model the forces driving the epidemic. The most common mathematical model is referred to as the dynamic compartmental model in which populations are divided into subgroups (compartments) often by the disease-related status. Transitions between compartments are governed by model parameters that describe the disease evolution. Since HIV infection is incurable, the model consists of at least susceptible and HIV-infected compartments. The dynamics of each compartment can be described by the following differential equation systems.

$$\frac{dS(t)}{dt} = -c\beta S(t)\frac{I(t)}{N} \tag{1}$$

$$\frac{dI(t)}{dt} = c\beta S(t)\frac{I(t)}{N}, \tag{2}$$

where *S(t)* and *I(t)* denote, respectively, the number of susceptible and HIV-infected individuals at time *t*. The negative sign represents flows out of the susceptible into the infected compartments which is determined by the effective contact rate [42], *c*, the transmission probability, β, and the prevalence of HIV infection at time *t*, $\frac{I(t)}{N}$. This is

the simplest form of the HIV dynamic system in which all individuals are considered to be identical (except HIV status), mix randomly, and population demographics (birth, death, and migration) are ignored. Far more sophisticated models have been developed by taking into account a number of heterogeneities resulting in models that are able to provide broader outcomes in a more precise way. These benefits are highlighted in the published review presented in this chapter [43].

Taking into consideration the primary research questions, dynamic compartmental model has a strong potential to fulfil the needs of this study. The flexibility of the model allows various research questions to be investigated in detail. A complex interaction among model parameters can be explicitly studied to facilitate the discovery of the actual problem causes. Therefore, the literature review is focused on dynamic compartmental modelling of HIV transmission and control among MSM.

2.4.1. Modelling approach

In this section, the disadvantages of the conventional approaches are described, followed by a review and discussion of the alternative methods including their strengths and weaknesses. The main purpose is to select the appropriate approach for modelling HIV transmission and control among MSM.

2.4.1.1. Disadvantages of the conventional approach

The conventional compartmental approach (also called a ‘mean-field’ model), in general, has two main drawbacks that make it far from being realistic. First, there is almost no limit to which a disease can spread into the population because an infected individual in the system will always influence, to some extent, an infection in the entire susceptible population. In the real-world situation, STIs are clearly limited by how individuals form their sexual partnership with the others and it is not possible that one infected individual can form partnerships with and pose an infection risk to every person in a large community. Even within the non-random mixing compartmental models where individuals from different classes mix according to some specific

characteristics (e.g. sexual activity, age), this unrealistic phenomenon still exists although it does not equally affect all individuals due to the mixing pattern. Another drawback is that, in the conventional approach, sexual partnerships are formed and separated instantaneously which, again, does not represent the actual partnership formation and break-up. The following two dynamic modelling approaches—the partnership-based model and the pairwise approximation model—are therefore proposed to address these limitations.

2.4.1.2. Overview of the partnership-based approach

In the partnership-based model, the common assumption of instantaneous interactions between members of a population is replaced by the sexual partnerships that last for some specific length of time depending on partnership formation and dissolution parameters. Time spent between partnerships is also explicitly taken into account. Sexually transmitted infections can be transmitted only between individuals within a partnership. For HIV transmission, the partnership-based approach was first introduced in 1988 by Dietz [44] with its primary aim of capturing changes over time in the number of single individuals (those without a partner) and the number of paired individuals (those with a partner). Following the notations used by Eames [45], the simplest form of the HIV transmission among MSM according to the partnership-based model can be described by the following differential equation system:

$$\frac{dS}{dt} = -\alpha S + \rho(P_{SI} + P_{SS}) \tag{3}$$

$$\frac{dI}{dt} = -\alpha I + \rho(P_{SI} + P_{II}) \tag{4}$$

$$\frac{dP_{SS}}{dt} = -\rho P_{SS} + \alpha \frac{S^2}{S+I} \tag{5}$$

$$\frac{dP_{SI}}{dt} = -\tau P_{SI} - \rho P_{SI} + \alpha \frac{SI}{S+I} \tag{6}$$

$$\frac{dP_{II}}{dt} = 2\tau P_{SI} - \rho P_{II} + \alpha \frac{I^2}{S+I}, \tag{7}$$

where α is the partnership formation rate, ρ the partnership separation rate, and τ the transmission rate within partnership. The numbers of single susceptibles and infecteds are denoted by S and I while P_{SS}, $P_{SI,}$ and P_{II} are the numbers of paired individuals of different types. A formation of a partnership between two susceptibles or two infected respectively increases the number of P_{SS} and P_{II} by two. P_{SI} and P_{IS} have the same values and thus the (fixed) population size, $N = S + I + P_{SS} + 2P_{SI} + P_{II}$. The schematic diagram in Figure 2-1 illustrates changes over time in the partnership status.

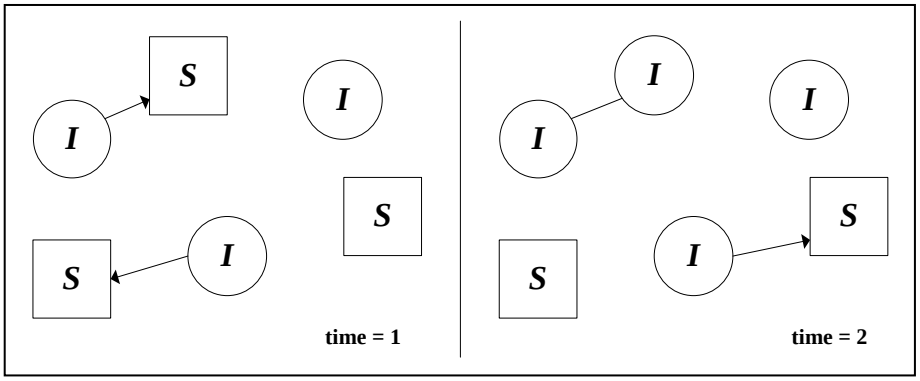

Figure 2-1: Example of transitions of partnership formation and separation

2.4.1.3. Disadvantages of the partnership-based approach

Although partnership duration is explicitly taken into account in the partnership-based model, all partnerships are assumed to be serially monogamous and overlapping partnerships are generally ignored. One way to address this limitation is to model concurrent partnerships as several rapidly changing monogamous interactions, each of which lasts for only a short period. Another way is to use a combination of the partnership-based and the mean-field models. The former is aimed to model HIV transmission within steady partnerships whereas the latter accounts for infection from concurrent partners.

Before the partnership-based model can be used as a predictive tool for the HIV epidemic in UK MSM, a number of important heterogeneities must first be incorporated. Two HIV MSM modelling studies included simultaneously the effects of

variable infectiousness due to disease stages, partnership concurrency, partner types, risky behaviour changes, HIV testing, and ART use at different disease stages [46,47]. Sexual activity levels and sexual roles were included in another study [48]. A partnership-based model with age structure has not been implemented.

2.4.1.4. Overview of the pairwise approximation model

The pairwise approximation model is the network-based transmission model that approximates the full set of partnerships between individuals in the sexual contact network by examining only the connections among nearby individuals [49]. The model allows the spread of infection in the network to be predicted and the control measures that strongly depend on the formation of partnership, such as contact tracing, to be properly investigated. In comparison with the results from the full network simulations, the pairwise approximation provides highly accurate estimates under the situation in which there is a small amount of clustering (partnerships are formed mainly with nearby individuals). Therefore, the method is expected to perform well for epidemics in large populations where majority of sexual contacts are formed randomly. Within highly clustered networks, this approach slightly overestimates the level of infection [50].

The formulations of the pairwise approximation model is described by following the notations used in a previous study by Eames and Keeling [50] with some modifications. Considering the basic HIV transmission model the susceptible individual becomes HIV infected through an infectious partner and progresses through the disease until being removed from the system. Using the notations given in Table 2-1, the dynamics of the number of susceptibles and infecteds can be explained by

$$\frac{d}{dt}[S^n] = -\tau \sum_m [S^n I^m] \tag{8}$$

$$\frac{d}{dt}[I^n] = \tau \sum_m [S^n I^m] - \mu [I^n] \tag{9}$$

$$\frac{d}{dt}[S^n I^m] = \tau \sum_p ([S^n S^m I^p] - [I^p S^n I^m]) - \tau [S^n I^m] - \mu [S^n I^m] \tag{10}$$

$$\frac{d}{dt}[S^n S^m] = -\tau \sum_p ([S^n S^m I^p] + [I^p S^n S^m]) . \tag{11}$$

Table 2-1: Notations used for model formulation

Term	Meaning
$[S^n]$	Number of susceptible individuals with *n* partners
$[I^n]$	Number of infected individuals with *n* partners
$[S^n I^m]$	Number of partnerships between an S^n and I^m
$[S^n S^m I^p]$	Number of triples with S^m having both S^n and I^p as partners
τ	Infection rate between a pair of partners
μ	Disease-induced mortality rate
$\sum_m [S^n I^m]$	Total number of infected partners of all S^n
$\sum_n [I^m S^n]$	Total number of susceptible partners of all I^m
$\sum_n \sum_m [S^n I^m]$	Total number of partnerships between susceptible and infected individuals
$[nm]$	Number of partnerships between individuals with *n* and *m* partners regardless of their infection status
$[n]$	Number of individuals with *n* partners

Changes in the number of $[S^n I^m]$ over time occur as a result of four events corresponding to four terms in Equation (10). First, the transformation from $[S^n S^m I^p]$ into $[S^n I^m I^p]$ occurs at rate τ as an S^m gets infected from an I^p (Figure 2-2) and increases the number of $[S^n I^m]$. The same pattern is also applied to the second term which represents the transformation from $[I^p S^n I^m]$ into $[I^p I^n I^m]$ which decreases the number of $[S^n I^m]$. Next, the infection within a pair converts $[S^n I^m]$ into $[I^n I^m]$, and hence reduces the number of $[S^n I^m]$. Finally, the pair of $[S^n I^m]$ is terminated because an infected individual is removed at rate μ by disease-induced mortality. The first terms in Equation (10) and (11) are identical corresponding to a transition between the two equations. The last term of Equation (11) which represents the transformation from $[I^p S^n S^m]$ into $[I^p I^n S^m]$ at rate τ will be accounted for when evaluating $\frac{d}{dt}[S^m I^n]$.

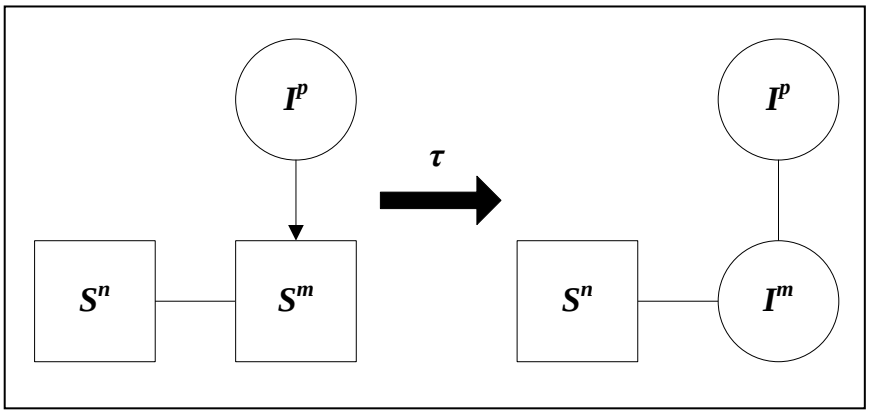

Figure 2-2: Transformation of pair as a result of infection

Since the number of new infections is proportional to the total number of $\sum_m [S^n I^m]$ as perceived from Equation (9), the number of pairs and triples in the system can be approximated by using the moment closure approximation method as follows.

$$[S^n I^m] \approx \frac{\sum_m [S^n I^m] \times \sum_n [I^m S^n]}{\sum_n \sum_m [S^n I^m]} \times \frac{[nm] \sum_p p[I^p]}{n[n]m[m]} \tag{12}$$

$$[S^n S^m I^p] \approx \frac{(m-1) \times [S^n S^m] \times [S^m I^p]}{m \times [S^m]}. \tag{13}$$

The size of the equation set depends on the maximum number of partnerships and is much smaller than the equivalent full pairwise network model, making the pairwise approximation model much more manageable. Approximating the number of pairs using Equation (12) and triples using Equation (13) requires only the mixing matrices identical to those used in the conventional approach, making a better use of regularly available data [49].

2.4.1.5. Disadvantages of the pairwise approximation approach

The main limitation of the pairwise approximation model used to date is that the network structure remains constant over time as well as the sexual activity level [49]. For STIs with a very long incubation period such as HIV/AIDS, this issue is of

particular importance. To cope with the problem, using a similar solution to the partnership-based model with additional mean-field compartments may be possible in which the static networks and partnerships with high turnover are modelled by the pairwise approximation model and the mean-field model, respectively. Another possible solution is to use the pairwise approximation model only for the recent past while the earlier periods are modelled by a mean-field approach. Adjustments will be required to properly merge together two sets of forecasts from the two different approaches. This issue is, however, still a challenge and will be investigated in this study as illustrated in the next sections. Another challenge is the possibility of including into the model a number of heterogeneities which have been confirmed to have marked effects on the epidemic projections. The inclusion must be made and tested before the model can be used to make quantitative predictions.

2.4.2. Method selection

The partnership-based model has been selected for further development in this PhD because it provides a more realistic approach to modelling HIV transmission. The partnership duration and time spent between partnerships can be explicitly taken into account which will result in more accurate epidemic estimates and evaluation of interventions. Change over time in partnership formation and break-up can be taken into account in the partnership-based model while in the pairwise approximation model, partnership between individuals is always fixed. Moreover, because of its relatively simple structure in comparison with the pairwise approximation model, the partnership-based model has more potential to be successfully integrated with a large number of heterogeneities among UK MSM populations.

2.5. Publication

A review on modelling HIV transmission and control among MSM populations entitled 'Mathematical models for the study of HIV spread and control amongst men who have sex with men' has been published in the *European Journal of Epidemiology* in September 2011 [43]. The main aims of this review were to gain an understanding of how models have been developed and used to explain the dynamics of the HIV MSM epidemic with and without control measures. The MEDLINE and EMBASE databases were searched up to the end of 2010 and a total of 127 studies were included in the review. The findings are used as inputs for designing the model and helped inform subsequent analyses in the next chapters. The published version of the review is presented below, followed by a summary of key findings and its implications on this research. The references located at the end of the published review are independent of other citations found in this chapter.

2.5.1. *Article submitted*

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Narat Punyacharoensin, 211356
Principal Supervisor	Richard White
Thesis Title	Modelling HIV transmission and control among men who have sex with men in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	European Journal of Epidemiology		
When was the work published?	September 2011		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No (Permission letter attached)	Was the work subject to academic peer review?	Yes

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed this review with inputs from all co-authors. I conducted all of the literature searches and collected the data from the included publications. I carried out all the analysis, wrote the paper, and did the revision based on comments from all co-authors.

Student Signature: Narat Punyacharoensin **Date:** April 15, 2015

Supervisor Signature: **Date:** April 15, 2015

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Your project

Requestor: Narat Punyacharoensin
Narat.Punyacharoensin@lshtm.ac.uk
University: London School of Hygiene & Tropical Medicine
University of London
Purpose: Dissertation/Thesis

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REVIEW

Mathematical models for the study of HIV spread and control amongst men who have sex with men

Narat Punyacharoensin · William John Edmunds · Daniela De Angelis · Richard Guy White

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Abstract For a quarter of century, mathematical models have been used to study the spread and control of HIV amongst men who have sex with men (MSM). We searched MEDLINE and EMBASE databases up to the end of 2010 and reviewed this literature to summarise the methodologies used, key model developments, and the recommended strategies for HIV control amongst MSM. Of 742 studies identified, 127 studies met the inclusion criteria. Most studies employed deterministic modelling methods (80%). Over time we saw an increase in model complexity regarding antiretroviral therapy (ART), and a corresponding decrease in complexity regarding sexual behaviours. Formal estimation of model parameters was carried out in only a small proportion of the studies (22%) while model validation was considered by an even smaller proportion (17%), somewhat reducing confidence in the findings from the studies. Nonetheless, a number of common conclusions emerged, including (1) identification of the importance of assumptions regarding changes in infectivity and sexual contact rates on the impact of ART on HIV incidence, that subsequently led to empirical studies to gather these data, and (2) recommendation that multiple strategies would be required for effective HIV control amongst MSM. The role of mathematical models in studying epidemics is clear, and the lack of formal inference and validation highlights the need for further developments in this area. Improved methodologies for parameter estimation and systematic sensitivity analysis will help generate predictions that more fully express uncertainty, allowing better informed decision making in public health.

Keywords Compartmental model · HIV/AIDS · Epidemic · MSM · Homosexual

N. Punyacharoensin (✉) · W. J. Edmunds · R. G. White
Centre for the Mathematical Modelling of Infectious Diseases and Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
e-mail: narat.punyacharoensin@lshtm.ac.uk

W. J. Edmunds
e-mail: john.edmunds@lshtm.ac.uk

R. G. White
e-mail: richard.white@lshtm.ac.uk

D. De Angelis
Heath Protection Agency, London, UK
e-mail: daniela.deangelis@mrc-bsu.cam.ac.uk

D. De Angelis
MRC Biostatistics Unit, Cambridge, UK

Introduction

Acquired immune deficiency syndrome (AIDS) was first recognized in homosexual men in 1981 [1]. As of 2008, worldwide, over 1.5 million individuals who were living with HIV had been infected through sex between men [2, 3]. The prevalence of HIV amongst men who have sex with men (MSM) markedly exceeds that of the general population in many developed countries [4]. For example, in the United Kingdom, there were an estimated 35,050 MSM living with HIV in 2009, corresponding to approximately 7% of the MSM population, in contrast to 0.19% prevalence in the total UK male population [5].

Mathematical models are used to gain an insight into the key epidemiological drivers, and simulate epidemic trajectories under a range of circumstances [6–8]. The ability to make projections and evaluate different interventions means that mathematical models are particularly useful for evaluating public health policies. As such, mathematical

models have been widely used in understanding and projecting the HIV epidemic amongst MSM; the first models of HIV transmission amongst MSM being published in 1986. How has the field evolved since these early papers, and what lessons have been learnt, both from the public health perspective, and for mathematical models?

This study reviews the 25-year literature on HIV MSM models focusing on the key findings for a public health readership. We highlight developmental milestones and synthesise what methods and model structures have been employed. We also review models parameterisation and the effects of parameter uncertainty on HIV epidemic forecasts. Finally, we summarise what interventions have been explored by these modelling studies, a key contribution to HIV control policy formation.

Methods

Search strategy and selection criteria

We searched MEDLINE and EMBASE databases for relevant studies published in English from earliest date to end 2010 using the following search terms: ("HIV" OR "HTLV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency*" OR "acquired immune deficiency") AND ("homosexual*" OR "transgender*" OR "gay*" OR "MSM" OR "men who ha* sex with men") AND ("mathematic*" OR "compartment*" OR "stochastic" OR "deterministic" OR "transmission" OR "epidemi*") AND ("model*" OR "framework*"). The references from relevant articles were also used to identify further publications. Titles and abstracts were reviewed for content on the epidemiology of HIV/AIDS in MSM, if found full articles were obtained. Publications that proposed or adopted dynamic compartmental models for HIV transmission amongst MSM and provided information on modelling approaches used were included.

Search results

Of the 742 studies identified from MEDLINE and EMBASE and a further 23 through bibliographies, 127 studies were included in this review (Fig. 1).

Milestones in model development

A quarter of a century has passed since the first mathematical model of the HIV epidemic amongst MSM was introduced [9] in 1986 (Fig. 2). Later that year, two other studies were published. One was the comprehensive preliminary work on the HIV transmission model [10] whereas in another study [11], existing transmission models for gonorrhoea and the human papilloma virus were adapted to explore the possible effects of a hypothetical HIV

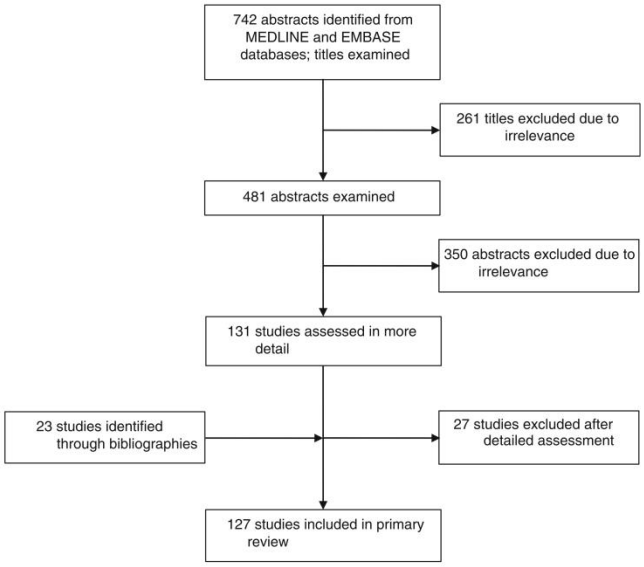

Fig. 1 Selection of studies and search results

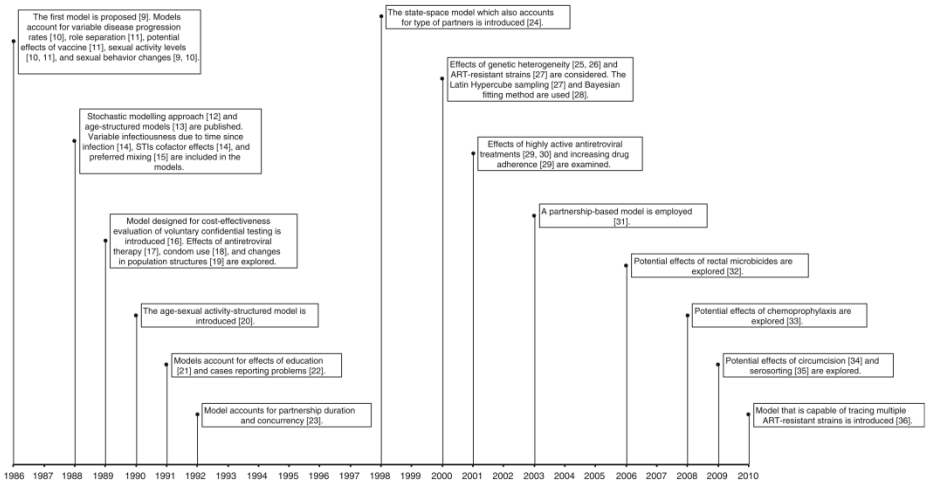

Fig. 2 Development timeline illustrating, by year of study publication, the important methodological improvements of mathematical models for HIV spread and control amongst MSM

vaccination. Since then various population and infection heterogeneities, such as variable progression rate through various disease stages [10] and variable infectiousness [12] due to time since infection, have been incorporated into models, and methodological improvement through the use of more sophisticated modelling formulations, such as the state-space [13] and partnership-based [14] formulations have been proposed.

Some refinements have emerged as additional information on the biological characteristics and control of HIV became available. For example, models incorporating the effects of highly active antiretroviral therapy [15, 16] have replaced monotherapy since the early 2000s, and around the same time, the genetic heterogeneity of HIV [17, 18], and drug resistance [19] was first modelled. Recently, a model that is capable of capturing the evolution of three drug-resistant strains under three types of resistance classes has been developed [20]. Other current developments include investigating the potential effects of new HIV prevention measures such as microbicides [21], chemoprophylaxis [22], circumcision [23], and serosorting [24].

Primary aims of model application

HIV transmission models were most commonly used to make projections for the HIV MSM epidemic (31%); to investigate the effect of incorporating various behavioural or biological characteristics on the projections (72%); and to evaluate the potential impact of interventions (44%).

Epidemic projections

San Francisco has been the most frequently studied population because of the availability of reliable data since the early days of the epidemic [25, 26]. The AIDS incidence amongst MSM in San Francisco has been estimated by several studies [9, 13, 25, 27–31] to reach the peak during the early to mid 1990s following trends similar to the observed data (Fig. 3a). The congruence is not surprising since most of these studies fitted their models to the reported AIDS incidence data. On the other hand, HIV prevalence has been estimated to have declined since its peak in the early 1980s [13, 27, 28, 30] (Fig. 3b). A second upward trend in the mid 1990s was also predicted [30, 31], though the match between the models and subsequently observed data for both the absolute level of prevalence and trend was generally poor.

In Australia, the plateau of the number of newly infected MSM for the period after the peak in 1980s was predicted [6, 32–34] in line with the data on newly acquired HIV infection that reported no sign of the second HIV incidence peak during 1991–2009 [35]. In the Netherlands, a recent study predicted an increase in HIV incidence and number of new HIV diagnoses amongst MSM after 1999 [36]. In the UK, four deterministic modelling studies provided

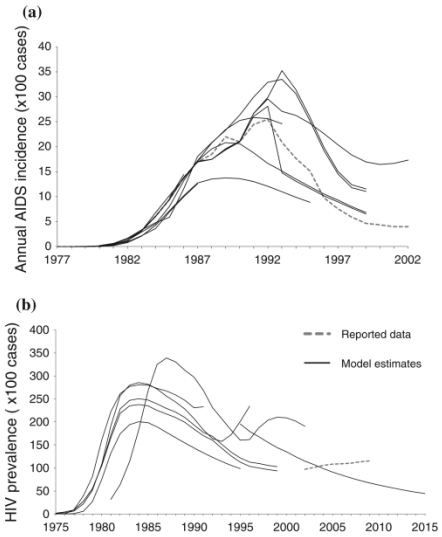

Fig. 3 Projections of HIV epidemics in men who have sex with men. **a** Annual AIDS incidence in San Francisco, 1977–2002. One study reported low and high estimates; averages were hence plotted [9]. **b** HIV prevalence in San Francisco, 1975–2015. The estimated curve from 1995 to 2015 was converted from percentages of HIV seroprevalence by assuming a constant reduction rate of total MSM population size from 55,800 in 1995 to 35,300 in 2015 [80]. Data on annual AIDS incidence and HIV prevalence were reported by the San Francisco Department of Public Health. Data were extracted from graphs using Engauge Digitizer version 4.1 if numbers were not reported in the articles

forecasts of the HIV MSM epidemic [37–40] and all dated back to before 1991.

We found a small number of modelling studies that look into the epidemics in developing countries. In Latin America, predictions were made with models that explicitly link the HIV transmission amongst homosexuals, bisexuals, and heterosexual males and females (Argentina [7], Cuba [41], and Mexico [42]); while the trajectory of HIV MSM epidemics in Asian (China [43]) and African countries [44] were investigated only recently.

Investigation into effects of HIV-transmission-related characteristics

Mathematical models allow epidemiologists to gain a better understanding of how various biological and behavioural characteristics might affect the dynamics of the epidemic. Examples include investigation into the impact of variable infectiousness [45, 46] and the role of primary HIV infection [47–49]. Such investigation may result in some crucial parameter estimates such as fluctuating infectivity over various disease stages [29, 50]. The influences of differing key behavioural parameters such as sexual contact patterns between sexual activity groups [39, 49, 51–57], age [34, 58, 59], and MSM sexual role separation [60–62], have been widely studied. Anal sex was the main and often the only route of HIV transmission in the models. There were only three studies that included transmission through intravenous drug use in MSM [63–65] and none accounted for the effects of substance abuse in increasing risky sexual behaviour. Other characteristics were explored including temporal effects of changes in unprotected sexual practices [66], the effects of other sexually transmitted infections on HIV prevalence [67, 68], and the relationship between perceptions on the future HIV epidemics and current sexual behaviour [69].

Intervention evaluation

A common use of mathematical models in public health is to evaluate the impact of proposed interventions, particularly in the long-term epidemics which are difficult to be quantified through epidemiological surveys. The benefits of antiretroviral therapy (ART) [15, 16, 19, 70–74] have been extensively evaluated under various settings. The combined effects on epidemic projections of ART and education [75], or host genetic differences [18], or both [76] have also been explored. The impact of an increase in unprotected sex as a consequence of ART has been repeatedly highlighted since early in the epidemic [32, 77–79]. New technologies for HIV prevention and control have been hypothetically evaluated before they even become available [21, 22, 65, 80–83]. Less commonly, mathematical models have been used in economic evaluations. Interventions such as ART [64, 84, 85], counselling to improve drug adherence [86], chemoprophylaxis [22], and expanding HIV screening [64, 87, 88] have been found to be cost-effective preventive measures under a series of implementation scenarios.

Key modelling methods

Figure 4a illustrates the proportion of studies using the following methods in five different periods over 1986–2010.

Deterministic versus stochastic models

Stochastic models take account of the role of chance in some or the entire simulated modelling processes, whereas deterministic models are concerned with the average values

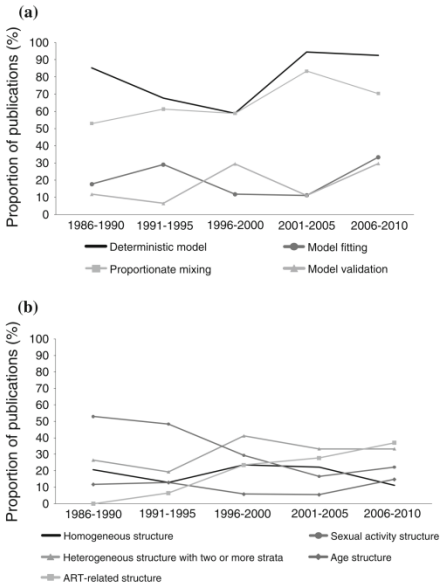

Fig. 4 Proportions of key modelling characteristics by the number of publications in period. **a** *Modelling method* Deterministic model: deterministic or stochastic model; Proportionate mixing: proportionate or non-proportionate mixing. Model was classified as 'proportionate mixing' if mixing by all attributes (e.g. sexual activity, age, or sexual role) available in the model were proportional; Model fitting: whether model was fitted to data or not; Model validation: whether model was validated or not. **b** *Model structure* Homogeneous structure: homogenous or heterogeneous structure. Heterogeneous structure with two or more strata: whether model was stratified by infection status and at least two other characteristics or not. Sexual activity structure: whether model was stratified by sexual activity or not. Age structure: whether model was stratified by age or not. ART-related structure: whether model was stratified by ART-related characteristics or not

only. This results in more complicated analytical expressions for stochastic approach which may help explain why 80% overall and more than 90% of recent studies employed deterministic methods (Fig. 4a). Moreover, as the epidemic has become more established, the effects of chance may be less influential and thus excluded from models. Overall around one fifth of studies adopted a stochastic framework and these tended to be theoretical studies published prior to 2000 (Fig. 4a).

Because a continuous time formulation of a model is complicated to handle [89], most stochastic models have been formulated within a discrete time framework. The degree of stochasticity may differ across the stochastic studies. For example, disease duration was the only factor that was modelled stochastically in two studies [90, 91], and deterministic processes were assumed for disease duration and probability of infection in another stochastic study [28].

The studies comparing methods reported that deterministic models tended to slightly overestimate the average number of infecteds in the early epidemic phase, but differences were minimal thereafter [92, 93]; although, some studies reported similar predictions [13, 30, 94]. More generally, these differences are less apparent for the epidemics that have a rapid growth [92], a large proportion of infected individuals [50, 95], or a large susceptible population [63, 96, 97], suggesting that the deterministic approach may be appropriate for the settings in which HIV is highly prevalent amongst MSM such as now occurs in many developed countries.

Mixing

The determination of how MSM select their sexual partners, within and between groups, can range from like-with-like (assortative) mixing at one extreme to like-with-unlike (disassortative) mixing at the other. In between, MSM can be assumed to mix proportionately according to the contribution of each subgroup to the total number of sexual contacts. In some cases a proportion of contacts is reserved for like-with-like mixing [47, 55, 98]. Proportionate mixing (also known as a random mixing) was used in 64% of all studies and has increased from around 60% to above 70% during the last decade (Fig. 4a), mainly to simplify the model and allow other heterogeneities to be incorporated without too much complexity.

Findings from three studies suggested that MSM in San Francisco had highly assortative mixing patterns [30, 31, 99], which contradicted the conclusion made by an earlier study that this population tended to mix proportionally with respect to activity levels [27]. In Australia, a recent study estimated that MSM tended to mix assortatively by age and as much as 30% of new partners were from the same age group [100].

Parameter estimation through model fitting

Fitting models to data is clearly uncommon (Fig. 4a). On average, 22% of all studies carried out some model fitting, adopting Chi-square [6, 27, 91, 101], sum of squares [9, 25, 29], and maximum likelihood [36, 71, 90, 102] as model fit criteria. The parameters estimated were often (57% overall) related to two primary quantities: HIV transmission probability [9, 13, 20, 23, 29, 38, 50, 103, 104] and the sexual contact rate [9, 20, 25, 27, 66, 71, 90, 101, 103–105]. In some studies multiple parameters were estimated

simultaneously using a larger number of data points [27, 29, 101]. In most cases, models were fitted using surveillance or cohort data but other sources, such as simulated data [99, 102], HIV incidence estimated using backcalculation methods [103], and mixing patterns derived beforehand from prospective cohort data [13], were also used to estimate parameters.

Using a model fitting procedure, in San Francisco and Australia, it was found that the slower growth of AIDS incidence during the early 1990s could not be explained entirely by the introduction of ART but also required a significant reduction in sexual contact rates [6, 27]. This was supported by the finding that a time-varying contact rate improved the model fit [25]. Statistical fitting also showed that the increased number of newly diagnosed MSM in the Netherlands during 1999–2004 was not only due to an increase in new HIV infections, but was also in part due to improved diagnosis rate [71].

Validity of model estimates

A comparison between the predicted and observed epidemic indicators can be used to evaluate the model validity. Figure 4a suggests model validation may have become more common over time, from around 10% prior to 1996, to almost 30% of studies after 2005. However, overall only 17% of all studies reported some model validation (Fig. 4a). Furthermore, validation criteria were often subjective and poorly described while explicit numerical criteria were employed in only four studies [33, 50, 81, 103]. Together, this infrequent model validation raises doubts regarding our confidence in the results of these modelling studies.

If models are to be fitted and also validated, at least two, ideally independent, data sets are required. Data are typically limited, and therefore non-ideal solutions have often been implemented. For instance, reported AIDS incidence data for three major US cities were separated into two parts; the early part was used to fit the model and the other was for model validation [9]. An age-mixing matrix during 1981–1991 was estimated using longitudinal cohort data in New York City whereas the observed numbers of new AIDS cases for the same time period were used to validate the model [66]. As also seen in two recent ART studies [16, 71], multiple datasets can be used for performing a series of validation tests and enhance model validity.

Model structures

Models can be classified into those with a homogeneous structure (populations only stratified by infection status) and those with a heterogeneous structure (populations stratified by infection status and one or more other characteristics of interest). Figure 4b illustrates that the proportion of models with homogeneous structure has remained relatively constant over time (17% overall), whereas more complex models have become more common. The proportion of models structured by infection status and at least two other characteristics has increased from around 20% prior to 1996 to 33% in the recent period. This increase has been at the expense of models that only stratified by infection status and one other characteristic (not shown in Fig. 4b). Such trends may reflect an increase in model complexity made possible by advances in computing technology.

Stratification by sexual activity level

MSM were most commonly stratified according to levels of sexual activity (37% overall). The proportion of models grouping MSM by sexual activity decreased from more than 50% in the earliest period to just above 20% more recently (Fig. 4b). This decline over time was probably the result of increases in the complexity of models with respect to ART-related characteristics. Investigations into the number of sexual activity groups suggested that using only two groups may suffice to capture the effects of sexual-activity heterogeneity [13, 30]. Models without sexual-activity heterogeneity tended to overestimate the proportion of infecteds in the early phase of the HIV epidemic [50].

Stratification by age

Overall, the proportion of the studies stratified MSM by age remained considerably unchanged over time with an average of 11% (Fig. 4b). The importance of age heterogeneity was highlighted by a finding suggesting that ignoring AIDS-induced age-specific mortality, the initial epidemic growth rate and endemic HIV prevalence would be substantially underestimated [58]. Three studies incorporated age as a continuous variable [58, 59, 106] whereas most divided the age into groups [6, 22, 23, 34, 37, 40, 66, 69, 107–109]. This grouping technique was often used to make models simpler to implement; two models, for example, were theoretically described with continuous sexual activity and age but in their practical application of sexual activity [58] and age [108] groups were used instead.

Stratification by therapy-related characteristics

Approximately 17% of studies stratified MSM by ART characteristics (Fig. 4b). This has been increasingly common since ART was introduced in the early 1990s and

become the most common stratification in the recent models (37%). The main groupings were whether or not infecteds received HIV therapy [18, 19, 27, 70, 73–75, 83, 110, 111] and, in some cases, combined with grouping by drug-resistant strains [15, 19, 20, 70, 86, 104, 110], or drug adherence [15, 22, 86], and were normally related to CD4 cell count. As receiving ART requires HIV testing, stratifying infected MSM by undiagnosed, diagnosed without ART, and diagnosed with ART, has increasingly become more common in recent studies [32, 33, 36, 72, 112].

Effects of parameter uncertainty on HIV epidemic forecasts

Because of uncertainty in model parameters values, it is crucial to investigate the effects of these uncertainties on model forecasts (Table 1). The five key elements—disease duration, infectivity, sexual behaviour, mixing patterns, and HIV testing and ART—were commonly investigated using the one-way sensitivity analysis. More complex approaches, such as Latin hypercube sampling of input parameters [14, 15, 19, 20, 22, 33, 34, 48, 68, 70, 72, 104, 105, 110], which was first introduced to HIV MSM models in 2000 [19], and a probabilistic sensitivity analysis [86], were less common.

If disease progresses at a slower rate without changes in infectiousness, increasing the duration of the lower infectiousness incubation period would reduce the number of new AIDS cases per unit time [84, 113]. The exact choice of incubation period distribution was found to affect the peak of both HIV [40] and AIDS incidence [40, 114] but the endemic prevalence was less affected. Conversely, one study showed that the long-term HIV incidence can be markedly decreased by only a slight increase in the mortality rate amongst HIV-infected MSM due to a smaller number of people that can pass infection to others [34].

Many studies illustrated a substantial impact of infectivity reductions on the epidemic spread and magnitude [33, 39, 42, 64, 70, 77, 79, 92], particularly for the early epidemic if the reductions occurred during the primary infection stage [29, 39, 45, 48, 52, 53, 100], and for the endemic prevalence if the reductions occurred in the HIV symptomatic stage [39, 49, 50, 100]. As a result of a smaller size of high-activity groups in the endemic state due to higher HIV mortality in this population, primary infection may have a less important role in spreading the disease than it did in the early epidemic [48]. The effects of transmission in a long period after the primary infection would be more pronounced in the case of a longer duration with steady partners or a decrease in the number of MSM with casual relationships [48]. However, two studies had differing views as to whether primary infection [49] or late infection [50] has stronger effects on endemic prevalence.

Findings from studies suggested that the greater the variation in sexual activity amongst MSM, the faster infection would spread in the early epidemic [12, 39, 58] because high-activity groups became infected more quickly and, once infected, spread the infection more rapidly. However, if the size of this group reduced rapidly due to AIDS, the endemic prevalence would be lower [10, 12, 102]. The profound effects of sexual contact rate reductions were confirmed [47, 51, 58, 63, 64, 79, 88, 96, 97, 115, 116], and even stronger impacts were reported if the reductions occurred in both infected and at-risk individuals, or earlier in the epidemic [37, 39, 42]. In terms of unsafe sex, both direct [24, 27, 32, 36, 70, 116] and indirect effects (increasing prevalence other sexually transmitted infections [33, 67, 68, 111]) on causing more HIV infections have been suggested.

Disassortative mixing by sexual activity have been commonly found to enlarge the HIV epidemic if HIV can invade a population [27, 51, 53–56, 98, 102] as it results in a larger number of low-activity individuals being exposed to infected high-activity individuals. If the average contact rate remained unchanged, infection spreads more slowly in high-activity groups under disassortative mixing [54, 98]. More assortative mixing by sexual activity can result in two HIV incidence peaks [51, 54, 55, 98]. The first peak is driven by a rapid spread in high-activity groups followed by a later epidemic in low-activity groups. The highest total number of infections is obtained if MSM mix proportionately by sexual activity [52, 55, 117] or when dual-role MSM mix primarily but not completely with themselves [61]. Within-age-group mixing may cause a lower endemic HIV prevalence in those under 25 years old because infections are prevented from spreading from the older to younger generations [66]. For partner types, one study suggested that a complete separation between MSM with and without casual partners would markedly delay the epidemic in the latter population [54].

The positive impact of HIV testing on preventing infection have been clearly illustrated in many studies [24, 33, 41, 48, 72, 79, 112], the total number of infections averted due to HIV testing has been estimated to be dramatically larger than the total number of those have been infected since the epidemic has settled amongst Australian MSM [72]. The epidemiological benefit would be greater if infected individual is tested earlier after infection [36, 113]. However, increasing frequency of population testing to more than once a year may not provide a marked further reduction in HIV incidence especially if the proportion of MSM who are HIV tested at least annually is already high [72].

Table 1 Summary of the effects of varying model parameters

Factors	Effects	References
Disease progression		
Longer average incubation or HIV asymptomatic periods	Lower AIDS incidence	[84, 113]
	Higher HIV prevalence in endemic state (slightly)	[66, 84]
Longer primary HIV infection stage	More peaked HIV prevalence in early state	[29]
Longer asymptomatic stage	Less peaked in early state and lower AIDS incidence in endemic state	[39]
Higher HIV/AIDS death rate	Lower HIV incidence	[34]
Infectivity		
Lower average transmission probability	Lower HIV incidence and prevalence over epidemic course	[33, 39, 42, 64, 70, 77, 79, 92]
Lower infectiousness in primary HIV infection stage	Slower spread in early state but less affected endemic state	[29, 39, 45, 48, 52, 53, 100]
Lower infectiousness in HIV symptomatic stage	Slower spread in early state	[52, 53]
	Lower HIV prevalence in endemic state	[39, 49, 50, 100]
Lower infectiousness in HIV asymptomatic stage	Lower HIV incidence in endemic state (slightly)	[48]
Sexual behaviour		
Higher heterogeneity in sexual activity	Faster spread in early state	[12, 39, 58]
	Lower HIV prevalence in endemic state	[10, 12, 102]
Lower sexual contact rates	Slower spread and lower HIV prevalence	[47, 51, 58, 63, 64, 79, 88, 96, 97, 115, 116]
	Stronger positive effect if happening in either earlier epidemic or both susceptible and infected populations	[37, 39, 40, 42]
Higher degree of unsafe sexual practices	Higher HIV incidence and prevalence	[24, 27, 32, 36, 70, 116]
	Higher prevalence of other STIs and hence higher HIV incidence	[33, 67, 68, 111]
	Higher proportion of new infections caused by ART-resistant strains	[104]
Higher number of MSM who have casual partners	Faster spread	[54]
Higher partnership concurrency	Faster initial spread followed by a slower phase	[125]
Higher number of dual-role MSM	Higher HIV incidence	[8, 60, 61]
	Higher proportion of new infections from primary HIV infections stage	[62]
Higher number of partners of dual-role MSM	Higher HIV prevalence	[43]
Mixing pattern		
Higher degree of sexual activity disassortative mixing (in comparison with assortative mixing)	Faster spread in early state and higher HIV incidence and prevalence in endemic state	[27, 51, 53–56, 98, 102]
	Slower spread in high-activity group (slightly)	[54, 98]
Extremely high degree of sexual activity assortative mixing	Two HIV incidence peaks	[51, 54, 55, 98]
Sexual activity proportionate mixing	Highest total number of infections over epidemic course (worst-case scenario)	[52, 55, 117]
Higher degree of sexual role assortative mixing	Higher HIV prevalence	[61]
	At some degrees of assortativity, can provide highest total number of infections over epidemic course (worst-case scenario)	[61]
Sexual role proportionate mixing	Lower (when R0 is low) and higher (when R0 is high) total number of infections than when dual-role MSM are completely separated	[61]
Higher degree of age assortative mixing	Lower HIV prevalence in adolescents and young adults in endemic state	[66]

Table 1 continued

Factors	Effects	References
HIV test and therapy		
Higher proportion of tested MSM	Slower spread and lower HIV prevalence	[24, 33, 41, 48, 72, 79, 112]
More frequent HIV testing	Lower HIV incidence	[36, 113]
Higher ART usage rate	Lower HIV incidence*	[19, 32, 36, 70, 73, 74, 79]
	Higher HIV incidence*	[111, 112, 116]
	Increased effects if ART is initiated during primary HIV infection	[33, 48]
	Lower HIV incidence can be counter-balanced by only a small increase in unsafe sexual practices	[14, 19, 79]

* Opposing findings, *MSM* men who have sex with men, *ART* antiretroviral therapy, *STIs* sexually transmitted infections, *R0* basic reproduction number

Whether or not the ART could reduce overall transmission remains a controversial issue. Lower HIV incidence was found to have resulted from a higher ART uptake [19, 32, 36, 70, 73, 74, 79], particularly if started during the primary infection stage [33, 48]. However, an increase in incidence was predicted as a consequence of a longer infectious period, higher bacterial sexually transmitted infections prevalence, and imperfect ART efficacy in decreasing infectiousness [111, 112, 116]. Another issue concerns the interaction between the widespread use of ART and changes in risky behaviour. Three studies reported that the ART efficacy in HIV prevention at the population level could be negated by an increase of 10–100% in unsafe sex depending on assumed infectiousness reduction and partner types [14, 19, 79], and one study reported that implementing ART was better even if it was accompanied by large increases in risk behaviour [43]. In contrast, the effects of improved ART adherence [86], increased prevalence [19, 110] and transmissibility of ART-resistant strains [70], and the potential effects of therapeutic vaccines [69, 81–83] were found to be small.

Intervention strategies supported by modelling studies

Mathematical models have been used to evaluate a wide range of HIV control interventions. The interventions can be grouped into those promoting information, education and communication (IEC), HIV testing, or HIV therapy (Table 2). A combination of strategies has been most commonly suggested to maximize the overall effectiveness of control programmes [19, 22, 36, 64, 72–74, 76, 81, 84, 87, 113, 116]. Each strategy has its own prevention purpose to achieve: IEC seeks to change behaviour; therapy intends to treat infection and reduce infectiousness; and HIV testing, if combined with IEC and therapy may achieve both goals.

For IEC, reducing the level of unsafe sex has been one of the main interventions studied since the early epidemic [19, 32, 33, 36, 64, 66, 71, 79, 113, 118], one study showing that it provided a larger impact on HIV transmission than earlier HIV diagnosis and treatment [36]. HIV-related education appeared to be more generalisable since it is effective in both low- and high-prevalence epidemics [87] and one study suggested that all MSM populations should be involved regardless of their age and infection status [39]. Another suggested HIV testing, on the other hand, should be targeted mainly on the high-activity groups [29, 42, 50, 72, 87] and would be more effective in low-prevalence epidemics [87]. However, a common theme is that, in any settings, both educational [75, 76] and HIV testing strategies [14, 33, 79, 87] should be well maintained and behavioural change be monitored [39, 66, 100] to detect potential threats as early as possible.

The controversial concept of using ART during the primary infection as an epidemic control measure has been explored. Three studies recommended that ART be initiated as early as possible in order to reduce high infectiousness in the early infection stage [33, 49, 109] while two other studies did not find ART effective for epidemic control [48, 72]. The reason for the differing recommendations lies in the assumed reduction in infectiousness that ART can achieve, which depends on drug regimens and other biological and demographical characteristics. A study showed that if treatments prolong the incubation period without successfully suppressing the transmission, using more ART may even increase HIV transmission [18]; therefore, the continuing development of treatments that can more effectively decrease the semen infectivity is still of high importance [18, 36, 64, 76, 116].

Abstaining from or replacing anal sex with oral sex or masturbation was not recommended in any of the modelling studies. This may be because abstinence interventions alone were believed to be ineffective as suggested by a systematic review of trials in heterosexual adolescents [119]. The ongoing HIV transmission amongst MSM in Europe, e.g. the UK [120] and France [121], highlights the need of improved HIV prevention strategies, and encouraging less frequent anal sex in the high risk groups may help support key interventions.

Table 2 Recommended strategies for HIV epidemic control

Programme strategies	Periods	References
IEC strategy		
Education should focus on:		
Both infected and non-infected individuals	1989	[39]
Not only adults but also adolescents	1989	[39]
MSM with steady partners	2003	[14]
MSM who perform dual-role sexual activity	2005	[8]
Initiated as early in the epidemic as possible	1989–1991	[39, 63, 97, 113]
More effective than HIV testing in high prevalence epidemic	1989	[87]
Encourage target groups to:		
Reduce partner change rate	1988–1991	[12, 54, 113]
Increase partnership duration	1988	[54]
Be more selective when choosing a sexual partner	1988	[54]
Practice safe sexual intercourse	1988–2010	[19, 32, 33, 36, 64, 66, 71, 79, 113, 115, 116, 118]
Provide news and recent information on HIV/AIDS	1993	[103]
Take into account different types of partners for strategy design and implementation	2003	[14]
Accompanied by other intervention programmes, e.g. condom use promotion, HIV testing, and treatment programmes	1989–2010	[36, 64, 72, 76, 87, 113, 116]
HIV testing strategy		
Testing should focus on high-activity groups	1989–2009	[29, 42, 50, 72, 87]
More effective in low prevalence epidemic	1989	[87]
Increase testing coverage and frequency in order to detect more infected individuals during primary HIV infection	1988–2010	[24, 36, 52, 72]
Accompanied by other intervention programmes, e.g. condom use promotion, education, and treatment programmes	1989–2010	[36, 64, 72, 76, 87, 113]
Therapy strategy		
Initiated as early as possible, particularly during primary HIV infection (so as to reduce infectivity and gain higher treatment efficacy)	1992–2008	[33, 49, 109]
Use ART during primary HIV infection is unlikely to be an effective control measure	2004–2009	[48, 72]
Delayed as long as possible (so as to reduce the level of drug resistance)	2001	[110]
Keep track of the success and failure rates of ART (so as to reduce the level of drug resistance)	2001	[16]
Increase usage rate and availability of ART	1992–2003	[14, 70, 126]
Also to be aimed at patients with both HIV and HSV-2 infections	2004	[68]
Accompanied by other intervention programmes that aim at reducing unsafe sexual practices	1991–2010	[19, 22, 36, 64, 73, 74, 76, 81, 84, 116]
Revise ART initiation threshold to CD4 cell count below 350 cells/μl	2010	[127]
Pre-exposure prophylaxis has a potential to substantially decrease new HIV infections	2010	[104]
Therapy development:		
Treatment designed specifically for treating infecteds with ART-resistant strains	2001	[110]
Focus on development of treatment that can effectively decrease the infectivity	2000–2010	[18, 36, 64, 76, 116]
Other strategies		
Monitor changes in sexual behaviour	1988–1994	[39, 66, 100]
Reduce the prevalence of other STIs	1988–2008	[12, 33]
Use microbicides for HIV control in bathhouses	2006	[21]
Serosorting accompanied with increased condom use	2009	[24]
Circumcision in MSM is unlikely to be an effective control measure	2009–2010	[23, 128]

Table 2 continued

Programme strategies	Periods	References
Elimination of bathhouses and commercial sex venues alone is unlikely to be an effective control measure	2010	[105]
Reduce HIV transmission from primary HIV infection stage	2010	[62]
High-efficacy preventive vaccines that target high-risk groups	2010	[65]
Use HSV-2 prevalence surveys to help monitor the extent of HIV infection	2010	[44]
Transmission elimination		
Sexual behaviour change		
Substantially reduce the number of dual-role MSM	1989	[61]
Highly effective sex-education programmes	1999–2004	[75, 76]
Substantial migration from high to low sexual activity groups	2001	[25]
Markedly decrease the level of unsafe sexual practices	2007–2008	[71, 118]
Combination of annual HIV screening test, counselling, and education	1991	[113]
Combination of ART intervention and increased condom use	2009	[43]
Moderately decrease the proportion of receptive sexual practices	2010	[128]
Reduction in infectiousness		
Treatments that substantially decrease infectiousness	2002–2004	[70, 76]
Completely eliminate infectiousness at the symptomatic stage	2005	[50]
Vaccination		
Effective preventive vaccines with high coverage	2004–2006	[76, 82]
Insufficient for elimination		
Proportional reduction in average transmission probability	1989	[39]
Extremely widespread use of ART	1994–2004	[32, 74, 75, 77]
and even accompanied with annual testing of all risk groups	2010	[64]
HIV testing programmes even with perfect diagnosis rate	2008	[112]
Promote condom use alone even with perfect compliance if R0 is very high (due to condom failure)	2010	[116]

IEC information, education and communication, *ART* antiretroviral therapy, *STIs* sexually transmitted infections, *R0* basic reproduction number

Reducing the basic reproduction number below one has often been used to determine if an intervention will eliminate HIV. Strategies similar to those shown above have been suggested but assuming a substantially higher efficacy, such as reducing the infectiousness of the late disease stage to zero [50], which seems optimistic. A combination of ART intervention and condom use was found to eliminate HIV under the assumption that ART-treated MSM were completely non-infectious [43]. A study suggested that if HIV elimination is possible, then it should have already been observed in the Australian epidemic where there existed a combination of effective interventions (a high testing rate, readily accessible ART, and effective education programmes) [32]. This was supported by findings that even a perfect HIV testing programme [112] or, due to condom failure in a setting with very high basic reproduction number such as Africa, 100% condom use [116] would still be insufficient to eliminate HIV. Another study indicated that elimination using ART would require a century or more to achieve and would be very sensitive to change in unsafe sex throughout the period [70].

Discussions and conclusions

Twenty five years of published literature on the use of mathematical models to understand the spread and control of HIV amongst MSM, a wide variety of methods have been used. There have been changes in the model structures adopted over time. For instance, stochasticity has almost been completely absent from HIV MSM models during the last decade, possibly as the infection is now much more prevalent. The introduction of ART has caused a marked shift towards a therapy-oriented modelling approach, and the recent decline in stratification by sexual activity is likely have been to allow for an increase in complexity of modelling therapy-related characteristics. Integrating effects of modern HIV therapy and prevention technologies into models with fundamental heterogeneities (e.g. age and sexual activity) remains both methodological and data availability challenges.

Our review has some limitations. The analysis relied heavily on the published model descriptions. Lack of information in any of the areas covered in this review may

affect the accuracy of the findings. For example, models may have been validated but if evidence of this was not presented in the published articles or supplementary documents, the studies were classified as 'not validated'. However, our review topics are quite fundamental for modelling studies and unlikely to be neglected; therefore we are confident that this issue would not have a strong effect on our findings. For the effects of parameter uncertainty and policy recommendations, we aimed to provide a summary of these topics rather than definite setting-specific findings. The results of these sections were thus simplified for the ease of understanding and should only be perceived as a guideline for further investigation.

On the basis of this review, several issues can be improved for the better use of mathematical models in the future research. First, the lack of model validation greatly reduced the confidence in model predictions. Validation should be an imperative in modelling processes to increase the credibility of modelling studies. The validation criteria must be as transparent as possible to reduce the possibility of bias or error in reaching any conclusions.

Next, improved methods for parameter estimation could help in the use of increasingly complex models that we are likely to see in the near future. A method adopted only by the recent drug resistance modelling studies [20, 104] is a good example of systematically estimating a large range of parameters in a complicated model. Another possible development is the implementation of a Bayesian approach that has been used in only one study to date [28]. This could provide potential benefits over the traditional parameter estimation methods; for example, multiple pieces of data can be included simultaneously in the estimation process using a Bayesian evidence synthesis and allows parameter uncertainty to be incorporated in a more robust way [122, 123]. Further investigation is required to properly integrate dynamic mathematical models into a Bayesian framework for exploring HIV epidemics as has been initiated amongst known high-risk groups in India including MSM [124].

Third, the profound effects some key and poorly known parameters have on the epidemic forecasts necessitate the use of uncertainty analysis, ideally multi-way and systematic sensitivity analyses, to ensure uncertainty is communicated when modelling results are reported. We have shown that it is important to differentiate between the effects of uncertainties on short-term and on long-term epidemic forecasts as they can greatly differ.

Fourth, almost all models were based on the 'mean-field' compartmental modelling that assumes instantaneous partnership formation and dissolution. These unrealistic assumptions have been replaced in a partnership-based model, used in three studies [14, 48, 118]. This allows partnership concurrency and interventions aimed at individuals within partnerships to be modelled more realistically.

Finally, the definition of modelled population should be clearer. We found that MSM population were vaguely defined in most models. Less than one fifth of the studies reviewed provided definitions in terms of age range. Modellers should provide clear definitions so that their results are most useful to other researchers and policy makers.

Mathematical models have been extensively used over the last quarter century to explore the spread and control of HIV and have lead to important insights that have been incorporated into prevention policy. Collaboration between social scientists, physicians, epidemiologists, mathematical modellers, statisticians, and public health officials should help to ensure this continues, to the benefit of the homosexual communities worldwide.

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2.5.2. Summary of findings

The first study on modelling HIV spread among MSM was published in 1986 [36] and no major improvements in modelling methodology can be identified after 2003. There are only three studies that explicitly take into account the partnership duration and concurrency through the use of the partnership-based approach [46-48], whereas only four studies attempted to predict the HIV epidemic in MSM in the UK [40,51-53] and all dated back before 1991. Updating the study by searching the same literature databases found only two HIV MSM modelling studies in the UK between the beginning of 2011 and the end of 2013 [54,55]. This provides an opportunity for this research to update the predictions and provide more recent insights into HIV spread among UK MSM. Moreover, there were only a small number of studies that validated the models and the validation criteria were rather subjective. This lack of properly fitted and validated modelling studies highlights the need for more rigorous procedures for fitting and validating the model in this research.

Several studies compared stochastic and deterministic methods and reported that the results were similar for epidemics that have rapid growth, a large proportion of infected individuals, or a large number of susceptible individuals. This suggested that using a deterministic approach may be appropriate for situations in which HIV is highly prevalent among MSM. HIV epidemics in the US, the UK, and Australia may provide a good example of such settings. Therefore, the deterministic modelling approach has been selected for model development in the next chapter.

Modelled MSM populations were commonly categorised by sexual activity levels (such as partnership formation rate, contact rate), age, and therapy-related indices (such as treatment status, drug adherence). Multiple disease stages were mainly used to facilitate an incorporation of variable infectiousness and disease progression rate as well as to allow medications to be effective at any specific disease stages. The mixing matrix was the most common approach for incorporating non-random sexual mixing

behaviour between different groups of MSM. All these population stratifications were incorporated into the model along with other classifications presented in Chapter 3.

Several studies confirmed that the following factors have a substantial impact on HIV epidemic estimates: variable disease progression rate, variable infectiousness due to disease stage, sexual contact rate, unsafe sexual practices, sexual mixing pattern, partnership concurrency, and increased ART usage rate, all of which have been taken into account in this research. There were still contradictions between studies for whether primary HIV infection or late infection is the predominant factor to influence HIV infection in a society, as well as the magnitude of the increase in unsafe sex that would offset the benefit of using ART to prevent new infections. Chapter 5 and 6 addresses these issues in details.

Finally, a combination of various HIV control strategies, i.e. sexual behavioural change campaign and monitoring system, HIV testing, and ART, was strongly recommended in several settings. However, disease eradication is unlikely even in the long-run and with effective combination interventions. This research explores the impact of HIV prevention interventions in UK MSM in Chapter 6.

2.6. Conclusion

The literature reviews in this chapter provide information necessary for designing a model as well as essential heterogeneities that should be incorporated. In the next chapter, I utilise this information to develop the mathematical model for HIV transmission and control among UK MSM.

Chapter 3

Model development

In this chapter:

The structure of the new model

MSM population stratification

Model equations and calculations

3.1. Introduction

This chapter presents the details underlying the structure of the HIV transmission model and all required calculations. This chapter has been submitted to *AIDS* as supplementary materials for the publication presented in Chapter 5. The contents presented in this chapter are kept in almost the same format and wording as in the submitted draft. Only slight modifications were carried out to comply with the thesis regulations.

3.2. Overview of the HIV transmission model

A mathematical model of the HIV transmission dynamics among men who have sex with men (MSM) aged 15-64 in the United Kingdom was developed based on a system of differential equations. A number of behavioural and biological heterogeneities were included in the model to simulate the epidemic over the 20-year time course from 2001 to 2020. The simulations were started from the beginning of 2000 to allow the model to become more stable before conducting further analyses from 2001 onwards. In Chapter 4, the model is parameterised based on available information from multiple sources including behavioural surveys, surveillance systems, and the literature. It is also fitted to the data and external estimates in Chapter 5 using the Monte-Carlo filtering method [56]. The model is used to estimate the current epidemic situation in various aspects and project how it would evolve in the near future (Chapter 5 and 6).

3.3. Key assumptions

A number of assumptions were made throughout the model. The main assumptions that this model was based on are as follows:

- The model is a deterministic population-based model therefore the members of any subgroups all share the same characteristics.

- MSM get infected with HIV only through anal or oral intercourse in a sexual partnership with a man.
- The model allows only two types of sexual partnership: one-off and repeat sexual partnership (the definitions are provided in Section 3.4.4).
- Concurrency of the same partnership types (one-off and repeated) is not allowed (serial monogamy).
- Anal-sex partnerships involve only anal sexual intercourse. Similarly, oral-sex partnership involves only oral sexual intercourse.
- All HIV-positive MSM start from the first disease stage (primary HIV infection) and progress to the next stages with decreased CD4 cell counts. The model does not allow an increase in CD4 cell counts.
- Once treated, individuals remain in the treatment stage until removed from the model.
- The sensitivity and specificity of the HIV test is 100%.
- Safe sex refers to sexual intercourse with condom use. Unsafe or unprotected sex refers to sexual intercourse without condom use.
- No HIV infection from outside the UK is included.
- The HIV epidemic in the UK was modelled as a whole and there was no differentiation by geographic area.

3.4. Model structure

Structuring the model concerns stratification of the modelled population according to various characteristics that have an essential effect on the model outputs [43]. The entire MSM populations in the UK were stratified simultaneously by MSM types, age, sexual activity level, partnership status, and HIV-related status.

3.4.1. Current and past MSM

Homosexual men in general have been considered at high risk for HIV infection specifically because of the frequent anal sexual intercourse they have. However, a

considerable number of UK homosexual males have never had anal sex with men and their last sex (defined as a genital contact) with men was more than 5 years ago [57]. These were excluded from the model. Those who have had sex with men in the last 5 years are included as 'current' MSM. Those who have had sex with men but not in the last 5 years and also who last had anal sex more than 5 years ago are less likely to contribute to further HIV transmission and were defined as 'past' MSM. Only current MSM acquire new partners and are at risk of HIV infection. The characteristics of past MSM resemble that of current low-activity MSM. All MSM in the model are the summation of the current and past MSM.

3.4.2. Age

The age range of the modelled population was 15-64 years and they were divided into two age groups of 15-34 and 35-64 years. Individuals in the younger group progress to the older group and individuals in the older group move out of the system at constant rates over time.

3.4.3. Sexual activity level

Two levels of sexual activity—low and high— was defined based on the number of sexual partners per year. The low-activity MSM have the average new male sexual partner per year of less than or equal to one. The high-activity MSM have more than one new male sexual partner per year. Together with the two age groups a total of four 'classes' of MSM in this model were formed, i.e. age group 1 – low activity, age group 1 – high activity, age group 2 – low activity, and age group 2 – high activity.

3.4.4. Partnership status

I distinguished between one-off and repeat sexual partners by defining that the one-off sexual partnership is a relationship that has only a single sexual contact which is assumed to start and end instantaneously. The repeat sexual partnership is defined as a

relationship in which sexual contact occurs more than once, such as a married couple, a steady partnership, or a casual partnership that has several sexual encounters. Unlike the typical mean-field model, the partnership-based model [44,46] allows a repeat sexual partnership to last for a finite duration of time, and only during that period can HIV transmission between partners can occur. Both individuals with and without a repeat sexual partner can have one-off sexual encounter and therefore be at risk for HIV infection.

3.4.5. Disease stage and CD4 levels

Based primarily on the CD4 cell counts, the long and variable natural history of HIV infection was divided into five stages: primary HIV infection (PHI), CD4 $\geq$ 500, 350-499, 200-349, and <200 cells/μL. This allowed us to distinguish among disease stages with respect to the three important factors: HIV transmission probability, HIV diagnosis rate, and the rate of initiating antiretroviral treatment (ART), determining the outcomes of the model. HIV-positive men progress from the first stage through the last without going backward. I assumed no CD4 stratification for MSM on treatment.

3.4.6. HIV diagnosis and treatment status

The five disease stages were further stratified into undiagnosed and diagnosed MSM. The latter was split into those who have never and ever been treated with ART. Note that ART-treated MSM included all men who have ever been treated with ART regardless of their current ART status. Furthermore, the model does not allow individuals to move back to the previous stages in which no ART is administered. Taken together, there are 12 different stages of HIV infection illustrated schematically in Figure 3-1.

3.5. Model equations and calculations

The model was constructed based on a set of ordinary differential equations. The numbers of single current MSM and single past MSM are denoted as *Y* and *Z*, respectively. The total numbers of single MSM, $X = Y + Z$. Let *P* be the numbers of pairs (not individuals) of current MSM. The total number of MSM in the model, $N = X + 2P$. The subscripts j, k, h of $X_{j,k,h}$ are denoted as age group (*j*=1 for age group 1, *j*=2 for age group 2), sexual activity group (*k*=1 for low-activity group, *k*=2 for high-activity group), and HIV infection stages ($h = 1, \ldots, 12$ according to 12 HIV stages presented in Figure 3-1: 1=susceptibles, 2=undiagnosed PHI, 3=diagnosed PHI, 4=undiagnosed CD4>500, 5=diagnosed CD4>500, 6=undiagnosed CD4 350-499, 7=diagnosed CD4 350-499, 8=undiagnosed CD4 200-349, 9=diagnosed CD4 200-349, 10=undiagnosed CD4<200, 11=diagnosed CD4<200, and 12=on treatment). The superscripts m, n, r of the numbers of pairs $P_{j,k,h}^{m,n,r}$ are denoted as age group *m*, sexual activity group *n*, and HIV stages *r* of the repeat sexual partner, and that $P_{j,k,h}^{m,n,r} = P_{m,n,r}^{j,k,h}$. This partnership-based model consists of 1,296 compartments which, following Xiridou et al [47] and Powers et al [58], can be described by the 46 equations listed in the appendix of this chapter. All parameters are summarised in Table 3-1. The time step in the model is a day (δ=1/365=0.0027). For any per-year rates, multiplying by δ will result in the corresponding rates per time-step.

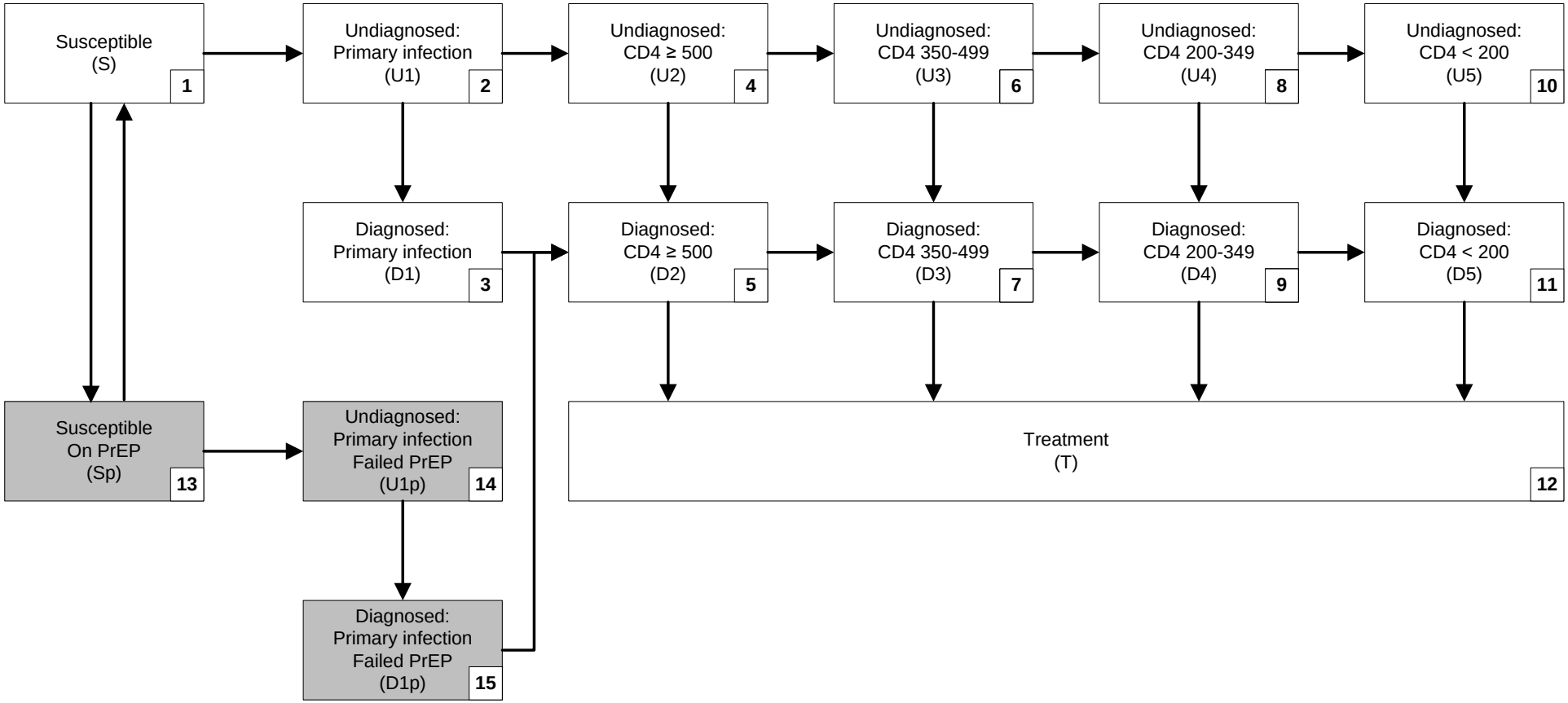

Figure 3-1: Model flow diagram

Table 3-1: Model parameters

Parameter	Definition
$N_{j,k,h}$	Total number of MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$X_{j,k,h}$	Total number of single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$Y_{j,k,h}$	Number of current single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$Z_{j,k,h}$	Number of past single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$P_{j,k,h}^{m,n,r}$	Number of pairs between an individual of age group *j*, sexual activity group *k*, and HIV stage *h* and an individual of age group *m*, sexual activity group *n*, and HIV stage *r*
$v_{j,k}$	Influx of new susceptibles in age group *j* (*j*=1), and sexual activity group *k*
$\eta_{j,k}$	Number of current MSM in age group *j*, and sexual activity group *k* (*k*=1) moving to past MSM
α_j	Ageing rate from an individual in age group *j* to next age group or out of the model
$\mu_{j,h}$	Mortality rate of an individual in age group *j* and HIV stage *h*
γ_h	Disease progression rate of an individual in disease stage *h* (*h*=2,...,11) to the next stage
$\phi_{j,k,h}$	HIV diagnosis rate of an individual in age group *j*, sexual activity group *k*, and undiagnosed stage *h* (*h*=2,4,6,8,10)
s_k	The proportion of MSM in sexual activity group *k* who switch to another sexual activity group after being diagnosed with HIV
τ_h	ART initiating rate of an individual in diagnosed stage *h* (*h*=5,7,9,11)
$\rho_{j,k}^{rep}$	Repeat sexual partnership formation rate of an individual in age group *j*, and sexual activity group *k*
$\sigma_{j,k}$	Repeat sexual partnership dissolution rate of an individual in age group *j*, and sexual activity group *k*
$\psi_{j,k,h}^{rep,m,n,r}$	Chance of an individual in age group *j*, sexual activity group *k*, and HIV stage *h* to acquire a repeat sexual partner of age group *m*, sexual activity group *n*, and HIV stage *r*
$\psi_{j,k}^{one,m,n,r}$	Chance of a susceptible in age group *j*, and sexual activity group *k* to acquire a one-off sexual partner of age group *m*, sexual activity group *n*, and HIV stage *r*
$\lambda_{Y,j,k}^{one}$	Force of infection in a relationship between a one-off sexual partner and a single susceptible individual of age group *j*, and sexual activity group *k*
$\lambda_{P,j,k}^{one}$	Force of infection in a relationship between a one-off sexual partner and a paired susceptible individual of age group *j*, and sexual activity group *k*
$\lambda_{j,k}^{rep,m,n,r}$	Force of infection in a relationship between a repeat sexual partner of age group *m*, sexual activity group *n* , and disease stage *h* (*h*=2,...,1) and a susceptible individual of age group *j*, and sexual activity group *k*

3.5.1. Calculating ageing

For each time step, individuals progress from the first to the second age group, and are removed out of the model from the second age group according to the proportion of MSM at the maximum age to all MSM in each age group. The derivation of the proportion is described in Section 4.3.1.2. Note that per-year rates must be converted to per-time step before being used as model input.

3.5.2. Calculating mortality

The death rate, $\mu_{j,h}$, stratified by age group and HIV stage is applied directly to the numbers of MSM in each corresponding group (see Section 4.3.1.4 for details of mortality rate). The number of deaths is subtracted from the model every time step and used for calculating the influx of new MSM.

3.5.3. Calculating influx of new MSM

A set of new MSM enters the model every time step and becomes a part of age group 1. This influx is calculated from the summation of the number of individuals who age from age group 1, those who die while in age group 1, and growth per time step of age group 1. The formula used is as follows:

$$\nu_{1,k} = (\alpha_1 + \mu_1 + g_1)N_{1,k} \tag{14}$$

where $N_{1,k}$ is the total number of MSM in age group 1 and sexual activity group k and g_1 is the growth rate of age group 1. See Section 4.3.1.3 for derivation of the population growth rate.

3.5.4. Calculating transition from the current to past MSM

A transition from the current to past MSM was modelled based on the assumption that the ratio between past and current MSM remains fixed over time (See Section 0 for

more detail about finding the ratio). Every time step the ratio $\frac{Z_{j,h}}{Y_{j,h}}$ is updated. If any updated ratios are less than that of the initial time step, a number of current MSM from age group *j* and HIV stage *h* will be moved to the same group of past MSM to preserve the original ratio. According to the definition of the past MSM (Section 3.4.1), only current MSM of low-activity group (See Section 4.3.2.1 for the definition) are legitimate for such movement. The numbers of past and current MSM of any groups remain unchanged if the updated ratio equals or exceeds that of the initial one. The model assumed no transition from past to current MSM.

3.5.5. Calculating disease progression

HIV-positive MSM progress from one disease stage to another according to declined CD4 cell counts (Figure 3-1). Multiplying the progression rate, γ_h, (Section 0) by the number of individuals in each disease stage ranging from PHI to CD4 200-349 cells/µL yields the number of MSM approaching the more advanced stages of HIV. Those with CD4<200 cells/µL remain in the last stage until they were either removed from the model by ageing or death, or get HIV diagnosed.

3.5.6. Calculating new HIV diagnoses

During the model year 2000–2009, the rates that HIV-positive MSM get diagnosed with HIV are updated every time step with an increase in diagnosis rate. I derived changes in HIV diagnosis rate (Section 4.3.4) and then updated the time-dependent HIV diagnosis rates by:

$$\phi_{j,k,h}(t) = \phi_{j,k,h}(t-1) + \Delta\phi_{j,k,h}(t) \tag{15}$$

where $\Delta\phi_{j,k,h}(t)$ represents change in diagnosis rate from time step *t*-1 to *t*. MSM newly diagnosed with HIV each time step move from undiagnosed CD4 stages to the corresponding diagnosed stages. I also compared model outputs to the reported numbers of new diagnoses by CD4 to validate the model (Chapter 5).

The model also allows current MSM to change their sexual activity levels due to HIV diagnosis. The constant proportions of individuals who switch from high- to low-activity group and vice versa, $s_{j,k}$ (see Section 4.3.4 for parameter values), were applied directly and instantly to the number of new diagnoses in each time step to obtain the number of MSM moving between sexual activity levels. Switching between sexual activity levels was permanent and thus individuals were not able to move back to the previous sexual activity levels.

3.5.7. Calculating MSM getting ART- treated

The diagnosed MSM in any CD4 stages except the PHI are given ART treatment every time step at the different rates, τ_h, with men in more advanced stages being more likely to be treated with ART. MSM new to treatment moved to a single compartment of 'on treatment' stage that no longer stratified by CD4 cell counts. Having no CD4 stratification is believed to have only a minor effect on the model outcome since the transmission probability of ART-treated MSM is very low, particularly in developed countries. This also helped simplify this model that already consists of a considerable number of heterogeneities. The rates of ART initiation change according to the updated guidelines for HIV treatment in the UK in 2008 [59]. The new rates were used once the model ran into the year 2009 and remain unchanged until the end of simulation. Section 4.3.5 summarises the derivation of ART initiating rates.

3.5.8. Calculating formation and dissolution of repeat sexual partnerships

The chance of an individual in any of the classes and stages to choose a repeat sexual partner from the same or another group is calculated based on two main components: the repeat sexual partnership formation rate and the sexual mixing preference. The odds ratio approach suggested by Goodreau and Golden [48] is used due to its flexibility in modelling multidimensional mixing preferences. The method also ensures that, at any modelling time steps, the number of new repeat sexual partners

that MSM of group *m* acquire from group *n* is identical to that of MSM of group *n* acquire from group *m* [60].

The mixing preferences by age group, sexual activity level, and the perceived HIV serostatus are included in the model. Each type consists of 2 subgroups: age group consists of the age group 1 and 2, sexual activity level consists of the low-activity and high-activity group, and the perceived HIV serostatus consists of the groups of perceived HIV-negative (stage S, and U1 to U5) and diagnosed HIV-positive (stage D1 to D5, and T). Consequently, the three odds ratios based on 2x2 mixing matrix for each mixing preference are required. The method for deriving the odds ratio can be found in Section 4.3.2.7. For simplicity, each mixing preference was modelled independently so that when all other mixing preferences are discarded, the chance of MSM selecting a new repeat sexual partner from the same or different groups matches exactly the original odds ratio of the remaining mixing preference.

At each time step, the calculations were initiated by finding the number of MSM who are looking for a new repeat sexual partner and stratified independently by age group, sexual activity level, and the perceived HIV serostatus. These numbers were then allocated between groups and created the following mixing matrix for each mixing preference:

	Group 1	Group 2
Group 1	*a*	*b*
Group 2	*c*	*d*

The matrix shows the number of MSM in pairs between the two groups. If the odd ratios *ad*/*bc* is greater than one the mixing is assortative, i.e. an individual is more likely to select a partner from their own group rather than from the other groups. Odds ratio of less than one represents the disassortative mixing, i.e. an individual is more likely to select a partner from the other groups rather than their own group. Odds ratio of one represents proportionate mixing, i.e. an individual selects a partner based on the proportion of group 1 and 2 to all available men. The elements of the mixing matrix are calculated by:

$$a = \rho_1^{rep} Y_1 - b \tag{16}$$

$$b = \frac{-\frac{1}{2}\rho_1^{rep} Y_1 - \frac{1}{2}\rho_2^{rep} Y_2 + \sqrt{\frac{1}{4}\left(\rho_1^{rep} Y_1 + \rho_2^{rep} Y_2\right)^2 + \rho_1^{rep} Y_1 \rho_2^{rep} Y_2 (w-1)}}{w-1}, b = c \tag{17}$$

$$d = \rho_2^{rep} Y_2 - b \tag{18}$$

where ρ_i^{rep} is the average repeat sexual partner formation rate of group *i*, Y_i is the number of current MSM in group *i*, and *w* is the odds ratio of the mixing preference.

I then combined any two of the three mixing preferences based on the assumption that the odds ratio of any type in any subgroup is identical to the same odds ratio in the overall population. In practice, I assigned the one mixing matrix to all elements of another mixing matrix and, within each of those elements of the latter matrix, calculated the mixing by the former matrix. For example, if mixing matrices by age group and sexual activity are:

Age	Group 1	Group 2
Group 1	*a* = A1	*b* = A2
Group 2	*c* = A3	*d* = A4

Activity	Group 1	Group 2
Group 1	*a* = B1	*b* = B2
Group 2	*c* = B3	*d* = B4

the sexual activity mixing matrix in an element *a* of age mixing matrix is:

	Group 1	Group 2
Group 1	*k*×B1	*k*×B2
Group 2	*k*×B3	*k*×B4

where $k = \frac{\text{B1} + \text{B2} + \text{B3} + \text{B4}}{\text{A1}}$. The resulting odds ratio of this sub-matrix equals the overall age-mixing odds ratio. The calculations for other elements and for combining all three mixing preferences can be achieved using the same logic. Note the order of combining the three mixing preferences has no effect on the final mixing matrix.

The combined 8x8 mixing matrix contains the numbers of MSM in repeat sexual partnerships between MSM of 8 subgroups stratified simultaneously by two age groups, two sexual activity levels, and two perceived HIV serostatuses. Comparing the partnership formation rates derived from the combined mixing matrix to the original

parameter values revealed some inconsistencies between the two sources which necessitated further adjustments. I therefore adjusted the numbers of men required for forming repeat sexual partnerships from the eight subgroups by multiplying the mixing elements that contribute the total number of required MSM in each subgroup with the ratio between original (data-derived) and actual repeat sexual partnership formation rates. The mixing elements are adjusted using the following formula:

$$a_{j,k,p}^{m,n,q} = a'^{m,n,q}_{j,k,p} \frac{\rho_{j,k}^{rep}}{\rho'^{rep}_{j,k}} \tag{19}$$

where $a'^{m,n,q}_{j,k,p}$ is a mixing element before adjustment between men of age group *j*, sexual activity group *k*, and perceived HIV serostatus group *p* and men of the corresponding groups *m*, *n*, and *q*, respectively, $\rho_{j,k}^{rep}$ is the original (data-derived) repeat sexual partnership formation rate for men in age group *j* and sexual activity group *k*, and $\rho'^{rep}_{j,k}$ is the partnership formation rate that derived from the combined mixing matrix. The above equation shows that all the non-diagonal elements ($[j,k,p] \neq [m,n,q]$) contribute concurrently to two mixing subgroups; I decided to adjust the subgroup that has a largest deviation of the partnership formation rates, $\left| \frac{\rho_{j,k}^{rep}}{\rho'^{rep}_{j,k}} - 1 \right|$, at each time step. After adjustment, the repeat sexual partnership formation rates of the subgroup that has the largest deviation would be identical to that of the original rate. The deviations in other subgroups may still remain but considerably smaller than without the adjustment. In exchange for more precise partnership formation rates, all types of odds ratio in the overall populations began to shift from the original values. However, the benefit of adjustment is clear since an improvement in accuracy of partnership formation rates after adjustment is substantial while only a minor difference in the odds ratio can be found. This is because the adjustment was aimed at subgroups with large deviations which usually are of small size and, in turn, having less effect on the odds ratio.

The final mixing matrix can now be used to obtain $\psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h}$. Since the proportionate mixing by disease stage was assumed, the numbers of repeat sexual partnerships were allocated proportionally to all pairs within each of the eight subgroups. In order for $P_{j,k,h}^{m,n,r} = P_{m,n,r}^{j,k,h}$ to remain valid at all times, the condition $\psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} = \psi_{m,n,r}^{rep,j,k,h}\rho_{m,n}^{rep}Y_{m,n,r}$ must always be satisfied. This can be achieved by using the adjusted repeat sexual partnership formation rates instead of one originally derived from the data in the main model equations.

The breakup between repeat sexual partners occurs every time step at the rate $\sigma_{j,k}$. The two members of a separated pair move to the single state and are ready for a new repeat sexual partnership. An average gap period between the end of the last repeat sexual partnership and the beginning of the next is incorporated to the dissolution rate to reflect the fact that, after the end of a long relationship, individual stays single for some period of time before acquiring a new partner.

3.5.9. Calculating force of infection in repeat sexual partnerships

In the partnership-based HIV transmission model, the force of infection for a repeat sexual partnership consists of two main components: the transmission probability and the frequency of sexual acts. The HIV transmission probabilities for each of the disease stages were calculated from a function of the average viral load in that stage (Section 4.3.3). Combining with all related factors, the per-act HIV transmission probability from an HIV-positive man of age group *m* (*m*=1,2), sexual activity *n* (*n*=1,2) and disease stage *r*, (*r*=2,...,12) to a susceptible of age group *j* (*j*=1,2), and sexual activity *k* (*k*=1,2) was calculated by:

$$\begin{aligned}\beta_{j,k}^{ste,m,n,r} = {} & p_{anal,j,k}^{rep}[p_{uai,j,k,r}^{rep}(p_{ins}\beta_{uiai,r}) + (1-p_{ins})\beta_{urai,r} \\ & + \varepsilon_{cdm}(1-p_{uai,j,k,r}^{rep})(p_{ins}\beta_{uiai,r}) + (1-p_{ins})\beta_{urai,r})] \\ & + (1-p_{anal,j,k}^{rep})[p_{uroi,j,k}^{rep}\beta_{uroi,r}]\end{aligned} \tag{20}$$

The notations are summarised in Table 4-7, Table 4-9, and Table 4-10.

The force of infection per time step is the product of the combined HIV per-act transmission probability and the average frequency of sexual acts per time step between MSM of class *j* and *k*, $\varphi_{j,k}$:

$$\lambda_{j,k}^{rep,m,n,r} = \varphi_{j,k}\beta_{j,k}^{rep,m,n,r} \tag{21}$$

The force of infection was calculated for all pairs between HIV-positive and HIV-negative MSM. Newly HIV-infected MSM at each time step move from HIV stage S to U1 while retain the current repeat sexual relationship.

3.5.10. Calculating formation and force of infection in one-off sexual partnerships

The same method used for the repeat sexual partnership formation is used to calculate the formation of one-off sexual partnership. Both single and paired MSM acquired a new one-off sexual partner at different rates. For paired MSM, only high-activity group members can form a one-off relationship while having a repeat sexual partner. Only mixing by age group and sexual activity were incorporated. The perceived HIV serostatus was accounted for differently by subsequently dividing MSM into subgroups according to unprotected anal intercourse (UAI) with one-off sexual partners. Within each perceived HIV serostatus, proportionate mixing by HIV stage was assumed.

The mixing matrices and one-off sexual partnership formation rates were adjusted in the same manner as for the formation of repeat sexual partnership. From the final mixing matrix I derived a chance of selecting a one-off sexual partner from different age and sexual activity groups, $\psi_{j,k}^{one,m,n,r}$. This was subsequently used to formulate the force of infection in one-off sexual partnerships. The one-off sexual partnerships were assumed to form and separate instantaneously, and hence a dissolution rate was not required.

To derive the force of infection within one-off sexual partnerships, susceptibles were divided into three groups: (A) no UAI at all, (B) only have UAI with perceived HIV-negative partners, and (C) can (but not only) have UAI with diagnosed HIV-positive partners. This allows us to model serosorting in one-off sexual partnership more comprehensively. The members of group A perform only safe anal sex regardless of the perception they have of their one-off sexual partner's serostatus. Group B will only have UAI with one-off sexual partners they believe are HIV negative (serosorting). However, it is not necessary that men of group B will always have UAI with an HIV-negative one-off sexual partner. Group C can have UAI with one-off sexual partners of any HIV serostatuses. The expression for the combined HIV transmission probability in one-off sexual partnerships that accounted for all UAI groups is given by:

$$\beta_{G,j,k}^{one,all} = p_{A,G}^{one}\beta_{G,A,j,k}^{one} + p_{B,G}^{one}\beta_{G,B,j,k}^{one} + p_{C,G}^{one}\beta_{G,C,j,k}^{one} \tag{22}$$

where $p_{A,G}^{one}$, $p_{B,G}^{one}$, and $p_{C,G}^{one}$ is the proportion of men in group A, B and C, respectively, and $G = Y, P$ denotes current single and paired MSM. The HIV transmission probabilities for each UAI group are:

$$\beta_{G,A,j,k}^{one} = \varepsilon_{cdm}\sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=2}^{12}\psi_{j,k}^{one,m,n,r}\beta_{G,j,k}^{one} \tag{23}$$

$$\begin{aligned}\beta_{G,B,j,k}^{one} &= (\varepsilon_{cdm}(1-p_{uai,G,B,j,k}^{one})\sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=2}^{12}\psi_{j,k}^{one,m,n,r}\beta_{G,j,k}^{one}) \\ &\quad + (p_{uai,G,B,j,k}^{one}\sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r\in d}\psi_{j,k}^{one,m,n,r}\beta_{G,j,k}^{one})\end{aligned}$$

where $d = 1, 2, 4, 6, 8, 10$ (24)

$$\beta_{G,C,j,k}^{one} = (\varepsilon_{cdm}(1-p_{uai,G,C,j,k}^{one}) + p_{uai,G,C,j,k}^{one})\sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=2}^{12}\psi_{j,k}^{one,m,n,r}\beta_{G,j,k}^{one} \tag{25}$$

The common term of transmission probability shared by all three groups is given by the expression:

$$\begin{aligned}\beta_{G,j,k}^{one} &= p_{anal,G,j,k}^{one}[p_{ins}\beta_{uiai,r}(p_{cir,j}\varepsilon_{cir} + (1-p_{cir,j})) + (1-p_{ins})\beta_{urai,r}] \\ &\quad + (1-p_{anal,G,j,k}^{one})[p_{uroi,j,k}^{one}\beta_{uroi,r}]\end{aligned} \tag{26}$$

The force of infection per time step is the product of one-off sexual partnership formation rates and the combined HIV transmission probabilities:

$$\lambda_{G,j,k}^{one} = \rho_{G,j,k}^{one} \beta_{G,j,k}^{one,all} \tag{27}$$

The notations used here are summarised in Table 4-7.

3.6. Conclusion

Up to this point, all computational mechanisms of the model have been developed. The model parameters defined in this chapter will be estimated in the next two chapters.

3.7. Appendix

3.7.1. Differential equations

Note that $[j,k] \neq [m,n]$ in all equations below, and the $\{condition\}$ denotes a specific condition that must be satisfied to enable the corresponding term.

Current single MSM

$$\frac{dY_{j,k,1}}{dt} = \nu_{j,k}\{j=1\} - \eta_{j,k,1}\{k=1\} + \sigma_{j,k}(P_{j,k,1}^{j,k,1} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,1}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,1}\{j=2\} - (\alpha_j + \mu_{j,1} + \rho_{j,k}^{rep} + \lambda_{Y,j,k}^{one})Y_{j,k,1} \tag{28}$$

$$\frac{dY_{j,k,2}}{dt} = \sigma_{j,k}(P_{j,k,2}^{j,k,2} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,2}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,2}\{j=2\} + \lambda_{Y,j,k}^{one}Y_{j,k,1} - (\alpha_j + \mu_{j,2} + \gamma_2 + \phi_{j,k,2} + \rho_{j,k}^{rep})Y_{j,k,2} \tag{29}$$

$$\frac{dY_{j,k,3}}{dt} = \sigma_{j,k}(P_{j,k,3}^{j,k,3} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,3}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,3}\{j=2\} + (1-s_k)\phi_{j,k,2}Y_{j,k,2} + s_l\phi_{j,l,2}Y_{j,l,2}\{l \neq k\} - (\alpha_j + \mu_{j,3} + \gamma_3 + \rho_{j,k}^{rep})Y_{j,k,3} \tag{30}$$

$$\frac{dY_{j,k,h}}{dt} = -\eta_{j,k,h}\{k=1\} + \sigma_{j,k}(P_{j,k,h}^{j,k,h} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,h}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,h}\{j=2\} + \gamma_{h-2}Y_{j,k,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,h} + \rho_{j,k}^{rep})Y_{j,k,h} \quad \text{for } h = 4, 6, 8, 10. \tag{31}$$

$$\frac{dY_{j,k,h}}{dt} = -\eta_{j,k,h}\{k=1\} + \sigma_{j,k}(P_{j,k,h}^{j,k,h} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,h}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,h}\{j=2\} + (1-s_k)\phi_{j,k,h-1}Y_{j,k,h-1} + s_l\phi_{j,l,h-1}Y_{j,l,h-1}\{l \neq k\}$$
$$+ \gamma_{h-2}Y_{j,k,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h + \rho_{j,k}^{rep})Y_{j,k,h}$$
for h = 5, 7, 9, 11. (32)

$$\frac{dY_{j,k,12}}{dt} = -\eta_{j,k,12}\{k=1\} + \sigma_{j,k}(P_{j,k,12}^{j,k,12} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,12}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,12}\{j=2\} + \sum_{g\in s}\tau_g Y_{j,k,g} - (\alpha_j + \mu_{j,12} + \rho_{j,k}^{rep})Y_{j,k,12}$$
where s = 5, 7, 9, 11. (33)

Past MSM

$$\frac{dZ_{j,1,1}}{dt} = \eta_{j,1} + \alpha_{j-1}Z_{j-1,1,1}\{j=2\} - (\alpha_j + \mu_{j,1})Z_{j,1,1}$$
(34)

$$\frac{dZ_{j,1,2}}{dt} = \eta_{j,2} + \alpha_{j-1}Z_{j-1,1,2}\{j=2\} - (\alpha_j + \mu_{j,2} + \gamma_2 + \phi_{j,1,2})Z_{j,1,2}$$
(35)

$$\frac{dZ_{j,1,3}}{dt} = \eta_{j,3} + \alpha_{j-1}Z_{j-1,1,3}\{j=2\} + \phi_{j,1,2}Z_{j,1,2} - (\alpha_j + \mu_{j,3} + \gamma_3)Z_{j,1,3}$$
(36)

$$\frac{dZ_{j,1,h}}{dt} = \eta_{j,h} + \alpha_{j-1}Z_{j-1,1,h}\{j=2\} + \gamma_{h-2}Z_{j,1,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,1,h})Z_{j,1,h}$$
for h = 4, 6, 8, 10. (37)

$$\frac{dZ_{j,1,h}}{dt} = \eta_{j,h} + \alpha_{j-1}Z_{j-1,1,h}\{j=2\} + \phi_{j,1,h-1}Z_{j,1,h-1} + \gamma_{h-2}Z_{j,1,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h)Z_{j,1,h}$$
for h = 5, 7, 9, 11. (38)

$$\frac{dZ_{j,1,12}}{dt} = \eta_{j,12} + \alpha_{j-1}Z_{j-1,1,12}\{j=2\} + \sum_{g\in s}\tau_g Z_{j,1,g} - (\alpha_j + \mu_{j,12})Z_{j,1,12}$$
where s = 5, 7, 9, 11. (39)

Paired MSM

Susceptible (HIV stage no.1) – Susceptible (HIV stage no.1)

$$\frac{dP_{j,k,1}^{j,k,1}}{dt} = \psi_{j,k,1}^{rep,j,k,1}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,1}\{j=2\} - (2\alpha_j + 2\mu_{j,1} + \sigma_{j,k} + 2\lambda_{P,j,k}^{one})P_{j,k,1}^{j,k,1} \tag{40}$$

$$\frac{dP_{j,k,1}^{m,n,1}}{dt} = \psi_{j,k,1}^{rep,m,n,1}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,1}\{j=2\} + \alpha_{m-1}P_{m-1,n,1}^{j,k,1}\{m=2\} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,1} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{P,m,n}^{one})P_{j,k,1}^{m,n,1} \tag{41}$$

Susceptible (HIV stage no.1) – Infected (HIV stage no.2-12)

$$\frac{dP_{j,k,1}^{j,k,2}}{dt} = \psi_{j,k,1}^{rep,j,k,2}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,2}\{j=2\} + 2\lambda_{P,j,k}^{one}P_{j,k,1}^{j,k,1} - (2\alpha_j + \mu_{j,1} + \mu_{j,2} + \gamma_2 + \phi_{j,k,2} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2})P_{j,k,1}^{j,k,2} \tag{42}$$

$$\begin{aligned}\frac{dP_{j,k,1}^{m,n,2}}{dt} &= \psi_{j,k,1}^{rep,m,n,2}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,2}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,1}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{P,m,n}^{one})P_{j,k,1}^{m,n,1} \\ &\quad - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,2} + \gamma_2 + \phi_{m,n,2} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,2})P_{j,k,1}^{m,n,2}\end{aligned} \tag{43}$$

$$\frac{dP_{j,k,1}^{j,k,3}}{dt} = \psi_{j,k,1}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,3}\{j=2\} + (1-s_k)\phi_{j,k,2}P_{j,k,1}^{j,k,2} + s_l\phi_{j,l,2}P_{j,k,1}^{j,l,2}\{l \neq k\} - (2\alpha_j + \mu_{j,1} + \mu_{j,3} + \gamma_3 + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,3})P_{j,k,1}^{j,k,3} \tag{44}$$

$$\begin{aligned}\frac{dP_{j,k,1}^{m,n,3}}{dt} &= \psi_{j,k,1}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,3}^{j,k,1}\{m=2\} + (1-s_n)\phi_{m,n,2}P_{j,k,1}^{m,n,2} + s_l\phi_{m,l,2}P_{j,k,1}^{m,l,2}\{l \neq n\} \\ &\quad - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,3} + \gamma_3 + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3})P_{j,k,1}^{m,n,3}\end{aligned} \tag{45}$$

$$\frac{dP_{j,k,1}^{j,k,h}}{dt} = \psi_{j,k,1}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,1}^{j,k,h-2} - (2\alpha_j + \mu_{j,1} + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,h} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h}$$

for h = 4, 6, 8, 10. (46)

$$\frac{dP_{j,k,1}^{m,n,r}}{dt} = \psi_{j,k,1}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,1}\{m=2\} + \gamma_{r-2}P_{j,k,1}^{m,n,r-2} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,r} + \gamma_r\{r \neq 10\} + \phi_{m,n,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r}$$

for r = 4, 6, 8, 10. (47)

$$\frac{dP_{j,k,1}^{j,k,h}}{dt} = \psi_{j,k,1}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,1}^{j,k,h-2} + (1-s_k)\phi_{j,k,h-1}P_{j,k,1}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,1}^{j,l,h-1}\{l \neq k\} - (2\alpha_j + \mu_{j,1} + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h}$$

for h = 5, 7, 9, 11. (48)

$$\frac{dP_{j,k,1}^{m,n,r}}{dt} = \psi_{j,k,1}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,1}\{m=2\} + \gamma_{r-2}P_{j,k,1}^{m,n,r-2} + (1-s_n)\phi_{m,n,r-1}P_{j,k,1}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,1}^{m,l,r-1}\{l \neq n\} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,r} + \gamma_r\{r \neq 11\} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r}$$

for r = 5, 7, 9, 11. (49)

$$\frac{dP_{j,k,1}^{j,k,12}}{dt} = \psi_{j,k,1}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,12}\{j=2\} + \sum_{g \in s}\tau_g P_{j,k,1}^{j,k,g} - (2\alpha_j + \mu_{j,1} + \mu_{j,12} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12})P_{j,k,1}^{j,k,12}$$

where s = 5, 7, 9, 11. (50)

$$\frac{dP_{j,k,1}^{m,n,12}}{dt} = \psi_{j,k,1}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,10}^{j,k,1}\{m=2\} + \sum_{g \in s}\tau_g P_{j,k,1}^{m,n,g} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,12} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12})P_{j,k,1}^{m,n,12}$$

where s = 5, 7, 9, 11. (51)

Undiagnosed PHI (HIV stage no.2) – Infected (HIV stage no.2-12)

$$\frac{dP_{j,k,2}^{j,k,2}}{dt} = \psi_{j,k,2}^{rep,j,k,2}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,2}\{j=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2})P_{j,k,1}^{j,k,2} - (2\alpha_j + 2\mu_{j,2} + 2\gamma_2 + 2\phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,2} \tag{52}$$

$$\begin{aligned}\frac{dP_{j,k,2}^{m,n,2}}{dt} &= \psi_{j,k,2}^{rep,m,n,2}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,2}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,2}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,2})P_{j,k,1}^{m,n,2} + (\lambda_{P,m,n}^{one} + \lambda_{m,n}^{rep,j,k,2})P_{j,k,2}^{m,n,1} \\ &\quad -(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,2} + 2\gamma_2 + \phi_{j,k,2} + \phi_{m,n,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,2}\end{aligned} \tag{53}$$

$$\frac{dP_{j,k,2}^{j,k,3}}{dt} = \psi_{j,k,2}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,3}\{j=2\} + 2\phi_{j,k,2}P_{j,k,2}^{j,k,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,3})P_{j,k,1}^{j,k,3} - (2\alpha_j + \mu_{j,2} + \mu_{j,3} + \gamma_2 + \gamma_3 + \phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,3} \tag{54}$$

$$\begin{aligned}\frac{dP_{j,k,2}^{m,n,3}}{dt} &= \psi_{j,k,2}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,3}\{m=2\} + \phi_{m,n,2}P_{j,k,2}^{m,n,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3})P_{j,k,1}^{m,n,3} \\ &\quad -(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,3} + \gamma_2 + \gamma_3 + \phi_{j,k,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,3}\end{aligned} \tag{55}$$

$$\begin{aligned}\frac{dP_{j,k,2}^{j,k,h}}{dt} &= \psi_{j,k,2}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,2}^{j,k,h-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h} \\ &\quad -(2\alpha_j + \mu_{j,2} + \mu_{j,h} + \gamma_2 + \gamma_h\{h \neq 10\} + \phi_{j,k,2} + \phi_{j,k,h} + \sigma_{j,k})P_{j,k,2}^{j,k,h}\end{aligned} \quad \text{for } h = 4, 6, 8, 10. \tag{56}$$

$$\begin{aligned}\frac{dP_{j,k,2}^{m,n,r}}{dt} &= \psi_{j,k,2}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,2}\{m=2\} + \gamma_{r-2}P_{j,k,2}^{m,n,r-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r} \\ &\quad -(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,r} + \gamma_2 + \gamma_r\{r \neq 10\} + \phi_{j,k,2} + \phi_{j,k,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,r}\end{aligned} \quad \text{for } r = 4, 6, 8, 10. \tag{57}$$

$$\frac{dP_{j,k,2}^{j,k,h}}{dt} = \psi_{j,k,2}^{rep,j,k,h}\rho_{j,k}^{ste}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,2}^{j,k,h-2} + (1-s_k)\phi_{j,k,h-1}P_{j,k,2}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,2}^{j,l,h-1}\{l \neq k\}$$
$$+ (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h} - (2\alpha_j + \mu_{j,2} + \mu_{j,h} + \gamma_2 + \gamma_h\{h \neq 11\} + \phi_{j,k,2} + \phi_{j,k,h} + \tau_h + \sigma_{j,k})P_{j,k,2}^{j,k,h}$$

for h = 5, 7, 9, 11. (58)

$$\frac{dP_{j,k,2}^{m,n,r}}{dt} = \psi_{j,k,2}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,2}\{m=2\} + \gamma_{r-2}P_{j,k,2}^{m,n,r-2} + (1-s_n)\phi_{m,n,r-1}P_{j,k,2}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,2}^{m,l,r-1}\{l \neq n\}$$
$$+ (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r} - (\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,r} + \gamma_2 + \gamma_r\{r \neq 11\} + \phi_{j,k,2} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,r}$$

for r = 5, 7, 9, 11. (59)

$$\frac{dP_{j,k,2}^{j,k,12}}{dt} = \psi_{j,k,2}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,12}\{j=2\} + \sum_{g \in s}\tau_g P_{j,k,2}^{j,k,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12})P_{j,k,1}^{j,k,12}$$
$$- (2\alpha_j + \mu_{j,2} + \mu_{j,12} + \gamma_2 + \phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,12}$$

where s = 5, 7, 9, 11. (60)

$$\frac{dP_{j,k,2}^{m,n,12}}{dt} = \psi_{j,k,2}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,2}\{m=2\} + \sum_{g \in s}\tau_g P_{j,k,2}^{m,n,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12})P_{j,k,1}^{m,n,12}$$
$$- (\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,12} + \gamma_2 + \phi_{j,k,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,12}$$

where s = 5, 7, 9, 11. (61)

Infected except U2 (HIV stage no.3-12) – Infected except U2 (HIV stage no.3-12)

Undiagnosed – Undiagnosed

$$\frac{dP_{j,k,h}^{j,k,r}}{dt} = \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{ste}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2}$$
$$-(2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 10\} + \phi_{j,k,h} + \phi_{j,k,r} + \sigma_{j,k})P_{j,k,h}^{j,k,r}$$

for h = 4, 6, 8, 10, and r = 4, 6, 8, 10. (62)

$$\frac{dP_{j,k,h}^{m,n,r}}{dt} = \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{r-2}P_{j,k,h}^{m,n,r-2}$$
$$-(\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 10\} + \phi_{j,k,h} + \phi_{j,k,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}$$

for h = 4, 6, 8, 10, and r = 4, 6, 8, 10. (63)

Undiagnosed – Diagnosed

$$\frac{dP_{j,k,h}^{j,k,r}}{dt} = \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2}\{r \neq 3\}$$
$$+(1-s_k)\phi_{j,k,r-1}P_{j,k,h}^{j,k,r-1} + s_l\phi_{j,l,r-1}P_{j,k,h}^{j,l,r-1}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 11\} + \phi_{j,k,h} + \tau_r\{r \neq 3\} + \sigma_{j,k})P_{j,k,h}^{j,k,r}$$

for h = 4, 6, 8, 10, and r = 3, 5, 7, 9, 11. (64)

$$\frac{dP_{j,k,h}^{m,n,r}}{dt} = \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,r} + \gamma_{r-2}P_{j,k,h}^{m,n,r-2}\{r \neq 3\}$$
$$+(1-s_n)\phi_{m,n,r-1}P_{j,k,h}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,h}^{m,l,r-1}\{l \neq n\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 11\} + \phi_{j,k,h} + \tau_r\{r \neq 3\} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}$$

for h = 4, 6, 8, 10, and r = 3, 5, 7, 9, 11. (65)

Undiagnosed – On treatment

$$\frac{dP_{j,k,h}^{j,k,12}}{dt} = \psi_{j,k,h}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,12}\{j=2\} + \sum_{g\in s}\tau_g P_{j,k,h}^{j,k,g} - (2\alpha_j + \mu_{j,h} + \mu_{j,12} + \gamma_h\{h\neq 10\} + \phi_{j,k,h} + \sigma_{j,k})P_{j,k,h}^{j,k,12}$$

for h = 4, 6, 8, 10, and s = 5, 7, 9, 11. (66)

$$\frac{dP_{j,k,h}^{m,n,12}}{dt} = \psi_{j,k,h}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,h}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,h}^{m,n,g} - (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,12} + \gamma_h\{h\neq 10\} + \phi_{j,k,h} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,h}^{m,n,12}$$

for h = 4, 6, 8, 10, and s = 5, 7, 9, 11. (67)

Diagnosed – Diagnosed

$$\frac{dP_{j,k,h}^{j,k,r}}{dt} = \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r}\{h\neq 3\} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2}\{r\neq 3\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{j,k,r} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{j,k,r}\{l\neq k\} + (1-s_k)\phi_{j,k,r-1}P_{j,k,h}^{j,k,r-1} + s_l\phi_{j,l,r-1}P_{j,k,h}^{j,l,r-1}\{l\neq k\} - (2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h\neq 11\} + \gamma_r\{r\neq 11\} + \tau_h\{h\neq 3\} + \tau_r\{r\neq 3\} + \sigma_{j,k})P_{j,k,h}^{j,k,r}$$

for h = 3, 5, 7, 9, 11, and r = 3, 5, 7, 9, 11. (68)

$$\frac{dP_{j,k,h}^{m,n,r}}{dt} = \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,r}\{h\neq 3\} + \gamma_{r-2}P_{j,k,h}^{m,n,r-2}\{r\neq 3\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{m,n,r} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{m,n,r}\{l\neq k\} + (1-s_n)\phi_{m,n,r-1}P_{j,k,h}^{m,n,r-1} + s_u\phi_{m,u,r-1}P_{j,k,h}^{m,u,r-1}\{u\neq n\} - (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h\neq 11\} + \gamma_r\{r\neq 11\} + \tau_h\{h\neq 3\} + \tau_r\{r\neq 3\} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}$$

for h = 3, 5, 7, 9, 11, and r = 3, 5, 7, 9, 11. (69)

Diagnosed – On treatment

$$\frac{dP_{j,k,h}^{j,k,12}}{dt} = \psi_{j,k,h}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,12}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,12}\{h \neq 3\}$$
$$+(1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{j,k,12} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{j,k,12}\{l \neq k\} + \sum_{g \in s}\tau_g P_{j,k,h}^{j,k,g}$$
$$-(2\alpha_j + \mu_{j,h} + \mu_{j,12} + \gamma_h\{h \neq 11\} + \tau_h\{h \neq 3\} + \sigma_{j,k})P_{j,k,h}^{j,k,12}$$

for h = 3, 5, 7, 9, 11, and s = 5, 7, 9, 11. (70)

$$\frac{dP_{j,k,h}^{m,n,12}}{dt} = \psi_{j,k,h}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,12}\{h \neq 3\}$$
$$+(1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{m,n,12} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{m,n,12}\{l \neq k\} + \sum_{g \in s}\tau_g P_{j,k,h}^{m,n,g}$$
$$-(\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,12} + \gamma_h\{h \neq 11\} + \tau_h\{h \neq 3\} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,h}^{m,n,12}$$

for h = 3, 5, 7, 9, 11, and s = 5, 7, 9, 11. (71)

On treatment – On treatment

$$\frac{dP_{j,k,12}^{j,k,12}}{dt} = \psi_{j,k,12}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,12} + 2\alpha_{j-1}P_{j-1,k,12}^{j,k,12}\{j=2\} + 2\sum_{g \in s}\tau_g P_{j,k,12}^{j,k,g} - (2\alpha_j + 2\mu_{j,12} + \sigma_{j,k})P_{j,k,12}^{j,k,12}$$

for s = 5, 7, 9, 11. (72)

$$\frac{dP_{j,k,12}^{m,n,12}}{dt} = \psi_{j,k,12}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,12} + \alpha_{j-1}P_{j-1,k,12}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,12}\{m=2\} + \sum_{g \in s}\tau_g P_{j,k,12}^{m,n,g} + \sum_{g \in s}\tau_g P_{m,n,12}^{j,k,g}$$
$$-(\alpha_j + \alpha_m + \mu_{j,12} + \mu_{m,12} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,12}^{m,n,12}$$

for s = 5, 7,9, 11. (73)

Chapter 4

Parameter estimation

In this chapter:

Data sources and data analysis

Estimating model parameters

4.1. Introduction

This chapter begins with a discussion on the available data and sources that are used for model parameterisation. The details on deriving parameter values according to the developed model from the previous chapter are then presented. The contents of this chapter have been published in *AIDS* as supplementary materials for the publication [61] presented in Chapter 5.

4.2. Data

The data from behavioural surveys and HIV surveillance systems that included men who have sex with men (MSM) in the UK were used in conjunction with information obtained from the literature to estimate model parameters. I adjusted and categorised data according to the MSM subgroups in the model before further analyses.

4.2.1. Data sources

The primary data sources for deriving model parameters are as follows.

4.2.1.1. The National Survey of Sexual Attitudes and Lifestyles (NATSAL)

NATSAL is a major survey of sexual attitudes and lifestyles providing detailed information about sexual and related behaviour patterns of the general UK populations aged 16-44 including MSM. This survey is conducted at ten-year intervals. The first round was initiated in 1990 [62], the second in 2000–2001 [57], and the third round in 2010–2012, the results of which has been published in 2013 [63]. The data from the 2000 survey was the primary data.

4.2.1.2. The Gay Men's Sexual Health Survey (GMSHS)

Initiated in 1996, GMSHS is a survey aimed primarily at gathering information on demographics, sexual behaviour, and HIV status among gay men aged 16 or above

who attend community venues in London [64]. Since 2000, survey respondents had also been offered an anonymous HIV test using the OraSure device. This allows linking respondent's serostatus to the data collected from the questionnaire. I used the data for years 2000–2008 except 2007 when the survey was not conducted. University College London, PHE, and the Medical Research Council are responsible for the survey.

4.2.1.3. The London Gym Survey (GYM)

GYM is a survey on demographics, social characteristics, sexual behaviour, HIV status, and risk factors among gay men who use gyms in London [65]. With collaboration between City University London and PHE, the survey was conducted annually between 1998 and 2005 and again in 2008. I used all data that are available from 2000 to 2008.

4.2.1.4. The HIV/AIDS diagnoses and deaths surveillance

This is the national HIV/AIDS surveillance reporting systems established in 1982. The data have been reported on a regular basis including the number of new HIV diagnoses, laboratory tests, probable routes of infection, demographics, and epidemiological data [66]. The data are made available by PHE.

4.2.1.5. The CD4 surveillance systems

As a supplementary to the HIV/AIDS surveillance, the CD4 systems monitor trends in CD4 cell count at HIV diagnosis among HIV-infected adults. The CD4 cell count at HIV diagnosis is defined as the CD4 cell count closest to, and within 30 days of, the date of HIV diagnosis. The data are reported as a supplement to HIV diagnoses [67].

4.2.1.6. The Survey of Prevalent HIV Infections Diagnosed (SOPHID)

SOPHID is a cross-sectional survey of all individuals with diagnosed HIV infection who require HIV-related care within the National Health Service in England, Wales,

and Northern Ireland within a calendar year run by the PHE. Scottish data are collected separately by Health Protection Scotland, and are included in the final UK totals. The survey began in 1995 and is conducted twice a year in London and annually outside London. The primary aim is to determine the total number of HIV prevalent patients seen for treatment and care [67].

4.2.2. Selecting survey respondents

The process involved selecting and categorising survey respondents to match the model structure. This began by selecting NATSAL respondents according to the definition of current and past MSM outlined earlier. Weights for the core sample and the ethnic minority boost sample were applied for all calculations. For GMSHS and GYM, there is no exact same set of questions as in NATSAL that can be used to categorise current and past MSM. I therefore assumed that GMSHS and GYM respondents were current MSM because the majority reported anal sex with men in the last year (GMSHS: 90%, GYM: 89%).

The survey respondents aged 65 or above or with missing age data were excluded. The remaining was divided into two age groups: 16–34 and 35–64. Most of the subsequent analyses were based on the two age groups except when the size of any groups was too small that the overall MSM would be used instead. Table 4-1 shows the numbers of sampled MSM from the surveys.

For data from HIV/AIDS surveillance systems including CD4 and SOPHID databases, I selected only men aged 15-64 who were reported to acquire HIV infection from sex between men. The large number of cases allowed us to divide the datasets by age groups for all data analyses.

Table 4-1: Number of survey respondents included for data analysis

MSM	NATSAL [a]		GMSHS		GYM	
	n	%	n	%	n	%
Current MSM						
Aged 16-34	101.5	65.4	9,936	57.5	1,894	44.2
Aged 35-64	53.7	34.6	7,347	42.5	2,393	55.8
Total	155.2	100.0	17,283	100.0	4,287	100.0
Past MSM						
Aged 16-34	7.1	25.7	-	-	-	-
Aged 35-64	20.5	74.3	-	-	-	-
Total	27.6	100.0	-	-	-	-
All MSM						
Aged 16-34	108.6	59.4	9,936	57.5	1,894	44.2
Aged 35-64	74.2	40.6	7,347	42.5	2,393	55.8
Total	182.8	100.0	17,283	100.0	4,287	100.0

NATSAL: The National Survey of Sexual Attitudes and Lifestyles
GMSHS: The Gay Men's Sexual Health Survey
GYM: The London Gym Survey
[a] With weights for core sample and the ethnic minority boost sample

4.2.3. Data adjustment

In the model, the population of interest is the entire MSM population aged 15-64 in the UK. However, the data from GMSHS and GYM were based on convenience-sampling from the MSM community in London. This may introduce bias into the data by including MSM with characteristics that are markedly different from the general MSM in the UK. Such differences can be observed by comparing the GMSHS and GYM data to the national-based NATSAL 2000 survey that used probability-sampling on a household basis. Table 4-2 shows, for example, that the mean number of male sexual partners in the last year of GMSHS men aged less than 35 were around 22 compared to that of 7 from NATSAL. Adjustment was necessary to improve the representativeness of survey populations. The adjustment method suggested by Reidy and Goodreau [68] was used here.

Table 4-2: Weight adjustment for GMSHS and GYM data

Variable	Reported								Adjusted (all weights simultaneously) [a]			
	NATSAL		GMSHS			GYM			GMSHS		GYM	
	n [b]	%	n	%	Weight	n	%	Weight	n	%	n	%
Age of respondents [c]												
16-24	29.4	18.9	892	16.6	1.138	68	5.2	3.645	1,322.9	23.4	318.7	23.8
25-34	72.1	46.5	2,763	51.5	0.902	652	49.8	0.933	2,626.8	46.5	596.1	44.5
35-44	53.7	34.6	1,711	31.9	1.086	590	45.0	0.769	1,702.4	30.1	425.3	31.7
median		32		32			35			32		32
Number of male sexual partners in the last year [d]												
Aged 16-34 [e]												
0	17.9	17.9	63	1.8	9.857	-	-	-	693.8	18.4	-	-
1	32.4	32.4	494	14.3	2.271	-	-	-	1,354.3	36.0	-	-
2	7.4	7.4	249	7.2	1.024	-	-	-	267.0	7.1	-	-
3	12.4	12.4	237	6.8	1.813	-	-	-	489.2	13.0	-	-
4	11.0	11.0	207	6.0	1.841	-	-	-	366.0	9.7	-	-
5-9	4.3	4.3	542	15.7	0.273	-	-	-	144.8	3.8	-	-
10-14	6.2	6.2	451	13.0	0.474	-	-	-	195.9	5.2	-	-
15-19	1.2	1.2	190	5.5	0.215	-	-	-	39.6	1.1	-	-
20-29	2.1	2.1	350	10.1	0.212	-	-	-	63.8	1.7	-	-
30-49	0.5	0.5	271	7.8	0.065	-	-	-	16.1	0.4	-	-
50+	4.6	4.6	408	11.8	0.389	-	-	-	134.6	3.6	-	-
mean		7.30		21.61			-			6.38		-
Aged 35-64												
0	9.7	18.1	84	3.8	4.714	-	-	-	353.3	15.7	-	-
1	19.8	37.0	320	14.6	2.532	-	-	-	921.0	41.0	-	-
2	5.8	10.8	161	7.4	1.468	-	-	-	241.4	10.7	-	-

Variable	Reported								Adjusted (all weights simultaneously) [a]			
	NATSAL		GMSHS			GYM			GMSHS		GYM	
	n [b]	%	n	%	Weight	n	%	Weight	n	%	n	%
3	2.3	4.3	139	6.3	0.678	-	-	-	89.6	4.0	-	-
4	2.6	4.9	106	4.8	1.008	-	-	-	113.4	5.0	-	-
5-9	3.8	7.1	282	12.9	0.552	-	-	-	158.4	7.0	-	-
10-14	5.6	10.4	284	13.0	0.802	-	-	-	221.1	9.8	-	-
15-19	1.1	2.0	92	4.2	0.475	-	-	-	38.6	1.7	-	-
20-29	1.8	3.4	254	11.6	0.289	-	-	-	69.9	3.1	-	-
30-49	0.3	0.6	164	7.5	0.086	-	-	-	13.6	0.6	-	-
50+	0.8	1.5	304	13.9	0.105	-	-	-	28.5	1.3	-	-
mean		4.48		23.14			-			4.87		-
Number of UAI male sexual partners in the last year [f]												
0	30.6	34.8	2,914	53.3	0.653	514	45.9	0.758	2,112.5	41.1	449.9	40.0
1	35.9	40.9	1,506	27.5	1.485	335	29.9	1.366	2,463.8	48.0	421.4	37.5
2	10.2	11.6	464	8.5	1.365	105	9.4	1.234	305.8	6.0	137.6	12.2
3	6.8	7.7	167	3.1	2.524	54	4.8	1.597	177.3	3.5	77.9	6.9
4+	4.4	5.0	418	7.6	0.653	111	9.9	0.503	78.4	1.5	37.2	3.3
mean		1.52		1.90			2.13			1.18		1.34
Time of last HIV test												
Aged 16-34												
In the last year	12.5	12.7	1,184	34.7	0.365	217	31.9	0.397	352.5	9.4	108.5	12.6
More than a year ago	34.5	34.9	1,147	33.6	1.039	290	42.6	0.819	1116.6	29.7	269.8	31.3
Never had an HIV test	51.8	52.4	1,080	31.7	1.654	173	25.4	2.059	2290.7	60.9	482.7	56.1
Aged 35-64												
In the last year	8.5	18.9	529	25.0	0.755	172	24.9	0.758	339.4	15.7	107.1	19.7
More than a year ago	11.1	24.8	948	44.8	0.554	355	51.4	0.483	518.2	23.9	136.6	25.1
Never had an HIV test	25.2	56.3	640	30.2	1.863	164	23.7	2.373	1308.5	60.4	300.8	55.2

Variable	Reported								Adjusted (all weights simultaneously) [a]			
	NATSAL		GMSHS			GYM			GMSHS		GYM	
	n [b]	%	n	%	Weight	n	%	Weight	n	%	n	%
Total weights [g]												
Aged 16-34												
Minimum	-	-	-	-	0.014	-	-	0.187	-	-	-	-
Maximum	-	-	-	-	18.558	-	-	11.984	-	-	-	-
Aged 35-64												
Minimum	-	-	-	-	0.031	-	-	0.187	-	-	-	-
Maximum	-	-	-	-	9.537	-	-	3.243	-	-	-	-

NATSAL: The National Survey of Sexual Attitudes and Lifestyles
GMSHS: The Gay Men's Sexual Health Survey
GYM: The London Gym Survey
UAI: Unprotected anal intercourse
Weight adjustment according to four variables: age of survey respondents, number of male sexual partners in the last year, number of UAI male sexual partners in the last year, and time of last HIV test. Proportions of some variables shown here may not sum to one due to rounding off decimals.
NATSAL data of the year 2000
GMSHS data of the year 1999, 2000, and 2001
GYM data of the year 2000 and 2001
[a] Adjustment with all weights simultaneously results in similar but non-identical proportions to NATSAL.
[b] The reported numbers may not be an integer due to the original NATSAL weighting.
[c] Age range in NATSAL is 16-44. Therefore, the age of GMSHS and GYM respondents were adjusted only of the same range. The remaining ages were left as reported.
[d] The number of male sexual partners in the last year is not available in GYM.
[e] The reported numbers and proportions of NATSAL for this variable are shown identical due to rounding off decimals.
[f] The variable was not categorised by age group due to the small number of NATSAL cases.
[g] Total weights are the product of all independent weights of the above four variables. The minimum and maximum rows represent the minimum and maximum total weight for the corresponding age groups, respectively. The total weights were then used for adjusting the original GMSHS and GYM data.

To adjust the GMSHS and GYM data, I selected only the surveys that were conducted during 1999–2001 which corresponded to the data collection timeframe of NATSAL. The data were then adjusted according to four variables: (1) age of respondent, (2) the number of male sexual partners in the last year, (3) the number of unprotected anal intercourse male partners in the last year, and (4) time of last HIV test. I calculated a probability weight for each GMSHS and GYM respondent independently by each of the four variables. The weight was calculated as:

$$w_{i,a} = \frac{p_{i,a}}{k_{i,a}} \tag{74}$$

where $w_{i,a}$ is the weight for respondents that fall into group *i* of the adjusted variable *a*, whereas $p_{i,a}$ and $k_{i,a}$ are the proportions of respondents from the reference dataset (NATSAL) and the adjusted dataset (GMSHS or GYM), respectively.

By applying the weights independently to each variable, the distribution of adjusted proportions of GMSHS and GYM respondents for the variable will be identical to that of NATSAL. Applying all weights simultaneously somewhat distorted the distribution of all variables (Table 4-2). The problem can be avoided by replacing the marginal distribution of each variable in equation (74) with the joint distribution of all four variables. However, the small sample size of MSM in NATSAL prevented us from properly deriving such joint distributions and thus the marginal distributions were used instead.

The weights were then applied to GMSHS and GYM data of all years that were used in this study. Consequently, all model parameter values derived from these datasets were affected by the adjustment. The total weights range from 0.014 to 18.558 for GMSHS and from 0.187 to 11.984 for GYM data. I conducted an analysis to see the effects of introducing weight limits on the derived repeat sexual partnership formation rates (Figure 4-1). To maintain the accuracy of the derived model parameters, the full weights were used.

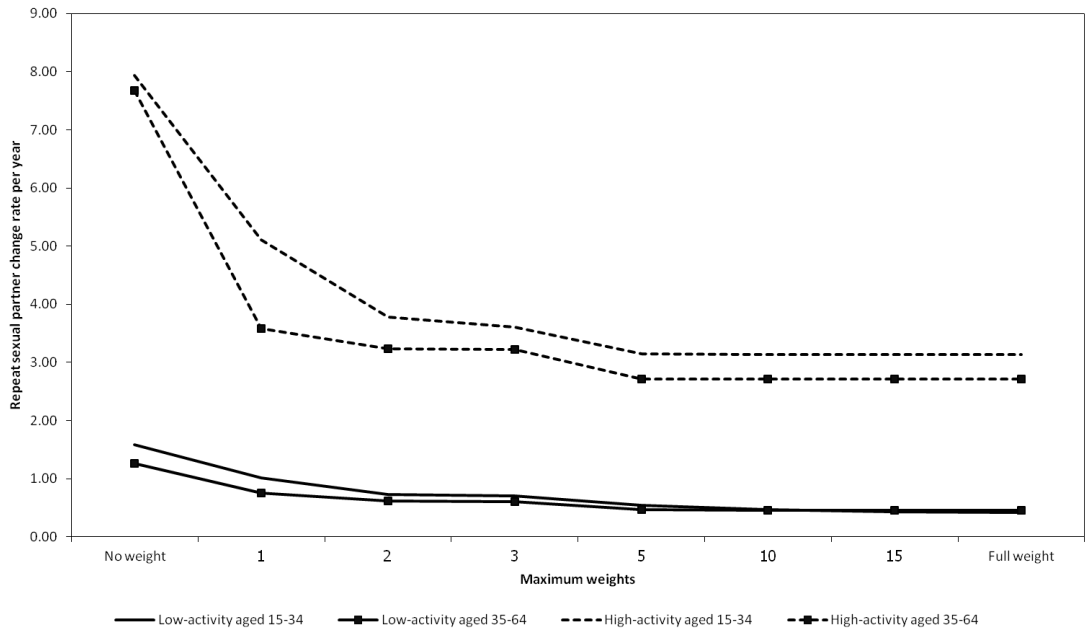

Figure 4-1: Comparison of repeat sexual partnership formation rates using different adjustment weights

Each line illustrates changes in repeat sexual partnership formation rates per year of the corresponding classes for different adjustment weights ranging from no weight at all to full weight. The full weights were used in this study.

4.3. Model parameterisation

The model parameters can be stratified into five categories: demographics, sexual behaviour parameters, biological parameters, HIV diagnosis parameters, and model initial conditions. All parameters were initially derived using either the data from surveys, surveillance systems, reports, or the literature.

4.3.1. Demographics

According to the demographic structure of the modelled population, the estimates of the UK MSM population size, rate of ageing, population growth rate, and mortality rate by age groups were required.

4.3.1.1. MSM population size

The data from the UK Office of National Statistics (ONS) and NATSAL were used to obtain estimates of MSM population size in the UK in 2000, the initial time point in the model. First, I calculated the proportions of MSM to all male respondents in NATSAL by regions and found that London had the highest proportion of MSM (6.3%) compared to elsewhere in England (2.5%), and outside England (1.7%). Since the age of the modelled populations (15-64) and NATSAL respondents (16-44) did not match, I derived the proportion of UK male population aged 45-64 to aged 40-44 from the 1999–2001 ONS data [69] and assumed the same proportion for UK MSM. For MSM aged 15, I simply assumed that the proportion of MSM in males aged 15-34 was the same as that of aged 16-34. The proportions of MSM by age groups and regions can now be obtained. The analysis also provided an estimated 5-year-interval age distribution of MSM aged 15-64 (Table 4-3) which will be used later for calculating the mortality rates (section 4.3.1.4).

Table 4-3: Estimated 5-year age distribution of MSM aged 15-64 of year 2000

Age group	Proportion (%) [a]
15-19	3.13
20-24	7.57
25-29	10.45
30-34	17.08
35-39	15.63
40-44	10.48
45-49	9.64
50-54	10.31
55-59	8.38
60-64	7.33
Total	100.00

[a] Estimated from NATSAL and ONS data

Combining all these estimated proportions provided the proportion of MSM aged 15-64 to the male population with the overall mean of 2.9% regardless of age groups and regions. However, the PHE estimated that 3.4% of all UK males are MSM [70]. I therefore adjusted the age group- and region-specific proportions of MSM derived above so that the total number of MSM accounted for 3.4% (not 2.9%) of male population in the UK. The adjusted proportions were then multiplied by the ONS mid-

year population estimates and yielded 648,500 MSM (aged 15-34: 259,500, aged 35-64: 389,000) living in the UK in 2000. Of these and according to the proportions of current and past MSM derived from NATSAL, there were 527,800 current MSM (aged 15-34: 242,678, aged 35-64: 285,122) and 120,700 past MSM (aged 15-34: 16,822, aged 35-64: 103,878). The data used for estimating the MSM size are summarised in Table 4-4 and the derived parameter values are shown in Table 4-5. The proportion of past MSM was also used to model the flow from current to past MSM (Table 4-5).

Table 4-4: Data used for deriving MSM population size in the UK of year 2000

Description	London	Elsewhere in England	Outside England	Entire UK
Adjusted proportion of MSM to male population (%) [a,b]				
Aged 15-34	6.60	2.67	2.78	-
Aged 35-64	8.55	3.26	0.94	-
Mid-year estimates size of male population size [b,c]				
Aged 15-34	1,196,000	5,436,300	1,266,400	-
Aged 35-64	1,263,000	8,087,000	1,824,800	-
Proportion of current MSM (%) [d,e]				
Aged 15-34	-	-	-	93.38
Aged 35-64	-	-	-	72.42
Proportion of past MSM (%) [d,e]				
Aged 15-34	-	-	-	6.62
Aged 35-64	-	-	-	27.58

[a] Data from NATSAL and PHE
[b] Data for the entire UK are not shown because they would result in total number of MSM population that are different from the current calculation which based on the three regions.
[c] Data from ONS
[d] Data from NATSAL
[e] The proportions were not stratified by regions because of the small number of cases.

Table 4-5: Demographic parameters

Parameter	Symbol	Value		Source
		Aged 15-34	Aged 35-64	
MSM size of year 2000				
Current MSM	-	242,678	285,122	NATSAL, ONS
Past MSM	-	16,822	103,878	NATSAL, ONS
All MSM	-	259,500	389,000	NATSAL, ONS
Proportion of past MSM	-	0.0662	0.2758	NATSAL
Ageing rate per year	a	0.0523	0.0261	NATSAL, ONS
Growth rate per year	g	0.0043	0.0056	NATSAL, ONS
Mortality rate per year				
HIV-negative MSM	μ	0.00094	0.00449	NATSAL, ONS
HIV-positive MSM	μ	0.00843	0.00899	Assumed [a]

[a] Assumed based on findings from ref [71]

4.3.1.2. Rate of ageing

The annual ageing rate equals the proportion of individuals at the maximum age in each age group. Since the age distribution of UK MSM populations was not available, I assumed that of the UK male population instead. The 2000–2020 estimated proportions of men aged 34 and 64 to all men aged 15-34 and 35-64, respectively, were obtained from the ONS projections [72]. The average proportions over the entire simulation period were 5.23% and 2.61% for younger and older groups (Table 4-5). These proportions were held constant at all time throughout model simulations.

4.3.1.3. Population growth rate

I assumed that size of the two age groups changes over time at the same rate as the general UK male populations of the same age group. The growth rate was derived by averaging the annual growth rates of men over 2000–2020. The average rate was estimated at 0.51% per year for all MSM populations (Table 4-5). The estimated growth rate of the younger age group (0.43%) was used for calculating the influx into the model of new MSM, while the rate of the older age group (0.56%) was used for validating the size of the modelled populations over time (see Chapter 5 for details).

4.3.1.4. Mortality rate

The mortality rates for HIV-negative MSM were derived based on the mortality rates of the overall UK males. Age-specific data were obtained from the historic interim life tables for three periods (1999–2001, 2002–2004, and 2005–2007) reported by ONS [73]. The data were averaged over the three periods and converted into 5-year age-specific mortality rates to match the previously defined age distribution of MSM (Table 4-3). Multiplying the age distribution with the mortality rates of the corresponding age group provided the rate by 5-year age band which were then collapsed into the two age groups using an arithmetic mean (Table 4-5).

For HIV-positive men, a study by UK Collaborative HIV Cohort [71] estimated that, depending on various factors, the mortality rates could increase from less than 1.1 to nearly 10 times due to HIV. The effect is more pronounced for younger age groups (age 20-44) compared to the overall. Based on this information, I arbitrarily assumed that the death rates in the first and second age group increased by 9 and 2 times, respectively (Table 4-5), which applied only to treated MSM in the model since the majority of deaths in HIV-positive MSM in the UK occurred after they have been diagnosed and treated with antiretroviral treatment (ART) in late disease stages [2,70]. Table 4-5 summarises all derived demographic parameter values.

4.3.2. Sexual behaviour

The three main sources of data for deriving sexual behaviour parameters were NATASL, GMSHS, and GYM survey. Although the national-based probability-sampling NATSAL survey was the primary source, I were unable to derive all parameters based on this survey alone due to the small sample size of MSM and lack of some required information. GMSHS and GYM were used when needed. Most sexual behaviour parameters were stratified by age and sexual activity levels simultaneously unless stated otherwise. Uncertainty ranges of parameters that later fitted to the data were also derived.

4.3.2.1. Sexual activity level

Before deriving sexual behavioural parameters, survey respondents were stratified into two activity groups—low and high—according to the reported number of male sexual partners in the last year. The risk groups were defined based on three conditions. First, the low-activity men have a similar rate of partner change to the average of UK heterosexual male [57] which helped distinguish MSM with normal risk from the whole MSM population. Second, MSM in the low-activity group have no more than one sexual partner at a time. This was to ensure that a low-activity individual can never get infected from having a concurrent relationship. Third, the proportion of any risk groups must be greater than 25% because modelling sexual mixing between two groups that differ greatly in size could be problematic. The number of individuals in the smaller group may be insufficient to satisfy the demand for sexual partners from within and outside the group. Consequently, one male sexual partner in the last year was chosen as a cut-off point: low-activity MSM reported one or no male partner in the last year, high-activity MSM reported two or more male partners in the last year. Observations with missing values for the variable were removed from the stratification, and excluded from any further calculations that must be stratified by sexual activity level. Information on the number of male sexual partners in the last year was not available from GYM. Instead, I used the reported number of male anal-sexual partners in the past 12 months and stratified GYM participants using the same cut-off point. The numbers of MSM by sexual activity level are shown in Table 4-6.

Table 4-6: Number of MSM stratified by sexual activity level

MSM	Aged 16-34	%	Aged 35-64	%	Total	%
NATSAL						
Low	50.3	50.3	29.4	55.1	79.7	52.0
High	49.7	49.7	24.0	44.9	73.7	48.0
Total	100.0	100.0	53.4	100.0	153.4	100.0
GMSHS						
Low	4943.9	54.1	3692.1	56.8	8636	55.2
High	4195.4	45.9	2809.4	43.2	7004.8	44.8
Total	9139.3	100.0	6501.5	100.0	15640.8	100.0
GYM						
Low	608.7	29.9	607.0	35.9	1215.7	32.6
High	1425.7	70.1	1084.6	64.1	2510.3	67.4
Total	2034.4	100.0	1691.6	100.0	3726.0	100.0

Table 4-7: Sexual behaviour parameters

Parameter	Symbol	Value				Source
		Aged 15-34		Aged 35-64		
		Low-activity	High-activity	Low-activity	High-activity	
Repeat sexual partnership						
Rate of repeat sexual partnership formation per year	ρ^{rep}	0.422 (0.405-0.438)	3.135 (2.761-3.509)	0.458 (0.438-0.478)	2.719 (2.445-2.994)	GMSHS
Gap length between two consecutive repeat sexual partnerships (days)	G	178	33	178	33	NATSAL
Rate of repeat sexual partnership dissolution per year	σ	0.530	4.372	0.590	3.604	Calculated
Proportion of repeat sexual partnerships that involve anal sex to all repeat sexual partnerships	p^{rep}_{anal}	0.958 (0.948-0.969)	0.706 (0.690-0.723)	0.879 (0.859-0.899)	0.643 (0.620-0.665)	GMSHS
Proportion of repeat sexual partnerships that involve oral sex to all repeat sexual partnerships	$1-p^{rep}_{anal}$	0.042	0.294	0.121	0.357	GMSHS
Proportion of susceptibles who have UAI with a perceived HIV negative repeat sexual partner [a]	$p^{rep}_{uai,pneg}$	0.369-0.657	0.328-0.556	0.288-0.548	0.231-0.426	GYM
Proportion of susceptibles who have UAI with a diagnosed HIV positive repeat sexual partner [b]	$p^{rep}_{uai,dpos}$	0.194-0.601	0.041-0.144	0-0.267	0-0.111	GYM
Frequency of sexual acts with a repeat sexual partner per week	φ	1.49-3.56	1.49-3.56	1.03-2.03	1.03-2.03	NATSAL
Proportion of UAI acts to all sex acts in UAI repeat sexual partnership	-	1.00	1.00	1.00	1.00	Assumed
Effects of HIV diagnosis on the proportion of UAI acts	-	0.3	0.3	0.3	0.3	[74]
One-off sexual partnership						
Rate of one-off sexual partnership formation per year						

Parameter	Symbol	Value				Source
		Aged 15-34		Aged 35-64		
		Low-activity	High-activity	Low-activity	High-activity	
MSM without a repeat sexual partner	ρ_{Y}^{one}	0.255 (0.218-0.291)	10.019 (6.235-13.803)	0.390 (0.342-0.438)	9.260 (6.343-12.178)	GMSHS
MSM with a repeat sexual partner	ρ_{P}^{one}	-	8.960 (7.675-10.246)	-	8.219 (6.841-9.596)	GMSHS
Proportion of one-off sexual partnerships that involve anal sex to all one-off sexual partnerships						
MSM without a repeat sexual partner	$p_{anal,Y}^{one}$	0.905	0.607	0.769	0.495	GMSHS
MSM with a repeat sexual partner	$p_{anal,P}^{one}$	-	0.547	-	0.518	GMSHS
Proportion of one-off sexual partnerships that involve oral sex to all one-off sexual partnerships						
MSM without a repeat sexual partner	$1-p_{anal,Y}^{one}$	0.095	0.393	0.231	0.505	GMSHS
MSM with a repeat sexual partner	$1-p_{anal,P}^{one}$	-	0.453	-	0.482	GMSHS
Proportion of susceptibles who have no UAI with a one-off sexual partner (Group A)						
MSM without a repeat sexual partner	$p_{A,Y}^{one}$	0.321	0.477	0.364	0.573	GMSHS
MSM with a repeat sexual partner	$p_{A,P}^{one}$	-	0.596	-	0.599	GMSHS
Proportion of susceptibles who have UAI only with a perceived HIV negative one-off sexual partner (Group B)						
MSM without a repeat sexual partner	$p_{B,Y}^{one}$	0.449	0.167	0.338	0.071	GMSHS
MSM with a repeat sexual partner	$p_{B,P}^{one}$	-	0.184	-	0.166	GMSHS

Parameter	Symbol	Value				Source
		Aged 15-34		Aged 35-64		
		Low-activity	High-activity	Low-activity	High-activity	
Proportion of susceptibles who have UAI with a diagnosed HIV positive one-off sexual partner (Group C)						
MSM without a repeat sexual partner	$p^{one}_{C,Y}$	0.230	0.356	0.298	0.357	GMSHS
MSM with a repeat sexual partner	$p^{one}_{C,P}$	-	0.220	-	0.234	GMSHS
Proportion of UAI one-off sexual partners in Group B						
MSM without a repeat sexual partner	$p^{one}_{uai,Y,B}$	1.000	0.535	1.000	0.844	GMSHS
MSM with a repeat sexual partner	$p^{one}_{uai,P,B}$	-	0.695	-	0.673	GMSHS
Proportion of UAI one-off sexual partners in Group C						
MSM without a repeat sexual partner	$p^{one}_{uai,Y,C}$	1.000	0.566	1.000	0.624	GMSHS
MSM with a repeat sexual partner	$p^{one}_{uai,P,C}$	-	0.578	-	0.559	GMSHS
Sexual roles						
Proportion of insertive acts in an anal-sex partnership	p_{ins}	0.5	0.5	0.5	0.5	Assumed [c]
Proportion of receptive acts in an anal-sex partnership	$1-p_{ins}$	0.5	0.5	0.5	0.5	Assumed [c]
Proportion of UROI acts in an oral-sex repeat sexual partnership	p^{ste}_{uroi}	1.0	1.0	1.0	1.0	Assumed
Proportion of UROI acts in an oral-sex one-off sexual partnership	p^{cas}_{uroi}	0.139	0.249	0.228	0.259	GYM

Parameter	Symbol	Value				Source
		Aged 15-34		Aged 35-64		
		Low-activity	High-activity	Low-activity	High-activity	
Sexual contact mixing						
Mixing odds ratio						
By age group	w_{age}	4.2				NATSAL
By sexual activity level	w_{sex}	3.0				[75]
By HIV serostatus	w_{hiv}	2.3				GYM

NATSAL: The National Survey of Sexual Attitudes and Lifestyles
GMSHS: The Gay Men's Sexual Health Survey
GYM: The London Gym Survey
UAI: Unprotected anal intercourse
UROI: Unprotected receptive oral intercourse
The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting.
[a] Perceived HIV negative stages include stage S, U1, U2, U3, U4, and U5
[b] Diagnosed HIV positive stages include stage D1, D2, D3, D4, D5, and T
[c] Assumed based on findings from ref [76], GMSHS, and GYM data

4.3.2.2. Rate of partnership formation

The rate of partnership formation was calculated from the reported number of male sexual partners in the last year categorising into repeat sexual and one-off sexual partners. GMSHS provided information that matched the previously defined definitions of partnership type (Section 3.4.4) and was hence used. The mean repeat sexual partnership formation rate of high-activity MSM is approximately seven times higher than that of the low-activity (Table 4-7). For one-off sexual partners, respondents were also stratified into those who are currently having a repeat sexual partner or not by assuming that individuals having concurrent relationships are those who reported both steady and casual partners in the last year. According to the definition of risk group, only high-activity MSM can have a one-off sexual partner while in a relationship with a repeat sexual partner. Both repeat sexual and one-off sexual partnership formation rates were included in the model fitting with the ranges derived from the 95% confidence interval of the GMSHS data. All derived rates are summarised in Table 4-7.

4.3.2.3. Rate of repeat sexual partnership dissolution

This began by finding the gap duration between two consecutive non-concurrent repeat sexual partnerships. NATSAL provided date (in month) of the first and last sex acts for the three most recent partners. Gap length was defined as time between the first sex act with the most or second most recent partner and the last sex act with the second or third most recent partner, respectively. A gap length of 15 days was assumed for those who reported the same month for the end of last relationship and the start of new relationship. I excluded any concurrent relationships from the calculation and derived the median gap duration by sexual activity level only due to the small number of cases. The results suggested that, after pair separation, low-activity MSM tend to stay single for a much longer period than the high-activity MSM before acquiring a new repeat sexual partner (Table 4-7).

With the above gap lengths, I calculated the mean duration of repeat sexual partnership as follows:

$$\sigma = \frac{1}{\rho} - G \tag{75}$$

where ρ is the repeat sexual partnership formation rate and G is the gap length. The rate of repeat sexual partnership dissolution was then derived from the inverse of repeat sexual partnership duration. The results are shown in Table 4-7.

4.3.2.4. Proportion of anal-sex and oral-sex partnerships

In order to model HIV infection via oral and anal sex separately, the model required the proportions of repeat sexual and one-off sexual partnership that involves anal sexual intercourse. This was estimated from GMSHS data by dividing the number of male anal-sexual partners by the total number of male sexual partners in the last year of the same partnership type. Table 4-7 shows the point and 95% CI estimates of the mean proportions of anal-sex repeat sexual partnership of around 90% for low-activity and 70% for high-activity MSM. This seems plausible since the high-activity MSM are able to have an anal-sex relationship with a one-off sexual partner while in a repeat sexual relationship.

Based on the assumption that all sexual intercourses in non-anal sex relationships were oral sex, subtracting the anal-sex proportion from one resulted in the proportion of oral-sex partnerships (Table 4-7). All oral sexual intercourses that might occur in an anal-sex partnership were ignored because the risk of HIV transmission through oral sex is much less than that of anal sex [33].

4.3.2.5. Unprotected sexual intercourse

There are a number of parameters related to unprotected anal intercourse (UAI) including proportion of UAI acts, proportion of susceptibles who perform UAI acts, and proportion of sexual roles—insertive and receptive act. All must be distinguished between repeat sexual and one-off sexual partnerships. For repeat sexual partnerships,

the first two parameters are the proportion of susceptibles who have UAI with a perceived HIV negative repeat sexual partner to all susceptibles who have a perceived HIV negative repeat sexual partner, and the proportion of susceptibles who have UAI with a diagnosed HIV positive repeat sexual partner to all susceptibles who have a diagnosed HIV positive repeat sexual partner. The perceived HIV negative partner included all those partners that have never been diagnosed with HIV. Data were available in the GYM survey. I selected only respondents who reported anal sex in the past 12 months and disclosed the perceived serostatus of their repeat sexual partner. Since this is the proportion of susceptibles only, those who tested HIV positive were excluded. Although some of the selected respondents may have been infected with HIV but were unaware of the infection, this was unlikely to add bias to the data since their sexual behaviour should remain unchanged. The mean estimates of the proportion were derived from dividing the number of respondents who reported UAI with perceived HIV negative regular partners in the past 3 months by the total number of those who had perceived HIV negative regular partners (Table 4-7). The same method was applied to a repeat sexual partner of diagnosed HIV positive status. The inconsistency in the definitions of sexual partner used in the GYM survey (survey-participant-defined regular partner) and this study (repeat sexual partner) may result in an increased uncertainty of the derived parameters. Subsequently, I arbitrarily expanded the derived lower limit of both parameters by 30% due to the fact that UAI should be less likely in a relationship that is more casual which is a part of the repeat sexual partnership. These two parameters were later assigned the uniform distribution and included in parameterisation by model fitting. Details are shown in the next chapter.

I further assumed that, in a pair of repeat sexual partners between susceptibles and undiagnosed MSM with UAI, all sex acts are UAI of which 50% were insertive acts. This was supported by GMSHS and GYM data that suggested that, on average, MSM across age group and sexual activity level performed versatile sexual roles with their regular partner. For a pair between susceptibles and diagnosed MSM, the proportion of UAI acts was reduced by 70% according to the findings from the meta-analysis study

of high-activity sexual behaviour in HIV-positive individuals in the United States [74]. The reduction in UAI acts was then added to safe sex to maintain the constant number of acts across all groups and time period. See Table 4-7 for summary of the parameter values.

For one-off sexual partnerships, susceptibles were categorised into: A) MSM who had no UAI with a one-off sexual partner, B) MSM who had UAI only with a perceived HIV negative one-off sexual partner, and C) MSM who had UAI with a diagnosed HIV positive one-off sexual partner. The proportions for these three groups were estimated using GMSHS data. This started from dividing perceived HIV negative respondents into those who had or had no UAI with a one-off sexual partner. The number of MSM without UAI was used for calculating the proportion of group A. For those who reported UAI with a one-off sexual partner, if the reported number of perceived HIV negative UAI one-off sexual partners was equal to the total number of UAI one-off sexual partners, they were included in group B. And group C corresponded to those who had at least one HIV-positive one-off sexual partner. I divided all groups by their sum to obtain estimates of the proportions of men in each group (Table 4-7). Similarly to one-off sexual partnership formation rate, the estimates were calculated separately for men who had and had no repeat sexual partners in the last year.

In group B and C, the proportion of UAI was derived from the mean proportion of reported number of UAI one-off sexual partners to all one-off sexual partners in the last year. For group B, perceived HIV negative partner is from susceptible or undiagnosed HIV-infected stages only. For group C, I assumed chance of choosing one-off sexual partners of any HIV stages is proportional to the number of individuals in each stage.

Similarly to the repeat sexual partnership, I assumed 50% for insertive and receptive act for both safe and unsafe sex with a one-off sexual partner of all classes. Although, studies among MSM in Australia [77] and the United States [78] suggested that in an

unprotected anal intercourse with an HIV positive partner, MSM were more likely to perform insertive rather than receptive acts, while receptive acts were performed more frequently with a perceived HIV negative partner, this was not evident in the UK [76]. Given that the sexual act is one-off, assuming the proportion of sexual roles based either on the number of partners or the number of acts makes no differences.

Regarding oral sex, UROI with ejaculation was assumed the only type of oral intercourse that presents a risk of transmitting HIV. I further assumed UROI occurs in all sex acts with an oral-sex repeat sexual partner (Table 4-7). This may seem an extreme case, but its effect is considered minor since the HIV transmission probability of UROI is substantially lower than that of anal sex [33]. For one-off oral sex, I derived the proportion of UROI from the number of GYM men who reported UROI with a one-off sexual partner (Table 4-7). For simplicity, modelling HIV spread via one-off oral sex was carried out without categorising MSM into three groups based on serostatus of partner as previously did for the anal sex.

4.3.2.6. Frequency of sexual acts

The mean numbers of sex acts per week with a repeat sexual partner were estimated through the model fitting. I started by obtaining the plausible ranges of the parameter values from the number of occasions of sex with men in the last 4 weeks reported in NATSAL. I selected only the respondents who, in the last 4 weeks, had only one male partner of any types. Due to a small number of eligible cases, the derived estimates could only be stratified by age groups which led to identical ranges for both sexual activity levels in the same age groups. The sampling distribution of the parameter in the fitting process was assumed uniform and the sampled values were allowed to vary independently by both age groups and sexual activity levels. Table 4-7 summarises the derived estimates.

4.3.2.7. Sexual mixing preference

In this model, mixing preferences were stratified by age group, sexual activity level, and perceived HIV serostatus. All are modelled using the odds ratio in a 2-by-2 mixing matrix [48,60].

NATSAL included information on mixing by age. However, the age cut-off point must be adjusted specifically for this calculation due to the small number of cases. Therefore, a median age of 28 was used as a new cut-off point for age stratification. To construct a mixing matrix by age, respondents were divided by their age and the age of their most recent partner on the first sex. For the younger group (under 28 years of age), 72% selected a partner in the same age group, while only 37% of the older group (28 years of age or more) did that. The corresponding odds ratio was 4.2 (Table 4-7) which indicated that MSM are 4.2 times more likely to choose a partner of the same age group than when choosing randomly (a proportionate mixing).

With insufficient data available to inform the mixing preference by sexual activity level of MSM in the UK, I adopted the estimated odds ratio of 3.0 of male heterosexuals in London [79] (Table 4-7).

The perceived HIV serostatus was divided into perceived HIV negative and diagnosed HIV positive status. The perceived negative status included non-infected and undiagnosed HIV-infected MSM. The diagnosed positive status included all MSM with diagnosed HIV. From the reported HIV status of GYM men and their regular partner, the odds ratio of 2.3 was estimated (Table 4-7). Mixing by the perceived HIV serostatus using odds ratio was only applied to a repeat sexual partner selection. A different method was used to model the effects of one-off sexual partner's serostatus and the proportion of UAI (serosorting). See Section 3.5.10 for more details of the method.

4.3.3. HIV transmission probability

To estimate the per-sex act probability of HIV transmission among MSM, sex acts were categorised according to the sexual types and roles existing in the model—insertive and receptive anal sex, and receptive oral sex. Each of these was divided into protected and unprotected acts according to condom use. Changes in HIV transmission due to disease progression on the basis of CD4 cell counts were included. The very low, but non-zero, HIV transmission probabilities of ART-treated MSM were calculated separately and allowed to change over time to reflect an increase in ART effectiveness on infectiousness reduction and improved drug adherence among HIV-infected patients. The main calculation steps were calculating the relative risks of HIV infection of the viral load of interest to the baseline viral load. The derived relative risks were then applied to the baseline transmission probability obtained from literature review to estimate the infectiousness according to viral load. Finally, the proportion of men by viral load in each CD4 stage was multiplied to the above transmission probability to provide the final per-act HIV transmission probability.

I started by analysing the viral load data from the survey of diagnosed HIV-infected MSM seen for HIV-related care at clinics in the UK [67] from 2005 to 2009. Only individuals who have never been treated with ART were selected and their reported viral load at that clinic visit was divided into five ranges: 0-399, 400-999, 1000-9999, 10000-49999, and 50000+ copies/mL of blood plasma, and the CD4 counts at the same visit into four ranges: <200, 200-349, 350-499, and ≥500 cells/µL. If there were more than one record of viral load in each CD4 stage, only the latest one available was used. The proportions of men by viral load ranges in each CD4 stage were then calculated (Table 4-8). It is clearly seen that in the lower CD4 stages, the proportion of men with high viral load is markedly higher than in higher CD4 stages. For example, 55% of MSM with CD4<200 cells/µL had viral load of 50000+ copies/mL while there were only 23% among MSM with CD4≥500 cells/µL. The uncertainty in these proportions were taken into account by running 10,000 simulations for each CD4 stage based on multinomial distribution with the number of cases parameter equals to the

number of included SOPHID respondents and the event probability parameter equals the average proportions. I then derived a median viral load to represent the five viral load ranges (Table 4-8). The CD4 stratification was neglected at this point because the minor effects it had on the derived median estimates.

Table 4-8: Data used for calculating HIV transmission probability of MSM who have never been treated with antiretroviral treatment

Description	Viral load (copies/mL)				
	0- 399	400-999	1,000-9,999	10,000-49,999	50,000+
Median viral load (copies /mL) [a]	49	1,690	6,234	22,948	102,077
Proportion of men by viral load in each CD4 stage [a]					
CD4 ≥ 500	0.1051	0.1700	0.1763	0.3219	0.2267
CD4 350-499	0.0700	0.1133	0.1487	0.3552	0.3129
CD4 200-349	0.0830	0.0840	0.1168	0.3341	0.3821
CD4 < 200	0.1085	0.0814	0.0492	0.2136	0.5475
HIV transmission probability (%) [b]					
URAI	0.135 (0.019-0.241)	0.535 (0.076-0.956)	0.889 (0.127-1.588)	1.477 (0.211-2.637)	2.640 (0.377-4.714)
UIAI	0.060 (0.007-0.162)	0.237 (0.027-0.642)	0.394 (0.044-1.067)	0.654 (0.074-1.772)	1.169 (0.132-3.168)
UROI	0.004 (0.001-0.016)	0.015 (0.004-0.065)	0.025 (0.006-0.108)	0.042 (0.011-0.179)	0.075 (0.019-0.321)

URAI: Unprotected receptive anal intercourse
UIAI: Unprotected insertive anal intercourse
UROI: Unprotected receptive oral intercourse
The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting.
[a] Estimated from SOPHID 2005–2009 data
[b] Not the final transmission probability

The baseline transmission probabilities per an unprotected receptive anal intercourse (URAI) act of 1.4% (0.2-2.5) suggested by Baggaley et al based on systematic review and meta-analysis were used [80]. For an unprotected insertive anal intercourse (UIAI) act, the estimates of 0.62% (0.07-1.68) from the cohort study among homosexual men in Sydney was adopted [81]. I used per an unprotected receptive oral intercourse (UROI) contact risk of 0.04% (0.01-0.017) suggested by Vittinghoff et al [33]. The viral load associated with the above baseline transmission probabilities was assumed

20,000 copies/mL which was derived from the median viral load of the survey participants who have never been on ART.

I then described the relationship between transmission probability and plasma viral load according to the function proposed by Smith & Blower [82], following the original notations, as:

$$\beta(v) = 2.45^{\log_{10}(v/w)}\beta(w) \tag{76}$$

where w is the initial viral load which, in this case, is the viral load of the baseline transmission probability, v is the viral load of interest, $\beta(v)$ and $\beta(w)$ are transmission probability at the corresponding viral load v and w. The lower and upper bound were derived from the corresponding limits of the baseline per-act transmission probability (Table 4-8). Based on these boundaries, I sampled from the beta distribution and produced 10,000 sets of per-act transmission probability by viral load for each CD4 stage. Multiplying these 10,000 samples with the previously sampled proportion of individuals by viral load in each CD4 stage, I obtained the combined sets of simulation results which were then used for deriving the median and 2.5^{th} and 97.5^{th} percentiles as lower and upper estimates of the final per-act transmission probabilities. The infectiousness of primary HIV infection (PHI) was estimated by applying a relative risk of 9.17, suggested by Boily et al [83], to the baseline transmission probabilities. All derived estimates are summarised in Table 4-9.

Table 4-9: Estimated per-act HIV transmission probability

HIV transmission probability (%)	Type of sexual act					
	URAI	Symbol	UIAI	Symbol	UROI	Symbol
ART-naïve MSM						
PHI	12.838 (1.834-22.925)	$\beta_{urai,2}, \beta_{urai,3}$	5.685 (0.642-15.406)	$\beta_{uiai,2}, \beta_{uiai,3}$	0.367	$\beta_{uroi,2}, \beta_{uroi,3}$
CD4 ≥ 500	1.336 (0.191-2.386)	$\beta_{urai,4}, \beta_{urai,5}$	0.592 (0.067-1.603)	$\beta_{uiai,4}, \beta_{uiai,5}$	0.038	$\beta_{uroi,4}, \beta_{uroi,5}$
CD4 350-499	1.553 (0.222-2.773)	$\beta_{urai,6}, \beta_{urai,7}$	0.688 (0.078-1.863)	$\beta_{uiai,6}, \beta_{uiai,7}$	0.044	$\beta_{uroi,6}, \beta_{uroi,7}$
CD4 200-349	1.662 (0.237-2.968)	$\beta_{urai,8}, \beta_{urai,9}$	0.736 (0.083-1.995)	$\beta_{uiai,8}, \beta_{uiai,9}$	0.047	$\beta_{uroi,8}, \beta_{uroi,9}$
CD4 < 200	1.863 (0.266-3.326)	$\beta_{urai,10}, \beta_{urai,11}$	0.825 (0.093-2.235)	$\beta_{uiai,10}, \beta_{uiai,11}$	0.053	$\beta_{uroi,10}, \beta_{uroi,11}$
ART-treated MSM						
Before 2005	0.363 (0.229-0.558)	$\beta_{urai,12}$	0.158 (0.072-0.303)	$\beta_{uiai,12}$	0.009	$\beta_{uroi,12}$
Changes per year during 2005–2009 [a]	-0.039	-	-0.016	-	-0.001	-

URAI: Unprotected receptive anal intercourse
UIAI: Unprotected insertive anal intercourse
UROI: Unprotected receptive oral intercourse
PHI: Primary HIV infection
The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting.
[a] HIV transmission probability after 2009 was assumed equal to that of 2009.

For HIV transmission probability of ART-treated MSM, only MSM in the UK who have ever been treated with ART were included in the calculation. A decrease over time in the derived per-act transmission probabilities was incorporated into the model. To achieve that, I fitted a linear function to the proportions of MSM by viral load, CD4 stages, and calendar year simultaneously and estimated an average changes over 2005–2009 in these proportions. The proportions before 2005 was assumed equal to that of 2005, and for the period after 2009 the same probabilities as of 2009 was assumed. The rest of the calculations were carried out in the same manner to that of ART-naïve MSM. I derived annual change rate in transmission probabilities by subtracting the linear estimates of the any calendar year by estimates of the immediate previous year. In the fitting process (Chapter 5), a lowest ART transmission probability of 0.001% was set for all types of sex acts to prevent the zero or negative values. The derived probabilities of transmitting HIV from ART-treated MSM and the changes over time are reported in Table 4-9.

The effects of circumcision were not included according to a recent study that found no evidence to support the effects of circumcision in reducing HIV transmission risk among MSM in Britain [84]. I also decided not to include the effects of STIs in the model due to a lack of evidence to support that STIs are risk factors for HIV transmission among MSM [85,86].

The average efficacy of condom at reducing transmission of HIV among MSM was taken from the meta-analysis estimates of the efficacy in reducing heterosexual HIV transmission [87-89]. I assumed the per-act efficacy of 80% and the lower and upper limit of 75-95% (Table 4-10). The estimates were adopted only for anal sexual intercourses. No risk of HIV infection for all types of oral sex with condom use was assumed.

Table 4-10: Condom efficacy in preventing HIV transmission

Parameter	Symbol	Value	Source
Condom efficacy per sexual act	ε_{cdm}	0.80 (0.75-0.95)	Assumed [a]

The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting.
[a] Assumed based on findings from ref [87-89]

4.3.4. HIV diagnosis rate

The rate of HIV diagnosis controls the number of MSM moving from undiagnosed to diagnosed stages in each time step. I defined time-dependent HIV diagnosis rates by assuming increasing rates over 2000–2004 according to the rise in the reported number of new diagnoses during that period [66]. The initial diagnosis rate as of the year 2000 increased by a constant rate of changes until the end of 2004 and remained unchanged until the end of the simulation.

The HIV diagnosis rates will be estimated through model fitting in the next chapter based on uninformative uniform priors. In this chapter, only the lower and upper estimates were derived from the reported numbers of new diagnoses by age and CD4

cell counts over 2000–2009. The effects of sexual activity level were also taken into account in this step.

The baseline rates of diagnosis with HIV in UK MSM were calculated by dividing the reported number of new diagnoses by the estimates of undiagnosed HIV prevalence with 95% credible intervals which were available from 2001 to 2007 [54,90]. Since the 2000 estimates of undiagnosed prevalence were not available, the 2001 estimates were used which provided the baseline rates of 0.15 to 0.27 per year. According to the reported median CD4 at diagnosis of UK MSM of 366 cells/µL in 2001, I assumed the above baseline diagnosis rates for HIV-positive MSM at CD4 350-499 cells/µL in the model.

I then reduced the lower and upper limits of the initial rates by 30% to account for three main uncertainties. First, the initial rates are likely to be lower if the 2000 estimates of undiagnosed prevalence were made available and used. Second, the difference in the age ranges which were 15-59 years for the reported undiagnosed prevalence and 15-64 years in this model should decrease the rates. Third, it is more likely for HIV-positive MSM at CD4 350-499 cells/µL to have lower average diagnosis rates than the baseline because the median CD4 at diagnosis of UK MSM is almost out of the lower range of the CD4 stage. Based on the fact that the diagnosis rates could vary substantially across different disease stages with a very low rate during PHI to a much higher rate in an advanced HIV stage [91], I allowed initial diagnosis rates to increase by 0.05–0.15 per a CD4 stage advanced in disease progression.

Data from all three behavioural surveys (NATSAL, GMSHS, and GYM) surveys showed that, regardless of age group, high-activity MSM tested for HIV considerably more frequently than low-activity men. The diagnosis rates were allowed to differ between low- and high-activity men according to the differences in frequency of HIV testing from the survey data. I analysed the reported time of the last HIV test from NATSAL and arbitrarily assumed that individual tests every 12 months if he reported

last test in the last year, 24 months for 1-2 years ago, and 60 months for 2-5 years ago. The rates of diagnosis were calculated as an inverse of the assumed frequencies of testing. Those who have tested more than 5 years ago or never had an HIV test were assigned a rate of zero. This resulted in an average testing rate of high-activity MSM that was 2.5-fold higher than that of low-activity MSM. Conducting the similar analysis on GMSHS and GYM data yielded estimates of 1.70 and 1.78, respectively. Furthermore, the analysis also suggested that this ratio tended to remain unchanged over time. I therefore assumed a range of 1 (no difference) through 3 for this ratio which, in the next step of model fitting, will be applied to the initial diagnosis rate to calculate diagnosis rates by sexual activity level. The derived initial diagnosis rates are summarised in Table 4-11.

Table 4-11: HIV diagnosis parameters

Parameter	Symbol	Value
Initial HIV diagnosis rates per year [a]	ϕ	0.102-0.191
Ratio of diagnosis rate of high-activity to low-activity MSM [b]	-	1-3
Increase in initial diagnosis rates per a CD4 stage [c]	-	0.05-0.15
Changes per year in HIV diagnosis rate during 2000–2004 [d]	$\Delta\phi$	0.001-0.0339
Proportion of MSM who change sexual activity group after HIV diagnosis		
From low-activity to high-activity group	s_1	0.07
From high-activity to low-activity group	s_2	0.66

Identical interval estimates of HIV diagnosis rate for MSM of different sexual activity level, age group, and disease stage were assumed. The interval estimates in this table will be used for constructing uniform priors used for estimating the diagnosis rates via model fitting.
[a] At the beginning of year 2000; for MSM at CD4 350-499 cells/µL
[b] Derived from NATSAL, GMSHS, and GYM data
[c] An absolute increase of the corresponding rates
[d] The lower bound was assumed 0.001 and the upper bound was derived from simulations based on uniform distribution.

The change rates per year were derived by conducting 10,000 simulations and uniformly drew from the interval estimates of the 2001–2004 baseline diagnosis rates. For each simulation, subtracting the rates of all calendar year by the rates of the immediate previous year provided the changes of rate over time that were further used for calculating the average changes for the period. The 2.5th and 97.5th percentiles of

these averages were -0.014 to 0.034. According to the reported numbers of new HIV diagnoses in MSM in the UK [66], it is unlikely that the diagnosis rates had decreased in that period, and hence the negative value was replaced with a very small positive value (0.001) for the lower limit of the change rates. No differences by CD4 stages and sexual activity levels were included. The derived estimates for changes over time in diagnosis rates are shown in Table 4-11.

I estimated the effects of HIV diagnosis on sexual activity level from a cohort study of 98 UK MSM [75]. The findings suggested that around 66% of MSM reduced the number of casual partners in the past 12 weeks after diagnosis of PHI while only 7% reported more casual partners. These percentages were used as the proportions of MSM who change sexual activity level after HIV diagnosis (Table 4-11).

4.3.5. Rate of initiating HIV treatment

The rate of diagnosed HIV-positive MSM starting an HIV treatment was taken from the UK Collaborative HIV Cohort (CHIC) Study [92] which provided the per 3-month period estimates by CD4 counts that ranged from 0.005 for CD4 350-499 cells/µL to 0.95 for CD4<100 cells/µL. The rates were derived based upon the guidelines regarding time to initiate HIV treatment in the UK [59]. Starting ART at CD4≥500 cells/µL is rather unusual; therefore, an assumption was made that the treatment initiation rate for MSM at CD4≥500 cells/µL is as low as 10% of those with CD4 350-499 cells/µL. For CD4 200-349 cells/µL, I used an average derived from the rates of CD4 200-249, 250-299, and 300-349 cells/µL. For those with CD4<200 cells/µL, an average rate of CD4 0-99 and 100-199 cells/µL was used (Table 4-12). There was no ART initiation during PHI due to a small number of cases.

Table 4-12: Rate of initiating HIV treatment

Parameter	Symbol	Value
Rate before 1st January 2009 (per year)		
CD4 ≥ 500	τ_5	0.002
CD4 350-499	τ_7	0.02
CD4 200-349	τ_9	1.80
CD4 < 200	τ_{11}	3.80
Rate from 1st January 2009 onwards (per year) [a]		
CD4 ≥ 500	τ_5	0.02
CD4 350-499	τ_7	1.80
CD4 200-349	τ_9	3.80
CD4 < 200	τ_{11}	3.80

HIV treatment during primary HIV infection was omitted from the model.
[a] Revised due to an increased ART initiation threshold [59]

4.3.6. Disease progression

The disease progression rate for each CD4 stage is equal to the inverse of the mean duration of that stage. I adopted the estimates provided by a study [93] that fitted a multistate Markov model to the historical CD4 data from the CASCADE database [94]. The study estimated an average time spent in each CD4 stage that is equivalent to a total time from seroconversion to AIDS of 8.6 years [93]. For PHI, I assumed according to Hollingsworth et al [95] a duration of 3 months with a range from 1 to 6 months and estimated this parameter via model fitting. All derived disease stage durations are shown in Table 4-13.

Table 4-13: Duration of HIV stages

Parameter	Symbol	Value (months)
PHI to CD4 ≥ 500	$1/\gamma_2, 1/\gamma_3$	2.90 (1.24-6.00)
CD4 ≥ 500 to 350-499	$1/\gamma_4, 1/\gamma_5$	67.27
CD4 350-499 to 200-349	$1/\gamma_6, 1/\gamma_7$	23.92
CD4 200-349 to < 200 [a]	$1/\gamma_8, 1/\gamma_9$	20.12

PHI: Primary HIV infection
The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting. An inverse of the above stage durations is the disease progression rates used in the model.
[a] In the model, individuals remained in the stage of CD4<200 cells/µL until they are either diagnosed, treated with ART, or removed from the model.

4.3.7. Initial population size

The initial MSM population size in the UK of the year 2000 (Section 4.3.1) was stratified according to various modelled subpopulations to form the initial size of each subgroup. Range of parameters that later fitted to the data were also derived. I began with stratification by HIV serostatus, HIV negative and positive. The 2000 UK annual HIV report [96] provided the estimated number of MSM aged 15-59 living with HIV in the UK at the end of 1999 of 17,200 which corresponded to the overall HIV prevalence of approximately 3.5%. The interval estimates were not provided so I selected the lower limit of 2.5% and the upper limit of 4.5% (Table 4-14). In the model fitting in the next chapter, these interval estimates were assigned to the low-activity men, of which I sampled the HIV prevalence parameters independently by age groups from the uniform distribution.

Table 4-14: Data used for constructing initial numbers of MSM by subgroups

Description	Value
HIV prevalence [a]	
Baseline estimates [b]	0.025-0.045
Multiplicative factor for high-activity group	1-2
Proportion of undiagnosed HIV to all HIV-positive MSM	
Undiagnosed proportion for age group 1	0.26-0.57
Undiagnosed proportion for age group 2	0.18-0.40
Multiplicative factor for high-activity group	1-2
Proportion distribution of diagnosed MSM by disease stage [c]	
PHI	0.01
CD4 ≥ 500	0.42
CD4 350-499	0.27
CD4 200-349	0.21
CD4 < 200	0.09
Proportion distribution of undiagnosed MSM by disease stage [c]	
PHI	0.02 (0.01-0.04)
CD4 ≥ 500	0.50 (0.40-0.60)
CD4 350-499	0.28 (0.18-0.38)
CD4 200-349	0.15 (0.05-0.25)
CD4 < 200	0.05 (0.02-0.08)
Proportion of ART-treated MSM to all diagnosed MSM	0.75
Proportion of past MSM to all MSM by HIV status	
Susceptibles	
Aged 15-34	0.066
Aged 35-64	0.276
Undiagnosed HIV	0.028
Diagnosed HIV	0.025
Proportion of single MSM to all current MSM by class [e]	
Aged 15-34	
Low-activity	0.463
High-activity	0.530
Aged 35-64	
Low-activity	0.334
High-activity	0.493

PHI: Primary HIV infection

The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting.

[a] At the beginning of year 2000; assumed for MSM at CD4 350-499 cells/µL

[b] Assumed for low-activity MSM in model fitting.

[c] The sum of proportions equals one.

[d] Single MSM are men who are currently not in a repeat sexual relationship with a man.

The differences in HIV prevalence by sexual actively level were accounted for by applying the multiplicative factors directly to the sampled prevalence parameters of low-activity men in the same age group to obtain the estimates of high-activity men. Analysing GMSHS data revealed that the prevalence in the high-activity group was around 1.4-fold higher than that of the low-activity. I therefore assumed the range of 1 to 2 and uniformly sampled the multiplicative factors from this range for both age groups. Altogether, the initial HIV prevalence for each class could be calculated and used for estimating its values through model fitting.

HIV-positive MSM were then stratified by diagnosis status. I adopted the estimates derived from the multi-parameter evidence synthesis method (MPES) of the proportion of undiagnosed MSM aged 15-44 in the UK in 2001, 0.39 (0.32-0.47) [54], for low-activity MSM in age group 1, and the MPES estimates of MSM aged 15-59, 0.36 (0.29-0.44) [54], for age group 2. The lower and upper limits were expanded by $\pm$20% to account for the uncertainty due to inconsistencies of age range and calendar year between MPES estimates and the model requirements. For age group 2, both upper and lower limits were further reduced by 25% according to the fact that the proportion of undiagnosed infections was likely to be lower than the population average.

Similarly to the prevalence of HIV, there was a higher undiagnosed proportion in the high-activity than in the low-activity group as suggested by GMSHS data. Consequently, I accounted for the effects of sexual activity level using multiplicative term that were assumed to range between 1 and 2 (Table 4-14). During the fitting process in the next chapter, the proportions of undiagnosed HIV in low-activity men of both age groups were first sampled based on uniform priors. After that I drew the multiplicative term for effects of sexual activity level and calculated the undiagnosed proportion for all classes.

Next, the proportion of ART-treated to all diagnosed MSM was derived by dividing the reported number of MSM who have ever been on ART obtained from the SOPHID

data by the estimated number of MSM living with diagnosed HIV in 2001 [54,90]. I obtained an estimate of 75% of diagnosed MSM who have ever been treated with ART. For the remaining 25% who have never been on ART, they were split by the five CD4 stages based on the data from the CD4 cell counts database of patients seen for HIV care in the UK. At that time, the number of MSM living with diagnosed HIV during PHI should be minimal. Hence, only 1% of all diagnosed MSM was allocated to the stage of PHI.

The distribution of undiagnosed MSM by CD4 stages was adopted from a recent study on HIV incidence in MSM in England and Wales [97]. The lower and upper limits were arbitrarily assumed according to the adopted estimates (Table 4-14). The proportion of MSM in the undiagnosed PHI stage was assumed to be very low (2%). Due to a considerable uncertainty in this parameter, it was included to the model fitting and sampled from the Dirichlet distribution (Chapter 5).

Combing all the above parameters (summarised in Table 4-14) resulted in the initial total number of MSM fully stratified by age group, sexual activity, CD4 disease stage, HIV diagnosis, and ART status. I further stratified the modelled population into current and past MSM. NATSAL estimates of the proportion of past MSM were approximately 7% and 28% of all MSM in age group 1 and 2, respectively. Presanis et al [90] also provided estimates of the proportion of past MSM among undiagnosed and diagnosed HIV prevalence (Table 4-14). I combined all this information to construct the initial numbers of past MSM by age group and disease stage. Sex between men in past MSM was assumed absent and therefore stratification by sexual activity was no longer applied. The ratio between past and current MSM by age group and disease stage was captured from the initial MSM size. This ratio was used for balancing the numbers of current and past MSM in the model at every time step.

Finally, among current MSM, a group of individuals who reported as currently in a relationship with a man based on GYM data was assigned to the ‘single’ group while

the remaining men belonged to the ‘pair’ group (Table 4-14). All calculations for the initial numbers of MSM were carried out in the model fitting before simulations.

4.4. Conclusion

The majority of model parameters have been estimated in this chapter using data from various sources. The remaining parameters will be estimated through model fitting at the beginning of the next chapter.

Chapter 5

The current HIV epidemic

In this chapter:

Model fitting and validation

Answers to research questions 1 and 2

Publication:

‘Modelling the HIV epidemic among men who have sex with men in the United Kingdom: quantifying the contributions to HIV transmission to better inform prevention initiatives’

AIDS (2015)

5.1. Introduction

In this chapter, the remaining unknown parameters from the previous chapter are estimated through model fitting. The model is then validated against external data that were not used in the fitting process. The final model with complete parameter values will be used to investigate the current HIV epidemic in men who have sex with men (MSM) in the UK and address the primary research questions 1 and 2. I made projections on the future course of the HIV epidemic from 2014 to 2020 and quantified the contribution of biological and behavioural factors driving the ongoing transmission using the population attributable fractions (PAFs). The resulting paper which has been published in *AIDS* [61] is presented later in this chapter (section 5.5).

5.2. Model fitting

The model was fitted using Monte Carlo filtering method [56] to match the HIV epidemic in MSM in the UK during 2001–2009. This began by conducting preliminary one-way sensitivity analyses on all model parameters to see the effects on the model estimates of HIV prevalence. All parameter values were varied by $\pm 50\%$ and the corresponding estimates of the overall HIV prevalence at the end of 2009 were compared to that of the baseline simulation. Any parameters that caused the 2009 prevalence to change greater than 10% compared to the baseline parameters were included in the fitting. Table 5-1 summarises results from the preliminary sensitivity analysis. I manually added the one-off sexual partnership formation rates, the proportion of susceptibles who have unprotected anal intercourse (UAI) with a diagnosed HIV positive repeat sexual partner, and three key model initial conditions: the HIV prevalence, the proportion of undiagnosed prevalence, and the distribution of undiagnosed prevalence by disease stages at the beginning of 2000. The probability distributions assigned for all fitted parameters are summarised in Table 5-1. The other parameters not involved in the fitting were held constant at their baseline values.

Table 5-1: Model parameters included in the model fitting

Parameter	Effects on prevalence (%) [a]	Distribution
UIAI transmission probability	18.31	Beta
URAI transmission probability	47.40	Beta
Condom efficacy	35.63	Uniform
Rate of repeat sexual partnership formation	19.21	Beta (low-activity) and gamma (high-activity)
Rate of one-off sexual partnership formation	-	Beta (low-activity) and gamma (high-activity)
Proportion of repeat sexual partnerships that involve anal sex to all repeat sexual partnerships	50.53	Beta
Proportion of susceptibles who have UAI with a perceived HIV negative repeat sexual partner	25.10	Uniform
Proportion of susceptibles who have UAI with a diagnosed HIV positive repeat sexual partner	-	Uniform
Frequency of sexual acts with a repeat sexual partner	59.71	Uniform
HIV diagnosis rate	17.06	Uniform
Duration of PHI stage	31.37	Gamma
Initial HIV prevalence at the beginning of 2000	-	Uniform
Initial proportion of undiagnosed HIV to all HIV-positive MSM at the beginning of 2000	-	Uniform
Initial proportion distribution of undiagnosed MSM by disease stages	-	Dirichlet

UAI : Unprotected anal intercourse
UIAI : Unprotected insertive anal intercourse
URAI : Unprotected receptive anal intercourse
PHI: Primary HIV infection
[a] The results from preliminary one-way sensitivity analysis prior to the model fitting that shows the maximum percentage changes in the model estimates of HIV prevalence at the end of 2009 due to ± 50% changes of the fitted parameters.

I then sampled 20,000 different combinations of the fitted parameters using Latin Hypercube sampling [98] and ran 20,000 model simulations from 2000 to 2009. Using Monte Carlo filtering, model outputs from each parameter set were compared against the 2001–2009 estimates of the reported HIV prevalence, both overall and undiagnosed [2,90,99]. The diagnosed prevalence had a particularly narrow reported range and thus was excluded from the filtering criteria. Any parameter sets that were unable to provide estimates within ranges of all fitting data simultaneously were filtered out. The interval estimates of HIV prevalence were taken directly from the reported ranges of MSM aged 15-59, the upper limits of which were then increased by 15% to account for the difference in the age range.

The filtering process reduced the number of parameter sets from 20,000 to 1,093. The model fit to the overall and undiagnosed HIV prevalence estimates are shown in Figure 5-1. The filtered parameter sets also provided an adequate fit to the diagnosed prevalence data judging from the resulting median estimates (Figure 5-1). The estimated number of MSM aged 15-64 living with HIV in the UK ranged from around 24,000 in 2001 to 38,000 in 2009 with a rather constant number of 9,000 men who were unaware of their infection. These 1,093 parameter sets were later used for simulating the HIV epidemic in MSM in the UK from 2001 to 2020 and evaluating the contributions to HIV transmission of various biological and behavioural factors.

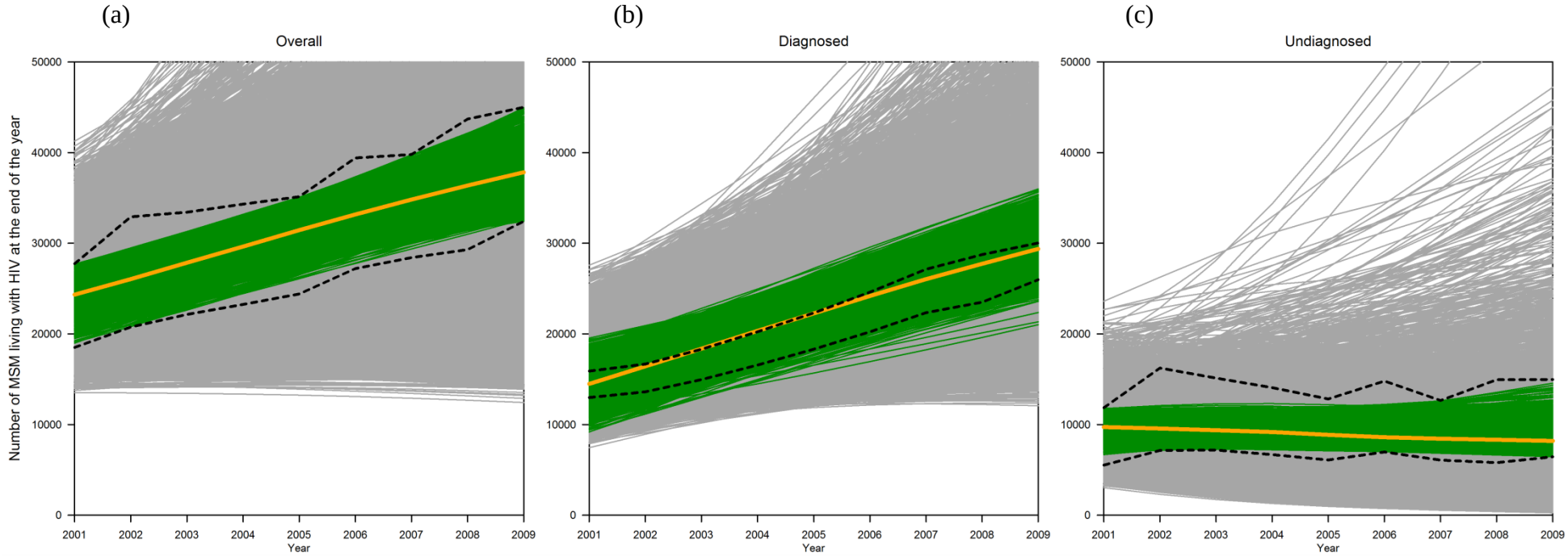

Figure 5-1: The model fitting of the number of MSM aged 15-64 living with HIV in the UK

(a) Overall HIV prevalence, (b) Diagnosed HIV prevalence (not used for model fitting), (c) Undiagnosed HIV prevalence. The dashed lines showed ranges of the fitting data. Note that the upper limits of reported estimates were increased by 15% to compensate for difference of age range between the reported estimates and this study (15-59 vs. 15-64, respectively). The grey lines represent model estimates from all 20,000 sampled parameter sets. The green lines represent model estimates from 1,093 parameter sets that yielded both the overall and undiagnosed HIV prevalence within the range of the 2001–2009 fitting data, simultaneously. The yellow lines indicated median of the green-line estimates.

5.3. Model validation

The model and its parameters values were validated collectively by comparing the output estimates derived from 1,093 parameter sets to the time-series surveillance data and reported estimates that were not used for fitting the model, which were the annual number of new HIV infections, the number of new HIV diagnoses, and the number of MSM on antiretroviral treatment (ART). Figure 5-2 shows a comparison of new HIV infections. The model yields a total of 21,677 (15,505-29,596) new infections during 2001–2009 with the annual numbers lie within the reported ranges [97] across the entire time period (Figure 5-2a). The upward trend of new infections during the early periods followed by a slight decline and levelling off can be observed from both the model and reported estimates. There were no reported estimates stratified by age groups. However, the smaller number of new infections of the older group (Figure 5-2c) compared to the younger group (Figure 5-2b) were also consistent with the 2010 data from the national monitoring system of recent HIV infections which suggesting much lesser proportions of recent infection in newly-diagnosed MSM aged 35 and over (7-23%) in contrast to those of aged less than 35 (24-41%) [54,70].

The median estimates of individuals in the ART stage at the end of the year during 2001–2009 were compared with the observed numbers of MSM on ART obtained from the PHE SOPHID database (Figure 5-3). The upward trend in the numbers of ART-treated MSM was observed during the last decade (from around 9,200 in 2001 to 21,300 in 2009) and the model estimates follow the trend consistently (from 10,952 in 2001 to 23,865 in 2009). Note that the estimates from this study were somewhat higher than the observed data, particularly in the early phase, probably because it was assumed that once an individual is treated with ART he remains in the ART stage until being removed from the model, while in the actual situation a proportion of MSM may stop the treatment due to a number of reasons, e.g. poor adherence.

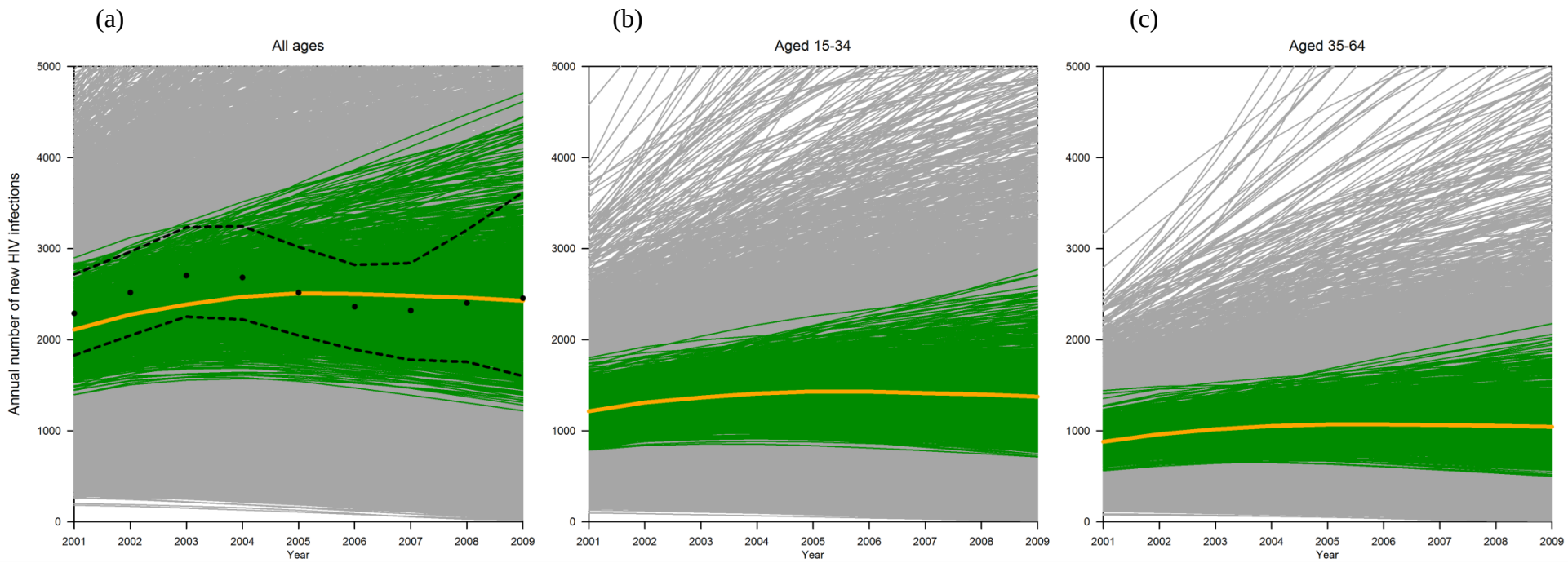

Figure 5-2: Comparison of annual numbers of new HIV infections between model and reported estimates for model validation

(a) Overall new HIV infections, (b) new HIV infections in MSM aged 15-34, (c) new HIV infections in MSM aged 35-64. The dots and dashed lines indicated the reported estimates and 95% credible intervals of annual numbers of new HIV infections in MSM in England and Wales. The explanations of all other items in this figure are provided in the legends of Figure 5-1.

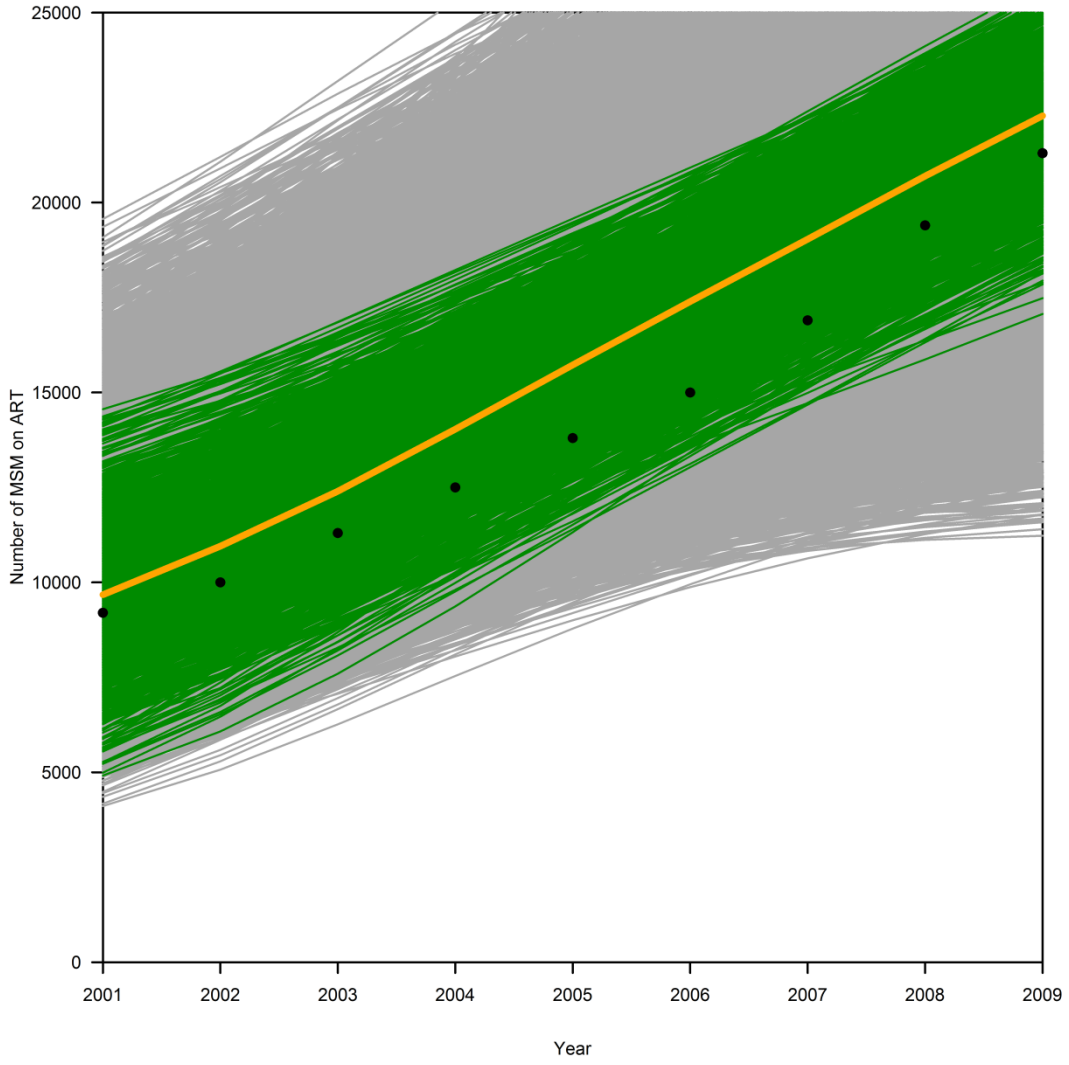

Figure 5-3: Comparison of the number of MSM on ART between model estimates and reported data for model validation

The dots indicated the reported numbers of UK MSM on ART from 2001–2009. The explanations of all other items in this figure are provided in the legends of Figure 5-1.

The numbers of new diagnoses stratified by age groups are shown in Figure 5-4. The 2001–2009 new diagnoses data in UK MSM aged 15-64 were obtained from PHE New diagnoses databases. Since the selected data matched exactly with the demographics of the modelled populations, I validated the HIV transmission model more quantitatively by calculating a simple goodness-of-fit indicator from percentage differences between observed data and model estimates for each available data points, $1-\frac{|O_t - E_t|}{O_t}\times 100\%$, where O_t and E_t are, respectively, the observed data and model estimates at time *t*. The combined value is an average of all individual data points' average goodness-of-fit. A larger value reflected a better consistency with the data. For the younger group, the goodness-of-fit value of the new diagnoses during 2001–2009 was 93.9% when comparing using the median estimates. For MSM aged 35-64, the goodness-of-fit value was 88.6%. Overall, the predicted trends of new HIV diagnoses in this research were well consistent with the national surveillance data with the goodness-of-fit value of 91.2%.

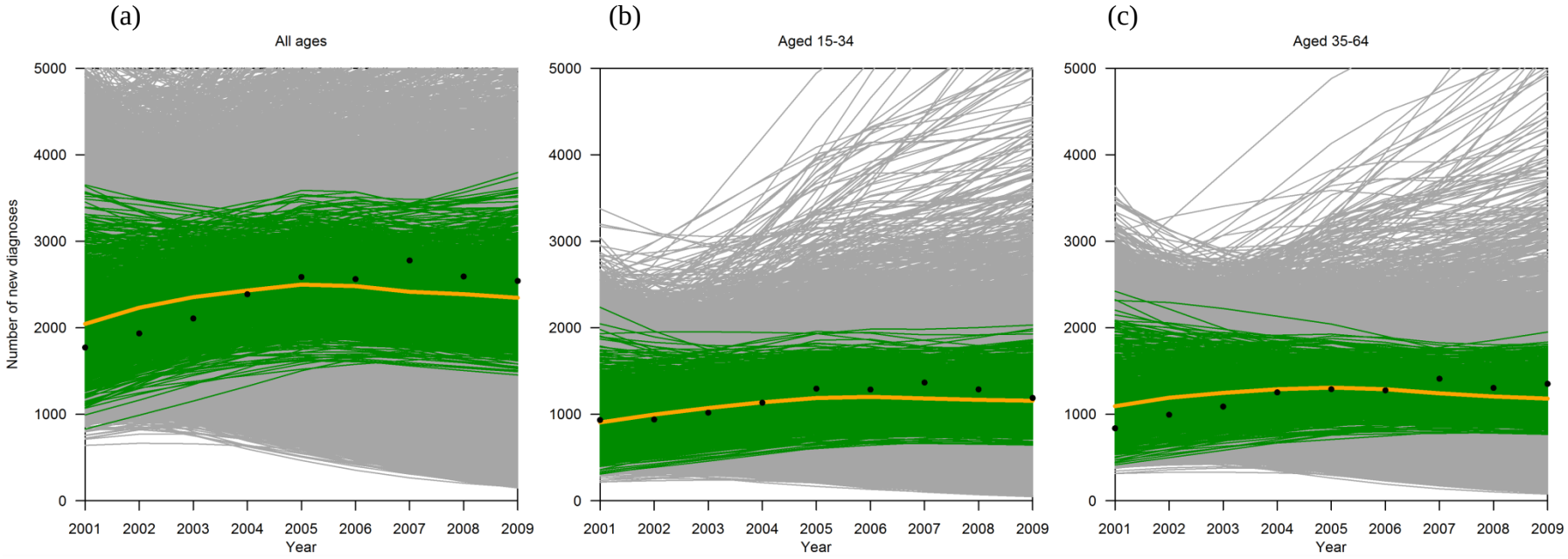

Figure 5-4: Comparison of the number of new diagnoses between model estimates and reported data for model validation

(a) Overall new HIV diagnoses, (b) new HIV diagnoses in MSM aged 15-34, (c) new HIV diagnoses in MSM aged 35-64. The dots indicated the reported new HIV diagnoses in UK MSM from 2001–2009. The explanations of all other items in this figure are provided in the legends of Figure 5-1.

The CD4-specifc new diagnoses data and the estimates are shown in Figure 5-5. Due to uncertainty associated with missing values of the reported data, I skipped the calculation of goodness-of-fit and visually inspected the consistency. The median estimates resembled quite closely both trend and magnitude of the new diagnoses data in all CD4 stages and both age groups. At the end of 2009, the estimation of the numbers of newly diagnosed MSM were 757, 571, 400, and 504 for CD4≥500, 350-499, 200-349, and <200 cells/µL, respectively, which matched closely the 805, 535, 426, and 440 cases of the reported data.

In addition, the model estimated a total of 39,295 HIV-positive MSM aged 15-64 at the end of 2010 which was in line with the 2010 estimates of 40,100 (35,300-46,700) MSM aged 15-59 living with HIV in the UK [70]. At the same period of time, the model also approximated that 21% of HIV-positive MSM were unaware of their infection compared to the reported estimate of 26% (16-36%) [70].

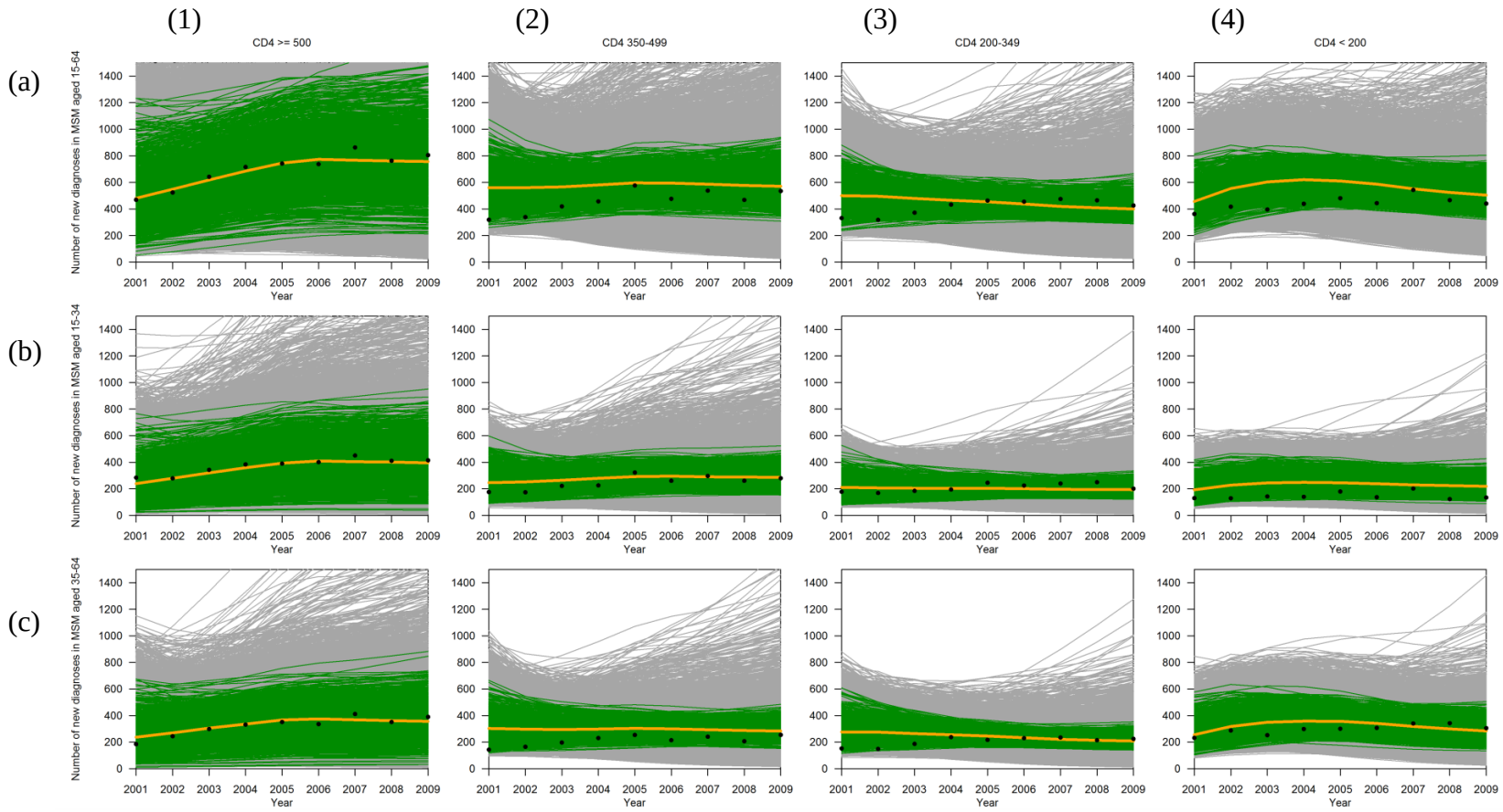

Figure 5-5: Comparison of the number of new diagnoses stratified by CD4 stages between model estimates and reported data for model validation

Rows (a), (b), and (c): Overall new HIV diagnoses, new HIV diagnoses in MSM aged 15-34, and new HIV diagnoses in MSM aged 35-64, respectively. Columns (1), (2), (3), and (4): New HIV diagnoses at CD4 500, 350-499, 200-349, and <200 cells/µL, respectively. The dots indicated the reported new HIV diagnoses in UK MSM from 2001–2009. The explanations of all other items in this figure are provided in the legends of Figure 5-1.

5.4. Model programming

The computational programming language R [100] is used for model construction and analysis in this study. Code processing time is also taken into consideration and was minimised as much as possible. Simple calculations and graphical outputs were carried out in both R and the spreadsheet application.

Programming a complicated model usually involves hundred or even thousand lines of computer codes and mistakes, although known to exist, are often difficult to identify. Two verifying procedures were used to ensure code correctness. First, there are certain rules that should never be violated if the codes are to be working properly. For instance, the probability and proportion sum to one, and the count data could never be a negative value. These rules can be placed throughout the programme to help identify any mistakes as soon as possible.

Another is that codes for solving differential equations were tested using the instructions suggested by Knupp and Salari [101]. Subsets of the R codes, particularly the complex ones, can be compared to the equivalent codes in other differential equation programmes, such as Berkeley Madonna [102]. Other types of code can be verified against manual calculation in a spreadsheet application.

5.5. Publication

The manuscript of the main findings on the current epidemic, entitled ‘Modelling the HIV epidemic among men who have sex with men in the United Kingdom: quantifying the contributions to HIV transmission to better inform prevention initiatives’, including supplementary materials on model fitting and validation has been published in *AIDS* in January 2015 [61]. The main aims of the article are to estimate the levels of HIV incidence and prevalence up to the year 2020 and assess the contribution of various MSM subgroups to HIV transmission among MSM in the UK.

5.5.1. Article submitted

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student	Narat Punyacharoensin
Principal Supervisor	Richard White
Thesis Title	Modelling HIV transmission and control among men who have sex with men in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	AIDS		
When was the work published?	January 2015		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study with inputs from all co-authors. I carried out all the model development and analysis in consultation with all co-authors. I wrote the paper and did the revision based on comments from all co-authors.

Student Signature: Narat Punyacharoensin **Date:** April 15, 2015

Supervisor Signature: Richard White **Date:** April 15, 2015

Modelling the HIV epidemic among MSM in the United Kingdom: quantifying the contributions to HIV transmission to better inform prevention initiatives

Narat Punyacharoensin[a], William John Edmunds[a], Daniela De Angelis[b], Valerie Delpech[c], Graham Hart[d], Jonathan Elford[e], Alison Brown[c], Noel Gill[c] and Richard G. White[a]

Objectives: HIV is a major public health problem among MSM in the United Kingdom with around 2400 new infections annually. We quantified the contribution of biological and behavioural factors.

Design: Modelling study.

Methods: A partnership-based model of HIV transmission among UK MSM aged 15–64 years was developed and calibrated to time series HIV prevalence. The calibration was validated using multiple surveillance datasets. Population-attributable fractions were used to estimate the contribution of behavioural and biological factors to HIV transmission over the period 2001–2002, 2014–2015, and 2019–2020.

Results: The contribution of most biological and behavioural factors was relatively constant over time, with the key group sustaining HIV transmission being higher-sexual activity MSM aged below 35 years living with undiagnosed HIV. The effect of primary HIV infection was relatively small with 2014–2015 population-attributable fraction of 10% (3–28%) in comparison with other subsequent asymptomatic stages. Diagnosed men who were not on antiretroviral therapy (ART) currently contributed 26% (14–39%) of net infections, whereas ART-treated MSM accounted for 17% (10–24%). A considerable number of new infections are also likely to occur within long-term relationships.

Conclusion: The majority of the new HIV infections among MSM in the United Kingdom during 2001–2020 is expected to be accounted for by a small group of younger and highly sexually active individuals, living with undiagnosed HIV in the asymptomatic stage. Bringing this group into HIV/AIDS care by improving testing uptake is a vital step for preventing onward transmission and will determine the success of using ART as prevention.

AIDS 2015, **29**:339–349

Keywords: compartmental model, epidemic model, HIV/AIDS, homosexual, mathematical model, MSM

[a]Centre for the Mathematical Modelling of Infectious Diseases and Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London, [b]Medical Research Council Biostatistics Unit, Cambridge, [c]HIV and STI Department, Public Health England, Colindale, [d]Centre for Sexual Health & HIV Research, Department of Infection & Population Health, Mortimer Market Centre, University College London, and [e]School of Health Sciences, City University London, London, UK.

Correspondence to Narat Punyacharoensin, MSc, Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

Tel: +44 20 7636 8636; fax: +44 20 7436 5389; e-mail: narat.punyacharoensin@lshtm.ac.uk, narat.punyacharoensin@yahoo.com

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Introduction

In the United Kingdom, more than 120 000 people have been diagnosed with HIV and the virus has accounted for more than 20 000 deaths since the start of the epidemic in the early 1980s [1]. During the past 5 years, the number of new HIV diagnoses has continued to decline in all population subgroups, except MSM, which currently represent the largest group of people diagnosed with HIV in the United Kingdom [2]. Despite the extremely high coverage of antiretroviral therapy (ART), which has been demonstrated to prevent HIV transmission, HIV incidence is continuing in this vulnerable group with no sign of a decline [2,3]. An estimated 41 000 MSM were living with HIV in 2012 (4.7% prevalence rate) [2], with approximately 2000–3000 MSM newly infected each year during 2001–2010 [4].

In this study, we sought to gain a better understanding of the factors that drive ongoing HIV transmission among MSM populations in the United Kingdom by developing a mathematical model of HIV transmission that simulates the underlying drivers of the epidemic. The comprehensive, well documented HIV epidemic among UK MSM allowed our model to be tailored-made to match the actual situation. The model was parameterized using multiple sources of survey and surveillance data, and fitted to the time-series estimates of HIV prevalence and followed with model validation and sensitivity analyses to confirm the resulting estimates. The key objective was to quantify the unknown contribution of various behavioural and biological factors to HIV transmission among MSM in the United Kingdom, including the stage of primary HIV infection (PHI), undiagnosed and untreated groups, type of partnerships, age groups, and sexual activity levels to better target prevention strategies. The future course of the epidemic was also projected in the absence of additional interventions.

Methods

We developed a mathematical model to simulate the HIV epidemic in MSM aged 15–64 years in the United Kingdom from the beginning of 2000 to the end of 2020. All the analyses started from year 2001, allowing a 1-year period to help stabilize the model estimates before being analysed. The Appendix (http://links.lww.com/QAD/A612) describes the model structure and analysis methods in detail. Here, we summarize them briefly.

Mathematical model

We formulated a deterministic partnership-based mathematical model in a system of ordinary differential equations (further details are provided in Appendix, section 1, http://links.lww.com/QAD/A612). The modelled populations were divided simultaneously into two age groups: 15–34 (age group 1) and 35–64 years (age group 2), and two sexual activity levels: low and high activity, defined, respectively, as MSM who have, on average, 1 or less and more than 1 new male sexual partner per year. Together, we had a total of four 'classes' of MSM, that is, age group 1 – low activity, age group 1 – high activity, age group 2 – low activity, and age group 2 – high activity. The HIV-negative individuals remain in the 'susceptible' compartment until either becoming infected with HIV and subsequently progressing through 11 HIV-positive stages defined by $CD4^+$ cell counts, HIV diagnosis status, and ART status (Fig. 1), or being removed from the model due to mortality or exceeding the age of 64 years. The five disease progression stages (PHI, $CD4^+ \geq 500$, 350–499, 200–349, and <200 cells/μl) were associated with different HIV transmission probabilities derived on a basis of the average viral load in each stage [5]. Transmission probability and plasma viral load were related according to the function proposed by Smith and Blower [6]. We sampled from a beta distribution to create 10 000 sets of per-act transmission

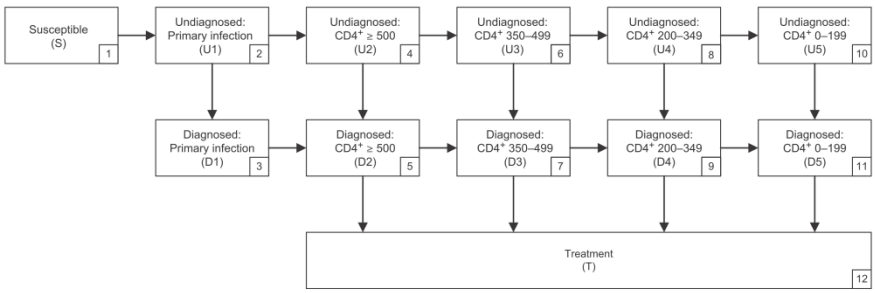

Fig. 1. Schematic representation of HIV infection stages in the HIV transmission model. A total of 12 HIV stages combine HIV infection status, $CD4^+$ stages, diagnosis status, and treatment status. Susceptible individuals get infected with HIV and move from the first stage of primary HIV infection (PHI) through the last stage of $CD4^+$ below 200 cells/μl. During such course, individuals who have been diagnosed with HIV move from undiagnosed to the corresponding diagnosed stages. Similarly after diagnosis, individuals who have been treated with antiretroviral therapy (ART) move from diagnosed to treatment stage.

probability by viral load for each $CD4^+$ stage and derived the lower, central, and upper estimates of the final per-act transmission probabilities using 2.5th, 50.0th, and 97.5th percentiles, respectively. The infectiousness of PHI stage was estimated by applying a relative risk of 9.17, as suggested by Boily *et al.* [7], to the baseline transmission probabilities suggested by Baggaley *et al.* [8]. A very low, but non-zero, calendar year-dependent transmission probability calculated using the 2005–2009 viral load and $CD4^+$ data was applied to the treatment stage. A change over time in infectiousness of ART-treated men was incorporated to reflect the improved drug efficacy and adherence [9–11]. No linkage to and retention in HIV care were explicitly modelled in this study. All derived estimates of HIV transmission probability are summarized in Table 1.

MSM were also divided into 'current' and 'past' MSM in which the former still acquire new male sexual partners, whereas the latter no longer have sexual relationship with men. We defined two types of sexual partnerships: a one-off sexual partnership and a repeat sexual partnership. The one-off partnership has only a single sex act, whereas the repeat sexual partnership consists of multiple sex acts with the same partner. Our partnership-based model [12,13] allowed a repeat sexual partnership to last for a finite period of time, during which HIV transmission can occur. MSM in a repeat sexual partnership could also acquire a one-off sexual partner and HIV transmission could occur from both types of partners. The repeat and one-off sexual partner change rates were stratified by four MSM classes with the lowest rate assigned to the low-activity MSM aged 35 years or more and the highest to high-activity MSM aged below 35 years (Table 2). Non-random mixing between partners according to age group, sexual activity level, and perceived HIV serostatus was implemented using the method based on odds ratios (ORs) [17]. Sex between men was the only route for transmitting HIV which included protected and unprotected receptive anal intercourse (URAI), protected and unprotected insertive anal intercourse (UIAI), and unprotected receptive oral intercourse (UROI). Condom use with repeat sexual partners was modelled using the class-specific proportions of susceptible individuals who have unprotected anal intercourse (UAI) with perceived HIV-negative and with diagnosed HIV-positive repeat sexual partners (Appendix, section 3.2.5, http://links.lww.com/QAD/A612). The perceived HIV-negative men included all susceptible (compartment 1 in Fig. 1) and undiagnosed HIV-positive MSM (compartments 2, 4, 6, 8, and 10). The diagnosed HIV-positive men included all diagnosed HIV-positive MSM (compartments 3, 5, 7, 9, and 11) and MSM on treatment (compartment 12). For one-off partnerships, susceptible individuals were categorized into three groups, that is, MSM who had no UAI one-off partner, MSM who had UAI only with a perceived HIV-negative one-off partner, and MSM who had UAI with a diagnosed HIV-positive one-off partner (Appendix, section 3.2.5, http://links.lww.com/QAD/A612). These proportions of MSM for modelling unsafe sex and condom use were assumed to remain constant over time and are presented in Table S8 (http://links.lww.com/QAD/A612) in the Appendix (http://links.lww.com/QAD/A612).

Data and parameter estimation

The National Survey of Sexual Attitudes and Lifestyles (NATSAL) for the year 2000 [18], the Gay Men's Sexual Health Survey (GMSHS) in London [19] for years 2000–2006 and 2008, and the London Gym Survey (GYM) [20] for years 2000–2008 were the primary sources for estimating demographic and behavioural parameters. We adjusted the data from the community-based convenience-sample GMSHS and GYM surveys to match four important variables from the national-based probability-sample NATSAL survey (Appendix, section 2.3, http://links.lww.com/QAD/A612). Table 2 summarizes the derived parameters for sexual behaviour.

Table 1. Estimated per-act HIV transmission probability for MSM in the United Kingdom.

HIV transmission probability (%)	Type of sexual act					
	URAI	Symbol	UIAI	Symbol	UROI	Symbol
ART-naive MSM						
PHI	12.838 (1.834–22.925)	$\beta_{urai,2}, \beta_{urai,3}$	5.685 (0.642–15.406)	$\beta_{uiai,2}, \beta_{uiai,3}$	0.367	$\beta_{uroi,2}, \beta_{uroi,3}$
$CD4^+ \geq 500$	1.336 (0.191–2.386)	$\beta_{urai,4}, \beta_{urai,5}$	0.592 (0.067–1.603)	$\beta_{uiai,4}, \beta_{uiai,5}$	0.038	$\beta_{uroi,4}, \beta_{uroi,5}$
$CD4^+$ 350–499	1.553 (0.222–2.773)	$\beta_{urai,6}, \beta_{urai,7}$	0.688 (0.078–1.863)	$\beta_{uiai,6}, \beta_{uiai,7}$	0.044	$\beta_{uroi,6}, \beta_{uroi,7}$
$CD4^+$ 200–349	1.662 (0.237–2.968)	$\beta_{urai,8}, \beta_{urai,9}$	0.736 (0.083–1.995)	$\beta_{uiai,8}, \beta_{uiai,9}$	0.047	$\beta_{uroi,8}, \beta_{uroi,9}$
$CD4^+ < 200$	1.863 (0.266–3.326)	$\beta_{urai,10}, \beta_{urai,11}$	0.825 (0.093–2.235)	$\beta_{uiai,10}, \beta_{uiai,11}$	0.053	$\beta_{uroi,10}, \beta_{uroi,11}$
ART-treated MSM						
Before 2005	0.363 (0.229–0.558)	$\beta_{urai,12}$	0.158 (0.072–0.303)	$\beta_{uiai,12}$	0.009	$\beta_{uroi,12}$
Changes per year during 2005–2009[a]	−0.039	–	−0.016	–	−0.001	–

The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting. ART, antiretroviral therapy; PHI, primary HIV infection; UIAI, unprotected insertive anal intercourse; URAI, unprotected receptive anal intercourse; UROI, unprotected receptive oral intercourse.
[a]HIV transmission probability after 2009 was assumed equal to that of 2009.

Table 2. Sexual behaviour parameters.

Parameter	Symbol	Value: Aged 15–34 years, Low-activity	Value: Aged 15–34 years, High-activity	Value: Aged 35–64 years, Low-activity	Value: Aged 35–64 years, High-activity	Source
Repeat sexual partnership						
Rate of repeat sexual partnership formation per year	ρ^{rep}	0.422 (0.405–0.438)	3.135 (2.761–3.509)	0.458 (0.438–0.478)	2.719 (2.445–2.994)	GMSHS
Gap length between two consecutive repeat sexual partnerships (days)	G	178	33	178	33	NATSAL
Rate of repeat sexual partnership dissolution per year	σ	0.530	4.372	0.590	3.604	Calculated
Proportion of repeat sexual partnerships that involve anal sex to all repeat sexual partnerships	p^{rep}_{anal}	0.958 (0.948–0.969)	0.706 (0.690–0.723)	0.879 (0.859–0.899)	0.643 (0.620–0.665)	GMSHS
Proportion of repeat sexual partnerships that involve oral sex to all repeat sexual partnerships	$1 - p^{rep}_{anal}$	0.042	0.294	0.121	0.357	GMSHS
Proportion of susceptible individuals who have UAI with a perceived HIV-negative repeat sexual partner[a]	$p^{rep}_{uai,pneg}$	0.369–0.657	0.328–0.556	0.288–0.548	0.231–0.426	GYM
Proportion of susceptible individuals who have UAI with a diagnosed HIV-positive repeat sexual partner[b]	$p^{rep}_{uai,dpos}$	0.194–0.601	0.041–0.144	0–0.267	0–0.111	GYM
Frequency of sexual acts with a repeat sexual partner per week	φ	1.49–3.56	1.49–3.56	1.03–2.03	1.03–2.03	NATSAL
Proportion of UAI acts to all sex acts in UAI repeat sexual partnership	–	1.00	1.00	1.00	1.00	Assumed
Effects of HIV diagnosis on the proportion of UAI acts	–	0.3	0.3	0.3	0.3	[14]
One-off partnership						
Rate of one-off partnership formation per year						
MSM without a repeat sexual partner	ρ^{one}_{Y}	0.255 (0.218–0.291)	10.019 (6.235–13.803)	0.390 (0.342–0.438)	9.260 (6.343–12.178)	GMSHS
MSM with a repeat sexual partner	ρ^{one}_{P}	–	8.960 (7.675–10.246)	–	8.219 (6.841–9.596)	GMSHS
Proportion of one-off partnerships that involve anal sex to all one-off partnerships						
MSM without a repeat sexual partner	$p^{one}_{anal,Y}$	0.905	0.607	0.769	0.495	GMSHS
MSM with a repeat sexual partner	$p^{one}_{anal,P}$	–	0.547	–	0.518	GMSHS
Proportion of one-off partnerships that involve oral sex to all one-off partnerships						
MSM without a repeat sexual partner	$1 - p^{one}_{anal,Y}$	0.095	0.393	0.231	0.505	GMSHS
MSM with a repeat sexual partner	$1 - p^{one}_{anal,P}$	–	0.453	–	0.482	GMSHS
Proportion of susceptible individuals who have no UAI with a one-off partner (group A)						
MSM without a repeat sexual partner	$p^{one}_{A,Y}$	0.321	0.477	0.364	0.573	GMSHS
MSM with a repeat sexual partner	$p^{one}_{A,P}$	–	0.596	–	0.599	GMSHS
Proportion of susceptible individuals who have UAI only with a perceived HIV negative one-off partner (group B)						
MSM without a repeat sexual partner	$p^{one}_{B,Y}$	0.449	0.167	0.338	0.071	GMSHS
MSM with a repeat sexual partner	$p^{one}_{B,P}$	–	0.184	–	0.166	GMSHS
Proportion of susceptible individuals who have UAI with a diagnosed HIV positive one-off partner (group C)						
MSM without a repeat sexual partner	$p^{one}_{C,Y}$	0.230	0.356	0.298	0.357	GMSHS
MSM with a repeat sexual partner	$p^{one}_{C,P}$	–	0.220	–	0.234	GMSHS
Proportion of UAI one-off partners in group B						
MSM without a repeat sexual partner	$p^{one}_{uai,Y,B}$	1.000	0.535	1.000	0.844	GMSHS
MSM with a repeat sexual partner	$p^{one}_{uai,P,B}$	–	0.695	–	0.673	GMSHS
Proportion of UAI one-off partners in group C						
MSM without a repeat sexual partner	$p^{one}_{uai,Y,C}$	1.000	0.566	1.000	0.624	GMSHS
MSM with a repeat sexual partner	$p^{one}_{uai,P,C}$	–	0.578	–	0.559	GMSHS

Sexual roles							
Proportion of insertive acts in an anal-sex partnership	p_{ins}	0.5	0.5	0.5	0.5	0.5	Assumed[c]
Proportion of receptive acts in an anal-sex partnership	$1 - p_{ins}$	0.5	0.5	0.5	0.5	0.5	Assumed[c]
Proportion of UROI acts in an oral-sex repeat sexual partnership	p^{ste}_{uroi}	1.0	1.0	1.0	1.0	1.0	Assumed
Proportion of UROI acts in an oral-sex one-off partnership	p^{ces}_{uroi}	0.139	0.249	0.228	0.259		GYM
Sexual contact mixing							
Mixing odds ratio							
By age group	w_{age}			4.2			NATSAL
By sexual activity level	w_{sex}			3.0			[15]
By HIV serostatus	w_{hiv}			2.3			GYM

The values in parentheses represent the lower and upper limits of the corresponding parameters that were included in the model fitting. More details about the symbols and notations are provided in the Appendix (http://links.lww.com/QAD/A612. UAI, unprotected anal intercourse; UROI, unprotected receptive oral intercourse.
[a]Perceived HIV-negative stages include stage S, U1, U2, U3, U4, and U5.
[b]Diagnosed HIV-positive stages include stage D1, D2, D3, D4, D5, and T.
[c]Assumed based on findings from Ref. [16], GMSHS, and GYM data.

The model's biological parameters were mainly derived from the systematic reviews and meta-analyses available in the literature. The data from the national HIV surveillance databases including HIV/AIDS diagnoses and $CD4^+$ surveillance [1,5] were used extensively throughout the parameterization. Other unknown parameters were estimated through model fitting to match the HIV epidemic in MSM in the United Kingdom during 2001–2009 using Monte-Carlo filtering method [21]. Model validation was achieved by comparing the model outputs to the estimates of annual new HIV infections, the number of new HIV diagnoses, and the number of ART-treated MSM during 2001–2009 (Appendix, section 5, http://links.lww.com/QAD/A612).

Analysis of factor contribution to HIV infections

The method suggested by Orroth *et al.* [22] was used to estimate the proportion of HIV infections contributed by the following factors: PHI and non-PHI stages stratified by $CD4^+$ cell counts, undiagnosed and diagnosed MSM, ART-treated and untreated MSM, repeat sexual and one-off partners, MSM aged 15–34 and 35–64 years, and low and high-activity MSM. We simulated counterfactual scenarios by setting HIV infectiousness corresponding to each factor to zero during 2001–2002, 2014–2015, and 2019–2020, independently. The period of 2001–2002 allowed the above factors to show their effects as early as possible in the modelling time frame, whereas the period of 2014–2015 represented an immediate intervention at the current transmission, and 2019–2020 represented the end of the decade and the modelling timeline.

To quantify the magnitude of contributions, population-attributable fractions (PAFs) associated with each factor were calculated from $\left(1 - \frac{\mathrm{IR_s}}{\mathrm{IR_b}}\right) \times 100\%$, where $\mathrm{IR_s}$ is the annual HIV incidence rate in the counterfactual scenarios and $\mathrm{IR_b}$ is the annual HIV incidence rate in the baseline scenario, where the default HIV infectivity was used throughout the simulation period. Within each scenario, we derived annual HIV incidence rates and calculated the PAF for each filtered parameter set. The median estimates, as well as the 2.5th and 97.5th percentiles of these PAFs, were obtained for 2001–2002, 2014–2015, and 2019–2020. The population sizes at the end of these years in relation to the sources of infections were derived from the model outputs. We also assessed differences in the PAFs across age groups and sexual activity levels in all scenarios. Note that PAFs do not need to sum to 100% [23].

The sets of parameters resulting from the estimation were used to obtain projections of the epidemic of HIV in MSM in the United Kingdom up to the end of 2020 based on the assumption that all model parameters remained constant at the values of the end of 2009 and no additional interventions implemented during the

projection period. The sensitivity of model projections was assessed using the regression trees technique [24] (Appendix, section 6.3, http://links.lww.com/QAD/A612).

Results

We present the findings from the analysis of factor contribution to HIV infections with median estimates and 2.5th and 97.5th percentiles. The proportions of HIV incidence attributable to various factors are shown in Table 3, with the average HIV-positive population sizes of the sources of infections at the end of analysis years. The projections of HIV epidemic among UK MSM are shown in Fig. 2. Additional results from model fitting and validation, as well as sensitivity analysis, are shown in the Appendix, sections 4, 5, and 6 (http://links.lww.com/QAD/A612).

Population-attributable fractions

Primary HIV infection

The transmission of HIV from individuals in the PHI stage accounted for the smallest proportion of infections with the current PAF (year 2014–2015) of 10% (3–28%), whereas around 98% (90–99%) are attributable to transmission after PHI. MSM in non-PHI stages (excluding treated) with $CD4^+$ at least 350 cells/μl, are estimated to contribute considerably more to new infections than those with lower $CD4^+$ cell counts (current PAF of 29–32 vs. 11–13%). However, dividing the average PAF of PHI by the average number of men in PHI stage shows that, on an individual basis, each MSM living with PHI contributes most among all disease stages (PAF ratio of 0.0185) to net transmission (Table 3). The later disease stages also contribute more to new infections which followed the pattern of the assumed transmission probability (Table 3).

Undiagnosed HIV

Undiagnosed HIV-positive men are currently estimated to contribute as much as 63% (49–80%) of onward transmissions, but only 19% (11–30%) are from those with $CD4^+$ below 350 cells/μl, whereas 47% (36–59%) are from MSM with higher $CD4^+$ cell counts. The current PAF of diagnosed men, including those on ART, is, on the contrary, considerably less, with around 44% (24–60%), although its contribution becomes more apparent as the epidemic progresses [from a PAF of 28% (17–41%) in 2001–2002 to 46% (26–61%) in 2019–2020]. Moreover, the average number of men living with undiagnosed HIV (7853) at any point in time is approximately four times smaller than that of diagnosed HIV (31 369), which clearly highlighted the importance of undiagnosed men in driving further HIV transmission in UK MSM.

Untreated HIV

The HIV epidemic in UK MSM is driven mainly by untreated men with 2014–2015 PAF of 85% (78–92%). However, an increased proportion of treated men due to widespread use of ART leads to a decline over time in the PAF of untreated men, whereas the PAF of treated men continues to increase, from 11% (5–18%) in 2001–2002 to 20% (11–28%) in 2019–2020. The PAF ratio of the untreated is more than 11-fold greater than that of ART-treated men (Table 3), which is influenced by a relatively small number of untreated men (12 884) in comparison to those on treatment (26 585).

Sexual behaviour

HIV transmission within repeat sexual partnerships accounts for almost all infections among MSM in the United Kingdom, with a current PAF of 90% (87–93%). The one-off partnership, on the contrary, is estimated to contribute substantially less with a PAF of 17% (12–24%), but this is accounted for by a small group of individuals engaging in one-off partnerships (885) in comparison with a large number of men having repeat sexual partners (15 350). The 2014–2015 PAF of repeat sexual partnerships dropped to 69% (63–74%) and to 23% (19–29%) if we consider only repeat sexual partners of high-activity and low-activity MSM, respectively.

Age and sexual activity groups

HIV-positive MSM aged 15–34 years contribute considerably more to HIV transmission than those aged 35–64 years with 2014–2015 PAFs of 62% (47–74%) and 44% (32–59%), respectively, although most HIV-positive MSM were in the older group (14 781 vs. 24 622). For sexual activity levels, the majority of new infections [current PAF of 80% (70–87%)] are associated with the high-activity MSM, who account for only 40% of all MSM in the model. This can be explained by their high-risk behaviours and the fact that HIV is highly prevalent within this group (22 231) compared to low-activity men (17 272). The PAFs of high-activity men as well as MSM aged 15–34 years remain consistent over the three analysis periods, suggesting their key role in consistently driving HIV transmission in the population of MSM in the United Kingdom.

Discussion

The study is among the first to show the contribution of various HIV-positive subpopulations to the epidemic of HIV among MSM in the United Kingdom. The epidemic has continued to expand during the past decade with the key group sustaining HIV transmission being high-sexual activity MSM aged below 35 years living with undiagnosed HIV and in the asymptomatic stage.

Our analyses of factor contributions to HIV infections showed that the effects of the PHI stage are smaller than

Table 3. Population-attributable fractions of sources of HIV transmission among MSM in the UK.

	2001–2002			2014–2015			2019–2020					
Scenario[a]	Number of new infection[b]	Incidence (% per year)[c]	PAF (%)[d]	Number of new infection	Incidence (% per year)	PAF (%)	Number of new infection	Incidence (% per year)	PAF (%)	Average PAF (%)[e]	Average HIV+ population size[f]	PAF ratio[g]
1.1 Baseline[h]	4387	0.334	–	4806	0.342	–	4860	0.338	–	–	39650	–
2.1 MSM in all PHI stages (stages: U1 and D1)	3839	0.292	11.0 (2.7–28.2)	4231	0.301	10.2 (2.5–28.2)	4294	0.299	10.0 (2.4–27.6)	10.4 (2.5–28.0)	561	0.0185 (0.0045–0.0499)
2.2 MSM in all HIV stages except PHI (stages: U2–U5, D2–D5, and T)	75	0.006	98.2 (91.6–99.8)	85	0.006	98.2 (89.9–99.8)	84	0.006	98.2 (90.2–99.8)	98.2 (90.6–99.8)	39019	0.0025 (0.0023–0.0026)
3.1 MSM in all PHI stages (stages: U1 and D1)	3839	0.292	11.0 (2.7–28.2)	4231	0.301	10.2 (2.5–28.2)	4294	0.299	10.0 (2.4–27.6)	10.4 (2.5–28.0)	561	0.0185 (0.0045–0.0499)
3.2 MSM at $CD4^+ \geq 500$ cells/μl (stages: U2 and D2)	2904	0.221	33.4 (28.0–38.7)	3239	0.231	32.4 (26.7–37.7)	3322	0.231	31.6 (25.9–36.7)	32.5 (26.9–37.7)	5242	0.0062 (0.0051–0.0072)
3.3 MSM at $CD4^+$ 350–499 cells/μl (stages: U3 and D3)	3093	0.235	29.2 (25.6–32.3)	3408	0.243	28.8 (25.1–31.9)	3502	0.244	27.9 (24.2–31.0)	28.7 (25.0–31.7)	4198	0.0068 (0.0060–0.0076)
3.4 MSM at $CD4^+$ 200–349 cells/μl (stages: U4 and D4)	3640	0.277	16.7 (13.9–19.4)	4176	0.298	13.1 (10.5–15.6)	4240	0.295	12.6 (10.1–15.3)	14.2 (11.5–16.8)	1687	0.0084 (0.0068–0.0100)
3.5 MSM at $CD4^+ < 200$ cells/μl (stages: U5 and D5)	3805	0.29	12.8 (9.6–16.8)	4292	0.306	11.1 (6.0–17.9)	4347	0.302	10.6 (5.7–17.5)	11.5 (7.1–17.4)	1127	0.0102 (0.0063–0.0154)
3.6 MSM on ART (stage: T)	3895	0.296	10.8 (5.5–17.8)	3970	0.283	17.1 (9.7–24.4)	3895	0.271	19.8 (11.1–28.4)	15.9 (8.8–23.6)	26585	0.0006 (0.0003–0.0009)
4.1 MSM in all undiagnosed stages (stages: U1–U5)	1024	0.078	76.2 (65.8–86.3)	1753	0.125	62.8 (48.6–79.2)	1853	0.129	61.2 (47.0–78.2)	66.7 (53.8–81.2)	7853	0.0085 (0.0069–0.0103)
4.2 MSM in all diagnosed stages including those on ART (stages: D1–D5 and T)	3104	0.236	28.4 (16.5–41.0)	2640	0.188	43.6 (24.4–59.9)	2575	0.179	45.6 (25.6–61.3)	39.2 (22.2–54.1)	31369	0.0012 (0.0007–0.0017)
5.1 MSM in all undiagnosed stages at $CD4^+ \geq 350$ cells/μl (stages: U1–U3)	1970	0.150	54.7 (46.0–64.0)	2560	0.182	46.4 (36.2–59.1)	2637	0.183	45.4 (35.3–58.1)	48.8 (39.2–60.4)	5908	0.0083 (0.0066–0.0102)
5.2 MSM in all undiagnosed stages at $CD4^+ < 350$ cells/μl (stages: U4–U5)	3234	0.246	25.8 (19.3–32.7)	3894	0.277	19.3 (10.8–29.9)	3956	0.275	18.5 (10.4–29.1)	21.2 (13.5–30.6)	1978	0.0107 (0.0068–0.0155)
5.3 MSM in all diagnosed stages excluding those on ART (stages: D1–D5)	3602	0.274	17.0 (10.0–26.9)	3473	0.248	26.1 (13.5–39.3)	3594	0.25	25.0 (13.3–37.7)	22.7 (12.3–34.6)	4818	0.0047 (0.0026–0.0072)
5.4 MSM on ART (stage: T)	3895	0.296	10.8 (5.5–17.8)	3970	0.283	17.1 (9.7–24.4)	3895	0.271	19.8 (11.1–28.4)	15.9 (8.8–23.6)	26585	0.0006 (0.0003–0.0009)
6.1 MSM in all untreated stages (stages: U1–U5 and D1–D5)	402	0.031	90.8 (84.9–95.3)	710	0.051	85.3 (78.0–91.8)	825	0.057	82.9 (74.6–90.8)	86.3 (79.2–92.6)	12884	0.0067 (0.0061–0.0072)
6.2 MSM on ART (stage: T)	3895	0.296	10.8 (5.5–17.8)	3970	0.283	17.1 (9.7–24.4)	3895	0.271	19.8 (11.1–28.4)	15.9 (8.8–23.6)	26585	0.0006 (0.0003–0.0009)
7.1 Repeat sexual partners	398	0.030	90.8 (87.4–93.2)	475	0.034	90.2 (86.8–92.7)	484	0.034	90.1 (86.6–92.6)	90.4 (87.0–92.8)	15350	0.0059 (0.0057–0.0060)

Table 3 (*continued*)

Scenario[a]	2001–2002 Number of new infection[b]	2001–2002 Incidence (% per year)[c]	2001–2002 PAF (%)[d]	2014–2015 Number of new infection	2014–2015 Incidence (% per year)	2014–2015 PAF (%)	2019–2020 Number of new infection	2019–2020 Incidence (% per year)	2019–2020 PAF (%)	Average PAF (%)[e]	Average HIV+ population size[f]	PAF ratio[g]
7.2 One-off sexual partners	3635	0.277	16.5 (12.1–24.0)	4007	0.286	16.5 (12.3–23.9)	4028	0.28	16.5 (12.4–23.8)	16.5 (12.2–23.9)	885	0.0186 (0.0138–0.0270)
7.3 Repeat sexual partners of low-activity MSM	3474	0.264	20.6 (17.0–24.9)	3671	0.262	23.4 (19.2–28.8)	3704	0.257	23.7 (19.5–29.2)	22.6 (18.6–27.6)	5365	0.0042 (0.0035–0.0051)
7.4 Repeat sexual partners of high-activity MSM	1206	0.092	72.5 (66.6–77.3)	1497	0.107	69.1 (62.6–74.3)	1532	0.107	68.6 (62.3–73.9)	70.1 (63.8–75.2)	9924	0.0071 (0.0064–0.0076)
8.1 MSM aged 15–34	1613	0.123	62.9 (47.2–75.7)	1829	0.13	62.2 (47.3–73.6)	1921	0.134	60.8 (45.6–72.5)	62.0 (46.7–74.0)	14781	0.0042 (0.0032–0.0050)
8.2 MSM aged 35–64	2428	0.185	43.8 (30.5–59.4)	2655	0.189	44.0 (32.0–58.8)	2604	0.181	45.2 (33.0–60.3)	44.3 (31.8–59.5)	24622	0.0018 (0.0013–0.0024)
9.1 Low-activity MSM	3370	0.256	23.0 (16.5–30.6)	3670	0.261	23.2 (15.4–33.3)	3704	0.258	23.6 (15.7–34.0)	23.3 (15.8–32.7)	17272	0.0013 (0.0009–0.0019)
9.2 High-activity MSM	871	0.066	80.0 (72.5–86.0)	978	0.07	79.6 (70.0–86.9)	1010	0.07	79.2 (69.4–86.6)	79.6 (70.7–86.5)	22231	0.0036 (0.0032–0.0039)

ART, antiretroviral therapy; PAF, population-attributable fractions; PHI, primary HIV infection.
[a]An absence in HIV transmission from the sources illustrated in this column was applied during 2001–2002, 2014–2015, and 2019–2020.
[b]The total number of new HIV infections during the corresponding intervention period.
[c]The average annual HIV incidence rate over the corresponding intervention period.
[d]PAF calculated from the average annual incidence rates.
[e]Average PAF over 2001–2002, 2014–2015, and 2019–2020.
[f]The average number of HIV-positive current MSM in the corresponding suspended sources of HIV transmission at the end of 2001, 2002, 2014, 2015, 2019, and 2020.
[g]Derived from dividing the average PAF by the average population size. The PAF ratio illustrates the PAF relative to size of the sources of HIV transmission.
[h]Simulated based on the filtered parameter sets without any interruptions in HIV transmission.

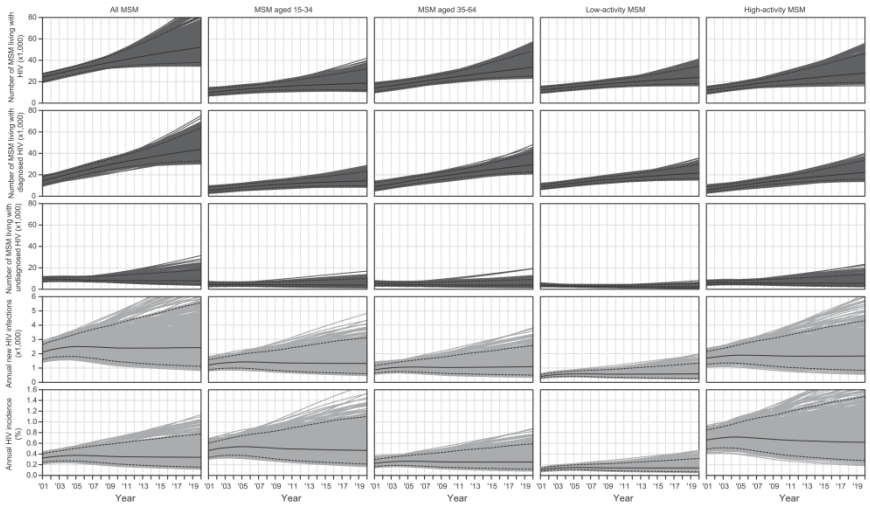

Fig. 2. Model projections of the number of MSM living with HIV and new HIV infections among MSM in the United Kingdom during 2001–2020. The plots of projections are presented in a matrix format. The five rows show the estimates of the overall, diagnosed, undiagnosed HIV prevalence, annual new HIV infections, and annual HIV incidence rates, respectively. The five columns show the estimates of all MSM, MSM aged 15–34, aged 35–64, low-activity, and high-activity MSM, respectively. The dark grey and light grey lines distinguish between the numbers of MSM living with HIV and the new infections. The black lines represent the median (solid lines) and 2.5th and 97.5th percentiles (dash lines) of the model estimates. The summation of diagnosed and undiagnosed prevalence equals the overall HIV prevalence. Similarly, the summation of the estimates of MSM aged 15–34 and 35–64 years, as well as the summation of the estimates of MSM in low-activity and high-activity groups equals that for all MSM. The projections were made based on the assumption that all model parameter values at the end of 2009 remained constant until the end of 2020. We estimated that in 2020 there will be 52 268 (38 064–81 006) MSM living with HIV, 7920 (4560–18 190) MSM living with undiagnosed HIV, and 43 685 (32 960–63 788) MSM living with diagnosed HIV. The 2020 estimates of new infections is 2435 (1126–5571) corresponding to the incidence rate of 0.32% (0.15–0.75%).

the following stages regardless of population subgroup. Our sensitivity analysis (Appendix, section 6, http://links.lww.com/QAD/A612) also confirmed that non-PHI infectiousness was one of the most important drivers of the epidemic, while PHI-related parameters were not among them. This is probably because of a relatively short duration of high infectiousness in the stage of PHI compared to all other subsequent stages. A recent systematic review by Blaser *et al.* [25] suggested that HIV transmission rate during PHI should be around 10 and 30 times higher than that of asymptomatic stage if PHI lasted, respectively, for 6 and 2 months. In comparison to our study in which the duration of PHI was assumed to be 1.24–6 months, we calculated transmission rate from the lower and upper bounds of the per-act transmission probability of PHI and compared to that of $CD4^+$ at least 500 (Table 1) and found that the PHI transmission rate ratio for URAI and UIAI could range from 0.4 up to 250, which is markedly wider than the review suggested [25]. However, even with the wide range of assumed PHI infectiousness, our findings still suggest that it is unlikely that PHI contributes more than 29% to all infections in UK MSM during 2001–2020, as illustrated by the upper limits of the PAF uncertainty ranges. There were also a number of recent studies that arrived at similar findings [26–29]. By contrast, Phillips *et al.* [30] showed in the simulation study that around half of the new infections in UK MSM were from men in PHI, which can probably be explained by assumptions about transmission risk and partnership formation that are different from our model.

The model suggested that around two in three new infections were attributable to men living with undiagnosed HIV, especially with high $CD4^+$ cell counts ($\geq$350 cells/μl). Similarly, a recent back-calculation study estimated large and stable numbers of undiagnosed MSM in England and Wales during 2001–2010, which suggests undiagnosed infections may continue to be a major driver of HIV transmission in the United Kingdom [4]. Outside the United Kingdom, an HIV transmission model predicted that around 82% of new cases among MSM in Switzerland were acquired HIV from undiagnosed men [31], whereas in the United States, the majority of

new infections could be attributable to persons living with undiagnosed HIV [32,33]. This may be explained by the prevalence of risky behaviours, that is, UAI among MSM, which is much higher in HIV-positive persons unaware of their serostatus compared to diagnosed men [14]. Our finding clearly emphasizes a major role of undiagnosed and untreated men at asymptomatic stages in transmitting HIV and consequently requires more effort to be invested in further improvement of the coverage and frequency of HIV testing to detect the virus as early as possible. This is also supported by a recent national survey in the United Kingdom that showed that almost half of MSM had not tested for HIV in the past 5 years [34]. While limited resources should be allocated primarily to promote testing in high-activity MSM under the age of 35, as they are the key group sustaining the epidemic, there is also a case for encouraging all MSM to test regularly for HIV regardless of their age. Including HIV testing in routine health checks or when MSM present with other health problems in the United Kingdom may increase HIV testing uptake and provide necessary counselling for HIV-positive MSM.

The study showed that the majority of new infections of MSM in the United Kingdom occurred within a repeat sexual partnership and the epidemic cannot be controlled by preventing HIV transmission within one-off sexual partnership alone. Our definition of repeat sexual partnership can be matched to any real-life relationships that involve more than one sex act, including both steady relationships and casual encounters. Unfortunately, we were unable to explicitly differentiate between these two types of relationships in our model (i.e. steady vs. casual) due to insufficient behavioural data. On the basis of our belief, however, that low-activity men are more likely to establish a long-term, steady relationship rather than have a one-off casual encounter, an estimated contribution of steady relationships to HIV transmission may be derived from the 23% PAFs of repeat sexual partnerships of low-activity MSM. If a cautious assumption was then made that a quarter of HIV infections attributable to repeat sexual partnerships of high-activity men actually occurred with their long-term, steady partner, the contribution of all steady relationships to HIV transmission could be as high as 40–50%. With such a level of impact, it may be sensible for policy makers to consider interventions that aim specifically at reducing transmission within long-term, steady relationships such as encouraging steady partners to test together at the beginning of their relationship or to test immediately after breaking up.

The key limitation of our study is the uncertainty around all model parameters even after rigorous filtering and validation. Several issues with the available data, including absence, completeness, and representativeness, are among the main sources of uncertainty. For instance, NATSAL2000 was a national-based probability-sampling survey of sexual behaviours and attitudes that were representative of the UK population. However, the survey included only a small number of MSM, so that further stratifications, for example, by age and sexual activity, were sometimes not practical. The age range of the surveyed populations of 16–44 years was also not compatible with the 15–64 age range in this study. In contrast, GMSHS and GYM studies were community-based convenience-sampling surveys in London which, without a prior adjustment, would not be suitable for representing MSM populations at the national level. The sample size and age range were, on the contrary, sufficiently large for in-depth analyses. We handled parameter uncertainty by sampling from wide ranges of plausible parameter values informed by various sources, and fit and validate the model outcomes to the multiple estimates and empirical datasets simultaneously. The derived uncertainty ranges of PAFs demonstrate that our conclusions are robust to variations in the key parameters of the model.

The majority of new HIV infections among MSM in the United Kingdom during 2001–2020 is expected to be accounted for by a small group of highly sexually active individuals under the age of 35 years, living with undiagnosed HIV in the asymptomatic stage. An intensification of the current interventions to increase HIV test uptake and bring this group into the HIV/AIDS care system is a vital step for the prevention of transmission and will determine the success of prevention measure using immediate ART. Intervention programs that are tailor-made for MSM in a long-term relationship could prevent more new infections than previously thought [20]. Taken together, reducing the incidence of HIV among UK MSM may be possible even without the introduction and implementation of any new prevention technologies: we have the means to reduce transmission now.

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Conflicts of interest

The authors have declared that no competing interests exist.

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5.6. Supplementary results

5.6.1. Epidemic projections

5.6.1.1. MSM living with HIV

The projections for the number of MSM living with HIV in the UK stratified by diagnosis status, age group, and sexual activity level are shown in Figure 2 in the main article. The model estimated that there would be 43,682 (35,833-56,387) MSM living with HIV by the end of 2013 corresponding to a prevalence rate of 6.3% (5.1-8.1%). By 2020, the estimated HIV prevalence rose to 52,268 (38,064-81,006) equivalent to 7.3% (5.3-11.3%). During this period (2013–2020), the overall HIV prevalence increased at an average annual rate of 2.6% with the majority of men being diagnosed, particularly those aged 35-64. The numbers of undiagnosed individuals stabilised over time in all age groups. For both sexual activity groups, the overall HIV prevalence at the end of 2013 are similar, but the numbers of undiagnosed men in the high-activity group is roughly twice the number in the low-activity group (5,584 vs. 2,311). The number of diagnosed HIV infections is similar in both activity groups (low: 17,951, high: 17,376).

5.6.1.2. New HIV infections

According to the median estimates of new HIV infections in Figure 2 in the main article, our model indicated that there was an increase in the overall HIV incidence during 2001–2005 before a slight decline during 2005–2009 and levelling off at around 2,400 cases per year (incidence rate of 0.35%) after that, however this is associated with large uncertainty. The 2001–2020 cumulative numbers of new infections were estimated to be 48,148 (29,254-83,713). The rates of new infections in the younger group were about twice as many as those in the older group (0.49% vs. 0.25% in 2013), while unsurprisingly, the incidence in the high-activity men was substantially higher than in the low-activity men (0.64% vs. 0.14% in 2013).

5.6.2. Population attributable fractions

The population attributable fractions (PAFs) stratified by age groups and sexual activity levels are shown in Figure 5-6. The details of analysis and calculation of PAF are provided in the main text.

The PAFs for all MSM are presented in Figure 5-6a. Figure 5-6b and Figure 5-6c show that eliminating HIV spread from MSM aged 15-34, while being highly beneficial within the age group (average PAF of 75%), would prevent a almost half of new infections in MSM aged 35-64 (average PAF of 46%) which is considerably high compared to only 61% in the case where there were no transmission from within the older group itself. Moreover, the contributions remained stable over the 20-year period which, taken together, indicated that interventions targeting young MSM could prove effective in tackling HIV infection. Other factors were shown to uniformly affect both age groups.

The PAF calculated from the incidence rates stratified by sexual activity levels are shown in Figure 5-6d and Figure 5-6e. For both groups, the largest PAF is still associated with transmission from men at non-PHI stages while the contributions of men at PHI are among the lowest. The smallest PAF for the low-activity group is 5% on average for one-off sexual partnership due to low rates of acquiring new partners (≤1 per year) of men in this group (Figure 5-6d). The treated men seem to contribute considerably low (average PAF of 14%) to HIV infections in high-activity group as a result of small proportions of men who still performed high activity after HIV diagnosis (Figure 5-6e). This also explains why the low-activity PAF of HIV diagnosis and treatment changed more rapidly over time than that of high-activity men. The analyses also indicate that HIV-positive men in high-activity group accounted for more infections in low-activity populations than do the low-activity men (Figure 5-6d and Figure 5-6e), which is similar to how young MSM contributed to new infections in both age groups (Figure 5-6b and Figure 5-6c).

Moreover, the repeat sexual partnerships of high-activity MSM make a small contribution to new infections in low-activity men (Figure 5-6d), whereas the repeat sexual partnerships of low-activity MSM make almost no contribution to HIV infection in high-activity men (Figure 5-6e), demonstrating the minor impact of HIV transmission between the two sexual activity groups.

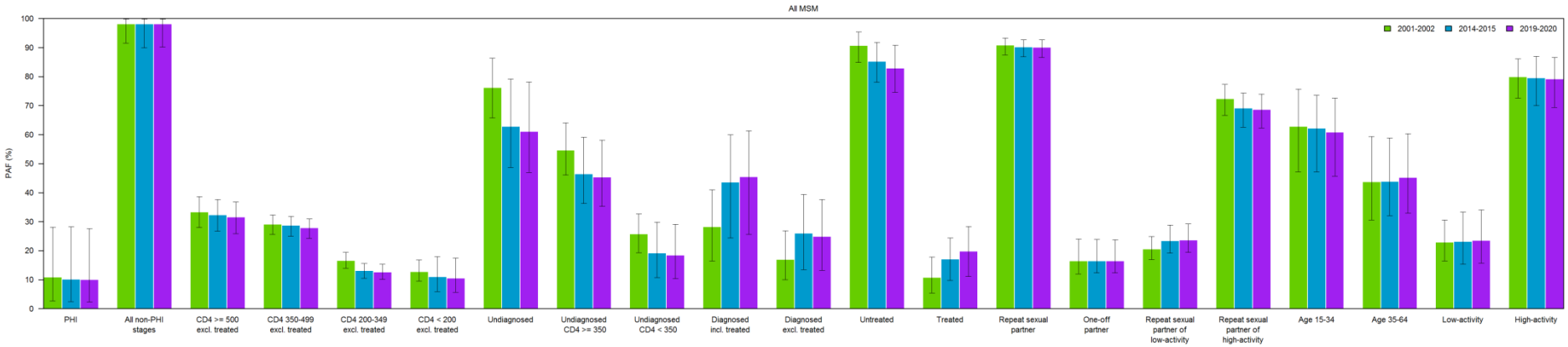
5.6.3. Sensitivity analysis

The sensitivity of model predictions was assessed using the regression trees technique [103]. We selected total new HIV infections during 2001–2020 as the response variable and all filtered parameters except the model initial conditions as the predictor variables (Table S14). We grew the tree and pruned it by selecting the tree size that minimised the sum of squared errors [103].

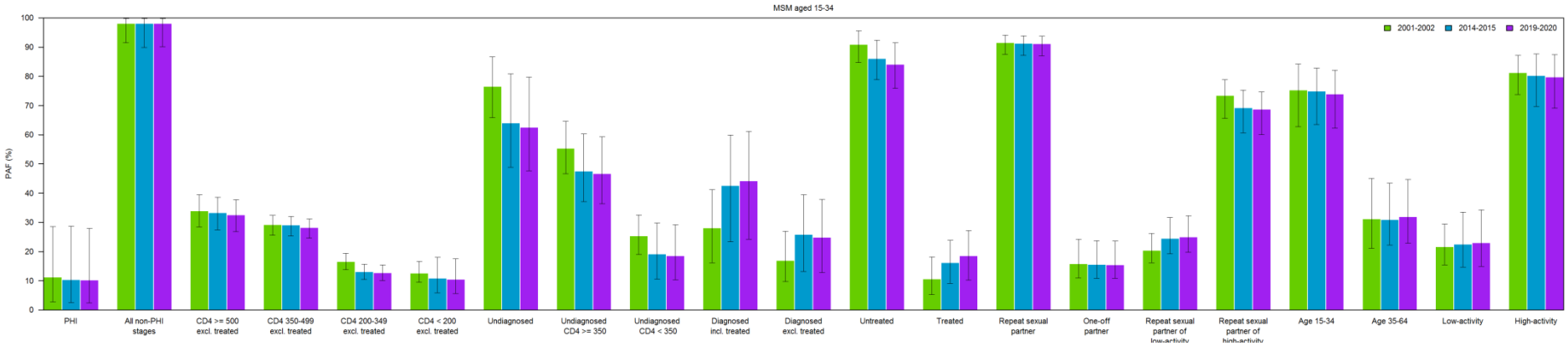
The sensitivity analysis regression tree a total of 7 splits, 8 terminal nodes, and 4 model parameters (Figure 5-7). The most influential model parameter for the new infections during 2001–2020 based on the number of appearances and its level in the tree was the per-URAI act transmission probability in non-PHI stages. The incidence estimates were also highly sensitive to the per-UIAI act non-PHI transmission probability, condom efficacy, and the frequency of sex acts with a repeat sexual partner.

The uncertainty of the estimated infections (43,560-64,980) indicated the importance of these factors in the epidemic of HIV in UK MSM. The number of new infection over 2001–2020 could be as high as 64,980 if the mean infectivity of an URAI and UIAI act at non-PHI stages was greater than 2.0% and 1.0%, respectively. Conversely, if several conditions represented by the route on the far left of the tree (Figure 5-7) were met simultaneously, the incidence of HIV could have been as low as 43,560, corresponding to 13% reduction from the mean estimates of 50,110 cases in the baseline scenario (root node).

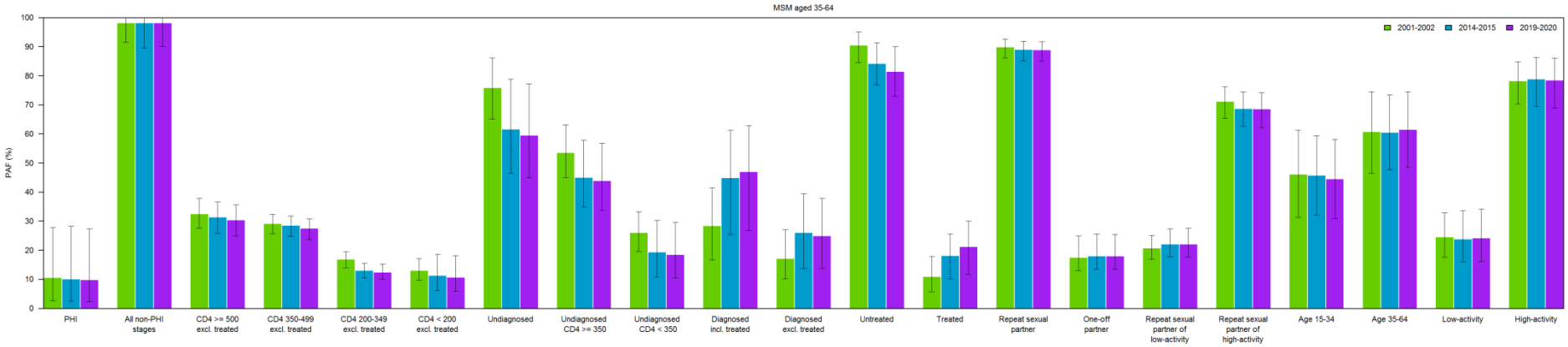
(a) All MSM



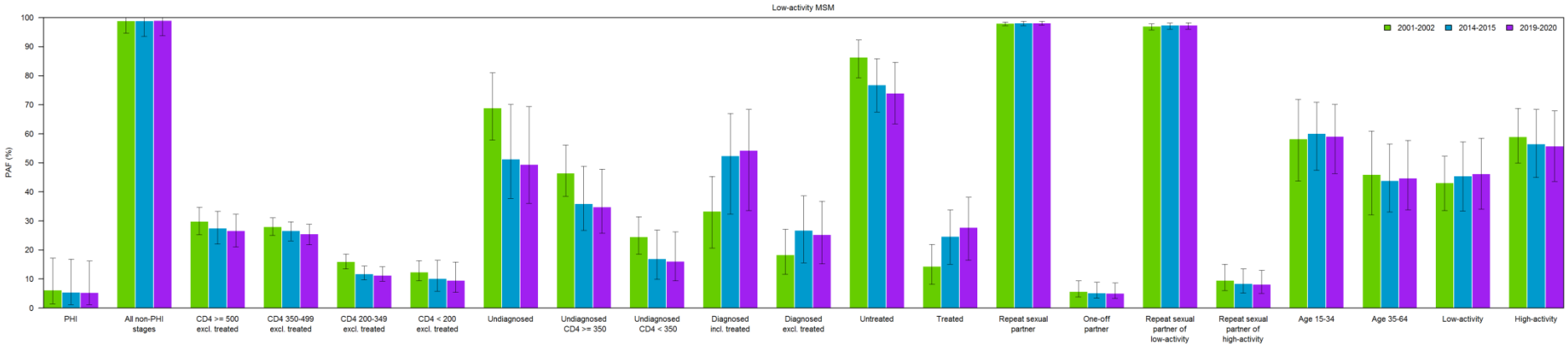
(b) MSM aged 15-34



(c) MSM aged 35-64



(d) Low-activity MSM



(e) High-activity MSM

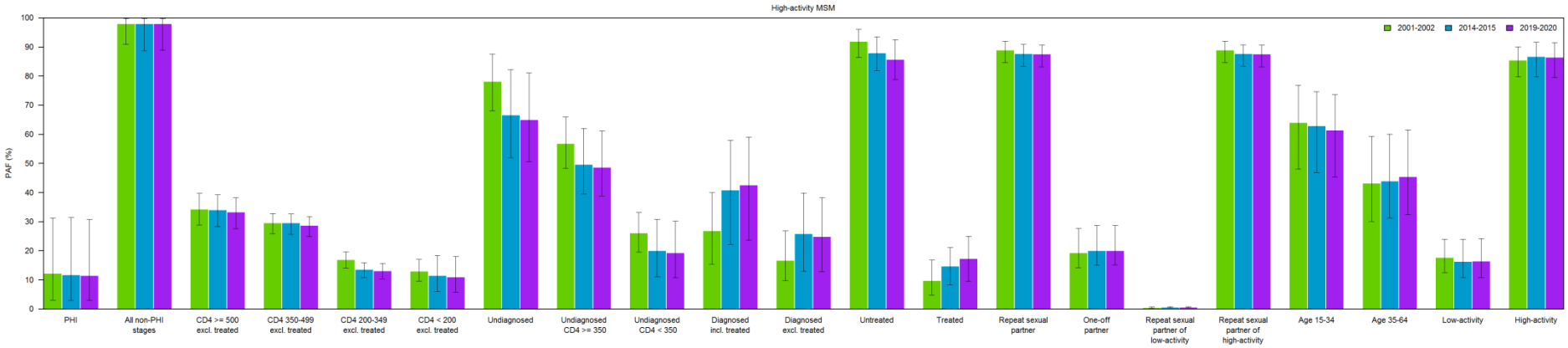


Figure 5-6: Population attributable fractions of various factors for HIV incidence among MSM in the UK stratified by age groups and sexual activity levels

PAF: Population attributable fractions; PHI: Primary HIV infection. The figure shows the impacts of removing the corresponding factors from all MSM on the incidence of HIV in (a) all MSM, (b) MSM aged 15-34, (c) MSM aged 35-64, (d) low-activity MSM, and (e) high-activity MSM. The green, blue, and purple bars represent 2001–2002, 2014–2015, and 2019–2020 PAF respectively. The error bars show the ranges between 2.5th and 97.5th percentiles of the estimated PAF.

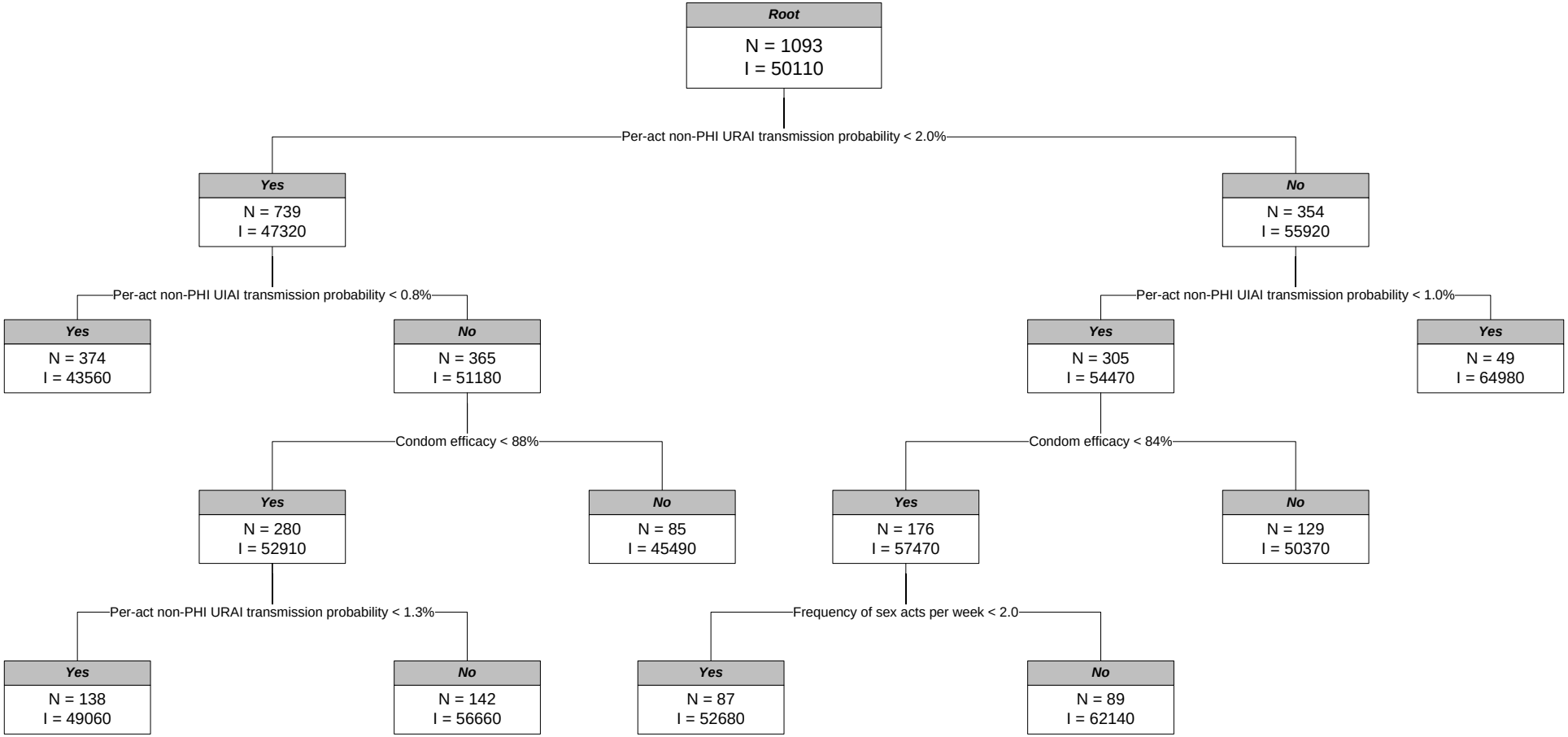


Figure 5-7: Model regression tree for sensitivity analysis

5.7. Conclusion

Chapter 5 has presented the findings on the contributions made by various HIV-positive subpopulations to HIV transmission among UK MSM. The majority of new HIV infections during 2001–2020 is expected to be accounted for by a small group of highly sexually active individuals under the age of 35 years, living with undiagnosed HIV in the asymptomatic stage. In the next chapter, a range of interventions will be investigated for the potential impact in preventing HIV transmission from sex between men in the UK.

Chapter 6

The impact of HIV interventions

In this chapter:

Model modifications for HIV interventions

Answers to research questions 3 and 4

Publication:

'Potential impact of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the United Kingdom: a mathematical modelling study'

6.1. Introduction

The main aim of this chapter is to assess the potential impact of a range of interventions to help inform effective HIV control strategies in the future. The HIV epidemic in men who have sex with men (MSM) in the UK with effects of HIV prevention interventions will be projected up to 2020. The primary research questions 3 and 4 will be addressed in this chapter.

6.2. Publication

The manuscript on the potential impact of HIV prevention interventions, entitled 'Potential impact of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the United Kingdom: a mathematical modelling study', has been submitted to *The Lancet HIV*. The details on model modifications to incorporate interventions have also been submitted as supplementary materials. Both the main text and supplementary materials of this article are presented in this chapter in the submitted format.

6.2.1. Article submitted

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Narat Punyacharoensin
Principal Supervisor	Richard White
Thesis Title	Modelling HIV transmission and control among men who have sex with men in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study with inputs from all co-authors. I carried out all the model development and analysis in consultation with all co-authors. I wrote the paper and did the revision based on comments from all co-authors.

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Main text

Manuscript title:

Potential impact of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the United Kingdom: a mathematical modelling study

Running title:

HIV interventions for MSM in the UK

Authors:

Narat Punyacharoensin, MSc [1]

Professor William John Edmunds, PhD [1]

Daniela De Angelis, PhD [2]

Valerie Delpech, FFPH [3]

Professor Graham Hart, PhD [4]

Professor Jonathan Elford, PhD [5]

Alison Brown, PhD [3]

Professor Noel Gill, FFPH [3]

Richard Guy White, PhD [1]

[1] Centre for the Mathematical Modelling of Infectious Diseases and Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Medical Research Council Biostatistics Unit, Cambridge, UK

[3] HIV and STI Department, Public Health England, Colindale, London, UK

[4] Centre for Sexual Health & HIV Research, Department of Infection & Population Health, Mortimer Market Centre, University College London, London, UK

[5] School of Health Sciences, City University London, London, UK

Corresponding author:

Narat Punyacharoensin, MSc

Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom.

E-mail: narat.punyacharoensin@lshtm.ac.uk, narat.punyacharoensin@yahoo.com

Tel: +4420-7636-8636

Fax: +4420-7436-5389

Abstract

Background

HIV transmission among men who have sex with men (MSM) in the United Kingdom (UK) has shown no sign of decreasing in the last decade. Additional prevention measures are required. We investigated a range of potential interventions implemented individually and in combination to estimate their impact in preventing HIV infections.

Methods

A deterministic partnership-based mathematical model, informed by detailed behavioural and surveillance data was extended to assess various HIV interventions including expanding HIV testing, test-and-treat, pre-exposure prophylaxis (PrEP), and sexual behavioural changes. Sensitivity analysis was conducted.

Findings

We predicted a total of around 17,000 new infections among MSM in the UK during 2014–2020. Based on 100% coverage, PrEP with 44% efficacy would prevent the largest number of infections, nearly 10,000 cases (59% of total incidence). At a low coverage (25%), test-and-treat had similar impact to PrEP and outperformed many other interventions. Combined impact of test-and-treat and increased HIV testing was greater than the impact of the interventions individually, unlike other intervention combinations. Simultaneously offering PrEP, expanding HIV testing, and initiating test-and-treat programme in 25% of different target populations could save around 7,400 UK MSM from HIV infection (44% of total incidence). A large increase in

unsafe sex and sexual partners would markedly increase incidence but is unlikely to completely negate the prevention benefit.

Interpretation

PrEP has the potential to prevent a large number of new HIV infections if other key strategies including HIV testing and treatment are simultaneously expanded and improved. Without PrEP, it is unlikely that there will be a marked decline in HIV incidence among MSM in the UK by the end of this decade.

Funding

None

Keywords

mathematical model, HIV/AIDS, homosexual, MSM, intervention, PrEP, treatment as prevention

Introduction

In the United Kingdom, the estimated number of people living with HIV in 2013 was 107,800, around 40% of which were men who have sex with men (MSM) which was equivalent to 0.59% prevalence in MSM aged 15-59 years.[1] Approximately 2,600 MSM have been infected with HIV each year during the past 10 years[2] with no sign of decrease in recent years,[1] and, without alternative HIV prevention measures, incidence is expected to remain at this level throughout the decade.[3]

Attempts to prevent HIV transmission in the UK have focused around promoting proper and consistent condom use and increasing coverage and frequency of HIV testing.[1] But since these interventions alone have shown to be insufficient to reduce HIV incidence among UK MSM over time, more attention has been paid to alternative strategies of HIV infection control including early antiretroviral treatment (ART) and the use of pre-exposure prophylaxis (PrEP). Two recent PrEP trails, PROUD study in England[4] and IPERGAY study in France and Canada,[5] had to discontinue the placebo arm and begin providing PrEP to all eligible participants after their interim results showed the high protective effect of PrEP.

As the combination of conventional and alternative prevention measures is now being considered, there is an urgent need to have a better understanding of their potential impact against HIV transmission among UK MSM. The aim of this study was to evaluate the potential impact of various HIV interventions, individually and in combination, using a mathematical model. The outcomes include reduction in HIV

incidence during 2014–2020. We also investigated the sensitivity of our results to variation in intervention coverage, PrEP efficacy, and the effects of potential risk compensation.

Methods

Mathematical model

A previous deterministic partnership-based model for HIV transmission among MSM aged 15-64 in the UK[3] was extended to investigate the effects of various alternative HIV prevention interventions. The R software package[6] was used for model building and analysis. The model time step was one day. The model consisted of 15 compartments (Figure S1). The five disease stages—primary HIV infection (PHI), CD4≥500, 350-499, 200-349, and <200 cells/μL—had different HIV transmission probabilities derived from the average viral load in each stage. Once progressed to the treatment stage, individuals remained there until being removed from the model due to mortality or exceeding 64 years old.

MSM were divided into 'current' and 'past' MSM. The current MSM were those who reported having sex with men in the past five years and were assumed to continue acquire new male sexual partners. Past MSM were those who reported having no sex with men in the past five years and were assumed in our model to no longer have sexual relationship with men. This was to exclude individuals who may have no contribution towards further HIV transmission among MSM. MSM were further divided into low and high sexual activity, defined respectively as MSM who have, on average, ≤1 and >1 new male sexual partner per year. We assumed that MSM did not change activity level except after being diagnosed with HIV. If diagnosed, 66% of high-activity MSM were assumed to become low-activity and 7% of low-activity

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MSM were assumed to become high-activity, derived from a cohort study in UK MSM.[7] Model MSM were categorised into two age groups: 15-34 (age group 1) and 35-64 years (age group 2). We assumed that size of the two age groups changes over time in line with the general UK male population. The initial model population size in year 2000 was 648,500 MSM, 259,500 of which were 15-34 and 389,000 were 35-64 years.[3]

The model simulated two types of sexual partnerships: one-off sexual partnerships and repeat sexual partnerships. One-off sexual partnership consists of only a single sex act, whereas the repeat sexual partnership lasts for a finite period of time and consists of multiple sex acts with the same partner. We assumed non-random mixing between partners using a method based on odds ratios[8] and assumed, in line with data, that MSM were more likely to select new sexual partners of the same age group, sexual activity level, and perceived HIV serostatus.[3] HIV can only be transmitted through five types of sex between men: protected and unprotected receptive anal intercourse (URAI), protected and unprotected insertive anal intercourse (UIAI), and unprotected receptive oral intercourse (UROI). Further details of the model and the force of infection derivation is in our previous paper.[3]

The main sources for estimating demographic and behavioural parameters were the 2000 National Survey of Sexual Attitudes and Lifestyles (NATSAL),[9] the 2000–2006 Gay Men's Sexual Health Survey (GMSHS) in London,[10] and the 2000–2008 London Gym Survey (GYM).[11] The data from the community-based convenience-sample GMSHS and GYM surveys were adjusted to match key important variables from the

national-based probability-sample NATSAL survey.[3] The national HIV/AIDS surveillance databases including HIV/AIDS diagnoses and CD4 surveillance provided data that were used extensively throughout the parameterisation. Unknown parameters were estimated through model fitting using the Monte Carlo filtering method.[12] We sampled 20,000 different combinations of the fitted parameters using Latin Hypercube sampling and ran 20,000 model simulations to match the 2001–2009 estimates of the overall and undiagnosed HIV prevalence simultaneously. 1,093 parameter sets fit to the data and were later used for simulating the HIV epidemic in MSM in the UK from 2001 to 2020. Model validation was then conducted by comparing the model estimates to the national estimates of annual new HIV infections, the number of new HIV diagnoses, and the number of ART-treated MSM during 2001–2009. Additional information on model parameterisation and calibration is in our previous paper.[3]

HIV interventions

The model simulations were conducted for the period 2001 to 2020 and intervention programmes were introduced in 2014. The impact of interventions was evaluated using the number of HIV infections prevented during the intervention period compared to the 'status quo' scenario where no additional interventions have been implemented. The changes over time in the number of new infections and the number of individuals living with HIV were also assessed. The model outputs are presented using median estimates with interquartile range (IQR).

Individual interventions

The previous study suggested that undiagnosed HIV, repeat sexual partnerships, and young and high-activity MSM were the most important drivers of the HIV epidemic in UK MSM.[3] Several interventions have been suggested by modelling studies[13] and are of recent interest.[14,15] We, consequently, formed and investigated seven individual HIV interventions as follows: 1.1) test for HIV once a year, 1.2) test for HIV twice a year, 1.3) a test-and-treat program—increasing the ART eligibility criteria from CD4<350 to CD4≥350, 1.4) PrEP, 1.5) reducing the number of repeat sexual partners, 1.6) reducing the number of one-off sexual partners, and 1.7) reducing unprotected anal intercourse (UAI) with repeat sexual partners. Each intervention was implemented in three target groups: all MSM, MSM aged 15-34, and high-activity MSM. The intervention coverage, which was defined as the proportion of MSM who adopted each intervention, was assumed to be 100% for clarity of exposition in all scenarios of individual and combined interventions and should be considered as a maximum impact of the intervention as this coverage is highly unlikely. The effects of reducing the coverage of the individual interventions to 75%, 50%, and 25% were also assessed. Changing PrEP coverage was analysed in conjunction with changing PrEP efficacy from 44% to 20%, 60%, 80% and 100% to show the joint effects these two parameters have on incidence reduction. Table 1 summarises key parameters and details for modelling the individual interventions.[3,16]

Combined interventions

We modelled the seven combinations of the individual interventions as follows: 2.1) test once a year and decrease UAI with repeat sexual partners, 2.2) reduce the number

of repeat sexual partners and decrease UAI with repeat sexual partners, 2.3) test once a year and test-and-treat, 2.4) PrEP and test-and-treat, 2.5) PrEP and decrease UAI with repeat sexual partners, 2.6) PrEP and reduce the number of repeat sexual partners, and 2.7) all individual interventions except test once a year. The combined interventions are applied only to all MSM. All parameter values in individual intervention scenarios remained unchanged in the combined intervention scenarios.

Practical scenarios

We then attempted to assess the impact of various combinations of selected interventions at more realistic levels of coverage. The results from the previous sections were used to inform a number of practical scenarios of implementing various interventions to different target groups simultaneously based on more conservative coverage assumptions. We mainly focused on the interventions that were able to perform well individually or in combination with specific interventions. We assumed that all interventions achieved 25% coverage of the target populations. The 'extreme' risk compensation assumption was used to represent a near worst-case scenario.

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Results

The model estimates of the number of new HIV infections among UK MSM during the last decade showed good consistency with the national estimates (Figure 1). The status quo scenario estimated a total of 16,955 (IQR: 13,156-21,669) HIV infections among MSM in the UK with around 2,400 new infections annually during 2014 to 2020, which is equivalent to approximately 6.6 new HIV infections every day. Without additional interventions, there is expected to be 52,268 (45,982-59,794) MSM living with HIV in the UK by 2020 with annual incidence rates of 0.34% (0.26-0.45%). Supplementary results including sensitivity analysis on risk compensation are also presented in the Appendix, section 2.

Individual interventions

With 100% programme coverage, PrEP was estimated to prevent the greatest number of HIV infections (9,955 (7,402-12,872) men, 59% (44-76%) of total incidence). Even targeted only at high-activity men, PrEP was more effective (reduced 51% (38-67%) of total incidence) than all other individual intervention that targeted with the entire UK MSM population (Table 2 and Figure S1a). A large number of MSM could also be protected from HIV infection (7,263 (5,565-9,424) men, 43% (33-56%) of total incidence) by decreasing the number of repeat sexual partners by 50%. Decreasing the proportion of men who performed UAI with repeat sexual partners by 50% achieved 31% (23-42%) incidence reduction during the intervention period.

An estimated 5,522 (4,021-7,807) new infections (33% (24-46%) of total incidence) would be prevented by testing annually. This increased to 7,089 (5,247-9,848) which is equivalent to a 42% (31-58%) incidence reduction if the average frequency of testing was increased to twice a year. Providing ART earlier (test-and-treat) reduced total incidence by 24% (16-33%) but one test-and-treat participant could prevent 0.322 new infections during 2014–2020, which is more than 17 times higher than PrEP (unit impact=0.019) (Table 2).

Coverage of interventions

Altering the coverage of interventions had a large impact on preventing new infections (Figure 2a). Reducing repeat sexual partnerships was the most affected intervention, with an approximate 75% decrease in impact as coverage reduced from 100% to 25%, whereas the same coverage fall resulted in a 55% and 37% decrease in impact for testing once and twice a year, respectively. The robustness to variation in programme coverage indicates that expanding HIV testing and treatment may still perform relatively well even when adopted by a smaller proportion of MSM. At 25% coverage of all interventions, testing twice a year produced the greatest impact; the impact of test-and-treat was greater than most other interventions, and was on par with PrEP (Figure 2a). The other individual interventions tended to show an approximately linear relationship between coverage and impact.

Coverage and efficacy of pre-exposure prophylaxis

Assuming an efficacy of 44%, if coverage was 50% rather than 100%, PrEP would fail to prevent 4,144 new infections. Increasing the efficacy increased the number of

infections prevented regardless of the coverage (Figure 2b). The PrEP intervention with 100% coverage and 20% efficacy was able to prevent 1,275 more cases than that with 25% coverage and 100% efficacy (6,893 vs. 5,618). However, at low to moderate efficacy (<60%) but high coverage (≥75%), increasing PrEP coverage appeared to lead to slightly higher impact than increasing efficacy. On average, a 1% increase in PrEP coverage led to an impact increase of 1.90%, whilst a 1% increase in PrEP efficacy led to an impact increase of 1.25% (Figure 2b).

Combined interventions

The highest impact from the 2 intervention combinations was obtained when combining PrEP with the intervention aimed at reducing repeat sexual partnerships. This would prevent 75% (57-96%) of total incidence (Table 2 and Figure S1b). A small number of new infections still occurred even when all interventions with 100% coverage were implemented simultaneously (Table 2). We calculated the rate that HIV prevalence declined in the 'all interventions' scenario, and applied this rate beyond the end of our projections; we estimated that HIV may reach zero prevalence around 2044 which suggested that disease elimination among UK MSM was very unlikely even after implementing a wide range of highly effective HIV interventions simultaneously.

Diminishing returns occurred in the majority of combined interventions. For example, separately implementing programmes to increase frequency of HIV testing and decrease UAI with repeat sexual partners was estimated to prevent 33% (24-46%) and 31% (23-42%) of new infections, respectively, while combining both achieved only 49% (37-65%) incidence reduction (Table 2). Only the combination of annual HIV

testing with the test-and-treat programme was able to provide an additional incidence reduction compared to the sum of the impacts of the two interventions individually (Table 2).

Practical scenarios

Table 3 shows the impact of all 12 practical scenarios and describes the scenario assumptions in more detail. The first scenario (3.1) assumed PrEP was provided to 25% of the high-activity HIV-negative MSM in the UK and for high-activity men who did not use PrEP, 25% had an annual HIV test. This package had impact on HIV incidence of 26%, and impact increased to 37% if PrEP coverage was increased to 50% (scenario 3.2). Adding test-and-treat to scenario 3.1 prevented 7,399 cases (44% of total incidence), the highest number among the practical scenarios assessed here (scenario 3.3). This scenario also provided the largest unit impact of 0.053. Replacing test-and-treat with programmes to encourage fewer sexual partners and fewer UAI had lower impact (scenario 3.4 and 3.5) (Table 3 and Figure S1c).

In the analysis of risk compensation in PrEP users, scenario 3.6 assumed that all PrEP men in scenario 3.1 completely stopped using condoms with repeat sexual partners. This resulted in HIV incidence impact falling to 12% (Table 3). Scenario 3.7 assumed all PrEP men in scenario 3.1 acquired twice as many repeat sexual partners. Surprisingly impact increased to 28% compared to scenario 3.1 (26%). This was because more sexual partnerships of PrEP men would require a larger number of non-PrEP partners including infected men, and this would reduce the probability that non-PrEP susceptibles had serodiscordant relationships, particularly with undiagnosed

MSM. However, it is possible that more demand for partners from PrEP users may result in an increase in the partnership formation rates of the general MSM population and with only a 10% increase in partnership formation rates the programme impact dropped to 22% (scenario 3.8).

In scenario 3.9, PrEP was replaced by an annual HIV test and we also assumed that 25% of the entire MSM population reduced repeat sexual partnerships by half. The impact was 22% in this scenario (Table 3). Adding the test-and-treat programme with 25% coverage to scenario 3.9 increased impact to 41% (scenario 3.10). However, the benefit of earlier ART was completely negated if high-activity men, instead, tested for HIV half as frequently (scenario 3.11). If even more risk compensation behaviour occurred by assuming that all ART-treated MSM completely stopped using condoms with repeat sexual partners due to the benefit of immediate ART, the impact would fall to 16% (scenario 3.12).

Discussion

Our analysis confirmed the importance of implementing a combination of interventions for effective HIV control among MSM.[13,17] The provision of PrEP as a part of combination strategy, even to one fourth of highly sexually active individuals, may prevent more than 7,000 new HIV infections in the UK before the end of this decade (scenario 3.3). The relatively small coverage the programme requires is highly feasible since around half of MSM in the UK have showed interest in participating in PrEP[18] and treatment as prevention programmes.[19] The fact that high-risk men are more likely to try PrEP[20] would also facilitate the programme launch.

One of the main concerns about PrEP is that risk compensation could reduce the impact of the intervention.[21] It has been suggested that MSM who would use PrEP would also be likely to decrease condom use,[22] although there was no evidence of risk compensation among participants in the open-label trial of iPrEx[23] and PROUD study.[24] Our risk compensation analyses suggested that a substantial increase in UAI would be required to negate the population-level benefits of PrEP. However, but in reality, the negative impact of risk compensation could be multiplied, for example, in PrEP men with poor drug adherence in whom there is an increase in unsafe sex and number of partners simultaneously. Approximating increased risk-taking in real-world situations using the behavioural insights gathered from clinical trials is, thus, highly important but may require more appropriate study designs other than a conventional longitudinal analysis.[25] With sufficient knowledge and understanding, the complementary risk-reduction programmes could be tailor-made to help adjust

perceptions of risks and benefits underlying the mechanism of risk compensation among PrEP users.

Another issue regarding PrEP is its protective efficacy against HIV. In this study we assumed a baseline efficacy of 44% for the daily FTC–TDF which was suggested by a clinical trial among MSM in six non-European countries.[16] The HIV protective effects of PrEP relied greatly on drug adherence of programme participants[14,16] which could differ greatly between the trial and actual implementation in the UK. The recent findings from PROUD open-label trail suggested a relative incidence reduction of 86% between participants who received PrEP immediately and after 12-month deferral period.[24] Moreover, PrEP program is not a stand-alone intervention but rather a package of several components including medication, HIV testing, counselling, and risk reduction. The impact of PrEP program will thus rely greatly on the quality of these supplementary programs and may exceed our estimates if all are successfully implemented.

In comparison to PrEP, our findings showed that the test-and-treat programme has a limited impact on HIV prevention at the population level (scenario 1.3), which is consistent with modelling studies in other settings.[26-27] This may be explained by the already small contribution of diagnosed MSM to total HIV infections[3] due to reductions in high-risk behaviours and the fact that some of these diagnosed men would eventually be treated with ART within a few years after diagnosis according to the ART eligibility of CD4<350 cells/µL in the UK.[28] Moreover, the benefit of early ART among MSM is still unknown, and there is a possibility that the high level of

HIV prevention found in heterosexuals may not hold for homosexuals due to high transmissibility of HIV via anal sex between men.[29] This issue should become clearer when results from the ongoing trial designed to investigate the prevention benefits of early ART in MSM are unveiled in 2015.[30]

The key strengths of test-and-treat (scenario 1.3) lie in various different aspects. First, the robustness of the programme in relation to risk compensation behaviour. This could be explained by the benefits of ART in reducing HIV transmission probability between serodiscordant couples[31] that exceed the adverse effects of plausible risk compensation. Second, the capability of the programme to perform well at low coverage makes it suitable for various practical situations where reaching full coverage is virtually impossible. Third, since earlier ART is only offered to diagnosed MSM, the required number of participants to reach the targeted incidence reduction is much smaller than that required by other programmes that focus on a pool of susceptibles and undiagnosed men. Finally, test-and-treat was the only intervention investigated here that, when implemented along with increased HIV testing frequency (scenario 1.1 and 1.2) and coverage, provided additional benefits over the sum of the two independent effects. This is due to the completely non-overlapping target groups (undiagnosed vs. diagnosed MSM) between the two interventions and the increased number of diagnosed individuals to be treated earlier with ART.

A modelling study among UK MSM by Phillips et al[32] reported that immediate ART would prevent 32% of new infections during 2006–2010 compared to our 100% coverage estimates of 24% during 2014–2020. The slight difference in the estimates

probably lies in different timescales and the underlying assumptions of the interventions. We assumed that the person diagnosed at CD4≥350 cells/μL except in primary HIV infection had the same ART initiating rate as those diagnosed at CD4<350 cells/μL, while in the above study ART was initiated immediately in all MSM diagnosed with HIV after 2000.[32] The study also reported a 25% decline in incidence if HIV test rate has been increasing since 2000 until 2010 when 68% of all MSM were tested each year,[32] whereas in our study testing once a year with 50-75% coverage would lower the incidence by 25-30%. Both our and Phillips et al[32] studies suggested the same 62% incidence reduction at the maximum if more frequently testing and earlier ART were implemented simultaneously.

The 90-90-90 targets proposed recently by UNAIDS aimed for a 90% reduction in HIV incidence by 2030 compared with that of 2010 by setting three ambitious targets.[33] The first target called for 90% of people living with HIV in 2020 to be aware of their infection.[33] The 2013 proportion of diagnosed MSM in the UK of 84%[1] made this target highly possible. The other two targets that expected 90% of diagnosed individuals to be treated with ART and 90% of which have an undetectable viral load[33] have already been achieved.[1] Despite all these achievements, the target incidence in 2030 is still unlikely without additional interventions. Our baseline scenario suggested a constant level of 2,000-3,000 new infections among UK MSM each year through 2020 with no sign of decreasing. Using linear regression on our 2014–2020 estimates to extrapolate the future incidence, we found that having at least 50% of MSM to consistently test once a year or use PrEP would be necessary to attain 90% incidence reduction by 2030. Both raised the proportion of diagnosed MSM to

around 95% while maintained the proportion of MSM on treatment at around 90%. Achieving 90-90-90 targets may not lead to 2030 goal[34] and in UK MSM setting achieving and sustaining 95-90-90 targets by 2020 would be required.

Our study has several limitations. First, our analyses are by necessity a simplification of the real-world, and may overestimate actual programme impact. For example, in the base case we assumed 100% coverage in analyses of individual and combined interventions. However, the overall conclusions remained similar when the coverage was reduced and we also applied a much smaller level of coverage in the practical scenarios to reflect more conservative outcomes. Second, the effects of ART resistance[35] and co-infection with other sexually transmitted diseases[36] on HIV transmission were not explicitly included in this study. Unless the prevalence of co-infection and drug resistant strains changes dramatically during the intervention period, their effects on the impact of interventions are not likely to be influential. Third, the UK regional difference was not accounted for in this study. Although this may not have a substantial effect on the impact of interventions at the national level, the regional difference may play an important role in some specific areas. Finally, our analysis did not include cost-effectiveness which is also crucial for informing public health decision making. It is possible that any highly effective programmes against HIV transmission suggested in this study may not be cost-effective in the real UK setting. Although a simple cost approximation of implementing the interventions can be carried out using the estimated numbers of programme participants provided in the tables, further in-depth economic analyses are still necessary to inform timely and accurate decision making. The future work should also involve investigating the

impact of changes in other behavioural factors, e.g. partnership duration and mixing preferences, on the impact of interventions.

In conclusion, our analysis suggests that a combination of PrEP, expanding HIV testing, and test-and-treat programmes implemented in relatively small groups of MSM in the UK could prevent thousands from HIV within a few years of implementation, particularly if risk compensation behaviour is successfully avoided. Integrating this enhanced version of conventional interventions with novel biomedical technologies is likely to deliver the optimal approach to HIV prevention that could determine the future course of the HIV epidemic in the UK.

Panel: Research in context

Systematic review

We searched PubMed for studies published in English up to December 31, 2014 using the search terms: “HIV”, “intervention” or “prevention”, “men who have sex with men” or “MSM” or “homosexual” or “gay”, and “model”. We identified four studies that used a mathematical model to estimate the potential impact of combinations of HIV interventions among men who have sex with men (MSM) in South Korea,[26] South Africa,[27] China,[37] and the UK.[32] All four studies evaluated the impact of increasing HIV testing and early treatment,[26-27,32,37] while only two of which included pre-exposure prophylaxis (PrEP) and increasing condom use.[26-27] PrEP showed a promising effect against HIV infection among MSM in many settings and appeared to be more effective than other included interventions.[26-27] No studies evaluated PrEP impact among MSM in the UK.

Interpretation

Our study used a mathematical model to estimate the impact of seven different HIV interventions implemented individually and simultaneously among MSM in the UK during 2014–2020. The majority of included interventions have not previously been assessed. The model incorporated a large number of important heterogeneities and was calibrated and validated against multiple surveillance datasets and national estimates. Our findings indicated that PrEP can be highly effective against HIV

transmission at the population level and could easily outperform other interventions at the same level of programme coverage. A feasible combination of PrEP, test-and-treat, and HIV testing programme implemented in relatively small groups of MSM could prevent a substantial number of new infections, even with a high level of risk compensation.

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Tables

Table 1: Summary of key parameters for modelling individual interventions

Parameter	Symbol	Value			
		Aged 15-34 years		Aged 35-64 years	
		Low-activity	High-activity	Low-activity	High-activity
1.1) Test for HIV once a year					
HIV diagnosis rate [a]	ϕ	0.0027			
1.2) Test for HIV twice a year					
HIV diagnosis rate [a]	ϕ	0.0054			
1.3) Test-and-treat program					
Rate of initiating ART [b]	τ	0.0104			
1.4) PrEP program					
Risk reduction of PrEP against HIV infection	ϖ	0.56			
Rate at which susceptibles start taking PrEP	κ^{on}	0.0252			
Rate at which susceptibles stop taking PrEP	κ^{off}	2.7×10^{-7}			
Reduction factor on transmission probability during PHI in failed-PrEP users	Ω	0.875			
HIV diagnosis rate for PrEP users	ϕ_{14}	0.0219			
Mean duration of PHI after diagnosed with HIV	γ_{15}	1.5 months			
1.5) Reduce repeat sexual partnerships					

Parameter	Symbol	Value			
		Aged 15-34 years		Aged 35-64 years	
		Low-activity	High-activity	Low-activity	High-activity
Rate of repeat sexual partnership formation	ρ^{rep}	0.00115 (0.00111-0.00120)	0.00857 (0.00756-0.00954)	0.00126 (0.00120-0.00131)	0.00744 (0.00672-0.00822)
1.6) Reduce one-off sexual partnerships					
Rate of one-off sexual partnership formation					
MSM without a repeat sexual partner	ρ_{Y}^{one}	0.00069 (0.00060-0.00079)	0.02729 (0.01827-0.03966)	0.00107 (0.00094-0.00119)	0.02523 (0.01802-0.03370)
MSM with a repeat sexual partner	ρ_{P}^{one}	-	0.02446 (0.02117-0.02822)	-	0.02244 (0.01892-0.02670)
1.7) Decrease UAI use with repeat sexual partners					
Proportion of susceptibles who have UAI with a perceived HIV negative repeat sexual partner	$p_{uai,pneg}^{rep}$	53.1% (37.8-65.2%)	45.6% (33.4-55.2%)	43.4% (29.5-54.4%)	34.1% (23.6-42.2%)
Proportion of susceptibles who have UAI with a diagnosed HIV positive repeat sexual partner	$p_{uai,dpos}^{rep}$	42.8% (20.8-59.7%)	9.9% (4.5-14.2%)	15.1% (9.2-25.9%)	6.3% (0.4-10.8%)

Abbreviation:
ART: Antiretroviral treatment
PrEP: Pre-exposure prophylaxis
PHI: Primary HIV infection
UAI: Unprotected anal intercourse

All rates are per modelling time step (one day). The values in parentheses represent the 2.5th and 97.5th percentiles of the corresponding parameters that were included in the model fitting. The parameters that were not included in the model fitting have no lower and upper limits. More detail about PrEP modelling are provided in the Appendix, section 1.3. The baseline values were identified in our previous study.[3] For the first and second intervention, we assigned the HIV diagnosis rates of once and twice a year to the target groups of all disease stages. This decreased the mean time between tests of UK MSM from 3.37 years to 1 and 0.5 year, respectively. The third intervention, the test-and-treat program, assigned the ART initiating rate of CD4<350 cells/μL to all other CD4 stages except in primary HIV infection in which it was assumed no ART was provided. Infectiousness during treatment was calculated from the observed viral load data of ART-treated MSM in the UK. The median estimates of the derived transmission probabilities were 0.207%, 0.094%, and 0.005% per unprotected receptive anal

intercourse, unprotected insertive anal intercourse, and unprotected receptive oral intercourse, respectively, which corresponded to about 7-9 times less than that of CD4 200-349 cells/µL. The morality rate per year of ART-treated MSM was assumed to be 0.00843 for those aged 15-34 and 0.00899 for aged 35-64, which was around 9-fold and 2-fold of that of HIV-negative MSM of the same age group. More details about the calculations are provided in the previous study.[3] In the PrEP intervention, PrEP is provided to HIV-negative men in the target populations in the form of a once-daily pill containing emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) with an assumed efficacy for HIV prevention among MSM of 44%.[16] More details on the PrEP intervention are given in the Appendix, section 1.3. The next two interventions were behavioural and were assumed to reduce the number of new repeat and one-off sexual partners by 50% in the target groups. Consequently, the mean repeat and one-off sexual partner acquisition rates in all MSM reduced from 1.68 and 6.18 to 0.84 and 3.09 partners per year, respectively. The partnership formation rates of individuals not involved in the programmes remained unchanged. The next sexual behavioural intervention motivated the target groups to reduce UAI with repeat sexual partners. We modelled this by decreasing the proportion of susceptibles who perform UAI with repeat sexual partners by 50%.

[a] Rate for all CD4 stages
[b] Rate for all CD4 stages except PHI

Table 2: The estimated number of HIV infections prevented by the individual and combined interventions at 100% coverage over 2014–2020

HIV intervention	Participant size [a]	No. infections prevented 2014-2020 [b]	% infections prevented 2014-2020 [c]	Total infections 2014-2020	Unit impact [d]	New infections in 2020	HIV incidence in 2020 (%)	No. living with HIV in 2020	HIV prevalence in 2020 (%)
Status quo scenario	-	-	-	16,955	-	2,435	0.34	52,268	7.26
				(13,156-21,669)		(1,854-3,226)	(0.26-0.45)	(45,982-59,794)	(6.37-8.30)
Individual interventions									
1.1) Test once a year									
All MSM	772,600	5,522	32.6	11,090	0.007	1,245	0.17	46,525	6.45
		(4,021-7,807)	(23.7-46.0)	(8,440-14,400)		(907-1,678)	(0.13-0.23)	(41,501-52,804)	(5.76-7.33)
MSM aged 15-34	366,400	3,547	20.9	13,136	0.010	1,629	0.23	48,549	6.74
		(2,488-5,273)	(14.7-31.1)	(10,148-16,783)		(1,213-2,131)	(0.17-0.30)	(42,982-55,148)	(5.96-7.65)
High-activity MSM	299,200	5,090	30.0	11,518	0.017	1,334	0.18	46,869	6.51
		(3,730-7,258)	(22.0-42.8)	(8,831-14,886)		(976-1,777)	(0.14-0.25)	(41,821-53,262)	(5.81-7.40)
1.2) Test twice a year									
All MSM	772,600	7,089	41.8	9,521	0.009	1,081	0.15	45,074	6.25
		(5,247-9,848)	(30.9-58.1)	(7,197-12,358)		(782-1,425)	(0.11-0.20)	(40,439-50,917)	(5.61-7.07)
MSM aged 15-34	366,400	4,651	27.4	11,999	0.013	1,477	0.21	47,398	6.58
		(3,374-6,746)	(19.9-39.8)	(9,242-15,286)		(1,096-1,914)	(0.15-0.27)	(42,116-53,809)	(5.85-7.47)
High-activity MSM	299,200	6,653	39.2	9,991	0.022	1,145	0.16	45,531	6.32
		(4,883-9,198)	(28.8-54.2)	(7,633-12,937)		(849-1,524)	(0.12-0.21)	(40,877-51,423)	(5.67-7.13)
1.3) Test-and-treat program									
All MSM	12,600	4,053	23.9	12,640	0.322	1,642	0.23	48,087	6.68
		(2,790-5,654)	(16.5-33.3)	(9,960-16,036)		(1,268-2,133)	(0.18-0.30)	(42,851-53,963)	(5.95-7.49)
MSM aged 15-34	4,300	2,579	15.2	14,229	0.600	1,918	0.27	49,650	6.89
		(1,708-3,583)	(10.1-21.1)	(11,177-18,117)		(1,477-2,500)	(0.21-0.35)	(44,192-56,028)	(6.13-7.78)
High-activity MSM	7,100	2,937	17.3	13,834	0.414	1,853	0.26	49,353	6.85
		(1,951-4,210)	(11.5-24.8)	(10,869-17,476)		(1,413-2,385)	(0.20-0.33)	(43,887-55,444)	(6.09-7.70)
1.4) PrEP program									
All MSM	537,800	9,955	58.7	7,036	0.019	642	0.09	42,980	5.97
		(7,402-12,872)	(43.7-75.9)	(5,566-8,775)		(504-803)	(0.07-0.11)	(38,757-47,726)	(5.38-6.63)

MSM aged 15-34	331,100	7,053	41.6	9,938	0.021	1,036	0.14	45,408	6.33
		(5,175-9,226)	(30.5-54.4)	(7,846-12,459)		(803-1,311)	(0.11-0.18)	(40,817-50,909)	(5.68-7.09)
High-activity MSM	294,100	8,665	51.1	8,272	0.029	819	0.11	44,134	6.15
		(6,513-11,336)	(38.4-66.9)	(6,581-10,292)		(637-1,023)	(0.09-0.14)	(39,677-49,168)	(5.52-6.85)
1.5) Reduce number of repeat sexual partners									
All MSM	558,900	7,263	42.8	9,637	0.013	1,143	0.16	45,454	6.32
		(5,565-9,424)	(32.8-55.6)	(7,612-12,277)		(884-1,489)	(0.12-0.21)	(40,720-51,150)	(5.67-7.12)
MSM aged 15-34	338,300	5,005	29.5	11,903	0.015	1,519	0.21	47,269	6.59
		(3,671-6,642)	(21.7-39.2)	(9,401-15,084)		(1,168-1,971)	(0.16-0.27)	(42,293-53,517)	(5.89-7.46)
High-activity MSM	304,300	5,513	32.5	11,426	0.018	1,436	0.20	47,045	6.53
		(4,080-7,314)	(24.1-43.1)	(8,975-14,318)		(1,099-1,831)	(0.15-0.25)	(41,996-53,100)	(5.84-7.38)
1.6) Reduce number of one-off sexual partners									
All MSM	558,900	1,973	11.6	14,901	0.004	2,055	0.29	50,530	7.02
		(1,455-2,706)	(8.6-16.0)	(11,585-18,961)		(1,558-2,672)	(0.22-0.37)	(44,561-57,528)	(6.19-7.99)
MSM aged 15-34	338,300	1,176	6.9	15,732	0.003	2,213	0.31	51,155	7.10
		(856-1,656)	(5.1-9.8)	(12,230-20,060)		(1,681-2,873)	(0.23-0.40)	(45,156-58,279)	(6.27-8.10)
High-activity MSM	304,300	1,922	11.3	14,951	0.006	2,063	0.29	50,584	7.02
		(1,416-2,646)	(8.4-15.6)	(11,622-19,022)		(1,564-2,683)	(0.22-0.37)	(44,595-57,578)	(6.19-8.00)
1.7) Decrease UAI with repeat sexual partners									
All MSM	558,900	5,271	31.1	11,529	0.009	1,479	0.21	47,166	6.54
		(3,948-7,114)	(23.3-42.0)	(8,930-14,891)		(1,111-1,955)	(0.15-0.27)	(41,987-53,395)	(5.82-7.42)
MSM aged 15-34	338,300	3,481	20.5	13,306	0.010	1,776	0.25	48,672	6.76
		(2,561-4,839)	(15.1-28.5)	(10,397-17,108)		(1,364-2,346)	(0.19-0.33)	(43,229-55,408)	(6.00-7.69)
High-activity MSM	304,300	4,134	24.4	12,691	0.014	1,672	0.23	48,273	6.69
		(3,011-5,647)	(17.8-33.3)	(9,898-16,292)		(1,267-2,199)	(0.18-0.31)	(42,811-54,546)	(5.94-7.58)
Combined interventions									
2.1) Test once a year and decrease UAI with repeat sexual partners	1,331,500	8,344	49.2	8,371	0.006	902	0.13	44,103	6.12
		(6,285-11,033)	(37.1-65.1)	(6,333-10,927)		(648-1,220)	(0.09-0.17)	(39,470-49,512)	(5.48-6.88)
2.2) Reduce number of repeat sexual partners and UAI with repeat sexual partners	1,117,800	10,225	60.3	6,721	0.009	724	0.10	42,745	5.95
		(7,802-13,171)	(46-77.7)	(5,279-8,530)		(554-937)	(0.08-0.13)	(38,473-47,564)	(5.35-6.62)

2.3) Test once a year and test-and-treat	785,200	10,471	61.8	6,430	0.013	609	0.08	42,016	5.83
		(7,996-13,873)	(47.2-81.8)	(5,078-8,005)		(468-768)	(0.06-0.11)	(37,973-46,511)	(5.27-6.46)
2.4) PrEP and test-and-treat	550,400	11,803	69.6	5,137	0.021	403	0.06	41,033	5.70
		(8,842-15,324)	(52.2-90.4)	(4,139-6,327)		(331-494)	(0.05-0.07)	(37,190-45,259)	(5.16-6.29)
2.5) PrEP and decrease UAI with repeat sexual partners	1,096,700	11,664	68.8	5,262	0.011	479	0.07	41,344	5.74
		(8,919-15,103)	(52.6-89.1)	(4,141-6,656)		(370-610)	(0.05-0.08)	(37,402-45,613)	(5.19-6.33)
2.6) PrEP and reduce number of repeat sexual partners	1,096,700	12,653	74.6	4,306	0.012	345	0.05	40,564	5.65
		(9,638-16,310)	(56.8-96.2)	(3,436-5,325)		(274-424)	(0.04-0.06)	(36,705-44,633)	(5.11-6.22)
2.7) All interventions except test once a year	2,999,700	16,368	96.5	626	0.005	15	< 0.01	36,375	5.07
		(12,673-20,911)	(74.7-123.3)	(507-777)		(12-19)	< 0.01	(33,219-39,720)	(4.62-5.53)

Abbreviation:
PrEP: Pre-exposure prophylaxis
UAI: Unprotect anal intercourse

The median and interquartile range of the estimates shown in parentheses were derived from 1,093 simulations. The status quo scenario shows the estimates without any additional interventions. Each individual intervention was implemented in three different target groups: All MSM, MSM aged 15-34, and high-activity MSM. The combined interventions were only applied to all MSM. The coverage was assumed 100% in both cases.

[a] The total number of participants covered by each intervention during the intervention period. For the combined interventions, this is simply the sum of the coverage of the individual interventions. The number of test-and-treat participants represents only those that were treated with ART earlier in their disease course because of the program.
[b] The numbers of HIV infections prevented were derived from the difference between the median estimates of infections in the status quo scenario and the numbers of infections in the scenarios with interventions.
[c] The percentages prevented was derived by dividing the median estimates of infections in the status quo scenario by the number of infections prevented by the interventions.
[d] The unit impact represents the number of infections prevented per a programme participant.

Table 3: The estimated number of HIV infections prevented in the practical scenarios over 2014–2020

Practical scenarios	Participant size [a]	No. infections prevented 2014-2020 [b]	%infections prevented 2014-2020 [c]	Total infections 2014-2020	Unit impact [d]	New infections in 2020	HIV incidence in 2020 (%)	No. living with HIV in 2020	HIV prevalence in 2020 (%)
3.1) PrEP and test once a year	137,400	4,480	26.4	12,363	0.033	1,466	0.20	47,879	6.66
• PrEP in 25% of HIV-negative high-activity MSM	78,500	(3,326-6,018)	(19.6-35.5)	(9,680-15,830)		(1,117-1,931)	(0.16-0.27)	(42,576-54,266)	(5.92-7.55)
• Test once a year in 25% of non-PrEP high-activity MSM	58,900								
3.2) More PrEP and test once a year	196,300	6,302	37.2	10,564	0.032	1,154	0.16	46,203	6.43
• PrEP in 50% of HIV-negative high-activity MSM	157,000	(4,739-8,483)	(28.0-50.0)	(8,306-13,409)		(891-1,494)	(0.12-0.21)	(41,246-52,048)	(5.74-7.25)
• Test once a year in 25% of non-PrEP high-activity MSM	39,300								
3.3) PrEP, test once a year, and test-and-treat	140,600	7,399	43.6	9,483	0.053	958	0.13	45,003	6.26
• As in scenario 3.1	137,400	(5,587-9,813)	(32.9-57.9)	(7,563-11,865)		(755-1,216)	(0.11-0.17)	(40,351-50,395)	(5.62-7.02)
• Added: Test-and-treat in 25% of diagnosed MSM [d]	3,200								
3.4) PrEP, test once a year, and less repeat sexual partnerships	257,500	5,743	33.9	11,137	0.022	1,270	0.18	46,784	6.51
• As in scenario 3.1	137,400	(4,339-7,634)	(25.6-45.0)	(8,730-14,223)		(975-1,672)	(0.14-0.23)	(41,688-52,846)	(5.80-7.36)
• Added: Reduce repeat sexual partnerships by 0.5-fold in 25% of all non-PrEP MSM	120,100								
3.5) PrEP, test once a year, and less UAI	257,500	5,229	30.8	11,579	0.020	1,348	0.19	47,203	6.57
• As in scenario 3.1	137,400	(3,952-6,999)	(23.3-41.3)	(9,069-14,780)		(1,029-1,770)	(0.14-0.25)	(41,955-53,422)	(5.83-7.44)
• Added: Reduce UAI by 0.5-fold in 25% of all non-PrEP MSM	120,100								
3.6) PrEP and test once a year but with (RC) no condom use with repeat sexual partners	137,400	1,950	11.5	14,836	0.014	1,862	0.26	50,237	6.99
• As in scenario 3.1	137,400	(1,195-3,056)	(7.0-18.0)	(11,650-18,992)		(1,421-2,454)	(0.20-0.34)	(44,401-57,316)	(6.17-7.98)
• Added: (RC) Completely stop using condom with repeat sexual partners in all PrEP MSM	-								
3.7) PrEP and test once a year but with (RC) more repeat sexual partnerships	137,400	4,750	28.0	12,065	0.035	1,411	0.20	47,561	6.62
• As in scenario 3.1	137,400	(3,582-6,412)	(21.1-37.8)	(9,455-15,432)		(1,082-1,852)	(0.15-0.26)	(42,340-53,899)	(5.89-7.50)
• Added: (RC) Increase repeat sexual partnerships by 2-fold all PrEP MSM	-								
3.8) PrEP and test once a year but with (RC) no condom use with repeat sexual partners and (RC) more repeat sexual partnerships	137,400	3,782	22.3	13,009	0.028	1,563	0.22	48,405	6.73
• As in scenario 3.7	137,400	(2,796-5,232)	(16.5-30.9)	(10,174-16,663)		(1,191-2,056)	(0.17-0.29)	(43,008-55,019)	(5.98-7.65)

• Added: (RC) Completely stop using condom with repeat sexual partners in all PrEP MSM	-								
3.9) Reduce repeat sexual partnerships and test once a year	214,500	3,761	22.2	13,054	0.018	1,610	0.22	48,561	6.75
• Reduce repeat sexual partnerships by 0.5-fold in 25% of MSM	139,700	(2,811-5,065)	(16.6-29.9)	(10,118-16,744)		(1,208-2,138)	(0.17-0.30)	(43,076-55,250)	(5.98-7.68)
• Test once a year in 25% of high-activity MSM	74,800								
3.10) Reduce repeat sexual partnerships, test once a year, and test-and-treat	217,700	6,879	40.6	10,029	0.032	1,060	0.15	45,550	6.32
• As in scenario 3.9	214,500	(5,213-9,062)	(30.7-53.4)	(7,947-12,604)		(823-1,348)	(0.11-0.19)	(40,729-51,080)	(5.66-7.11)
• Added: Test-and-treat in 25% of diagnosed MSM	3,200								
3.11) Reduce repeat sexual partnerships and test-and-treat but with (RC) less HIV testing	142,900	3,729	22.0	13,072	0.026	1,732	0.24	48,610	6.75
• Reduce repeat sexual partnerships by 0.5-fold in 25% of MSM	139,700	(2,706-5,104)	(16.0-30.1)	(10,272-16,582)		(1,328-2,241)	(0.18-0.31)	(43,186-54,611)	(6.00-7.59)
• Test-and-treat in 25% of diagnosed MSM	3,200								
• (RC) Reduce HIV testing frequency by 0.5-fold in 25% of high-activity MSM	-								
3.12) Reduce repeat sexual partnerships and test-and-treat but with (RC) less HIV testing and (RC) no condom use with repeat sexual partners	142,900	2681	15.8	14124	0.019	1932	0.27	49625	6.90
• As in scenario 3.11	142,900	(1,751-3,917)	(10.3-23.1)	(11,231-17,837)		(1,503-2,484)	(0.21-0.35)	(44,075-55,910)	(6.12-7.77)
• Added: (RC) Completely stop using condom with repeat sexual partners in all ART-treated MSM	-								

Abbreviation:
PrEP: Pre-exposure prophylaxis
UAI: Unprotect anal intercourse
RC: Risk compensation
The list of interventions implemented in the practical scenarios. The median and interquartile range of the estimates shown in parentheses were derived from 1,093 simulations.
[a] The total number of participants covered by each intervention during the intervention period. The total number of participants in each set of interventions is the sum of the number of participants from each individual intervention.
[b] The number of HIV infections prevented was the difference between the median estimates of infections in the status quo scenario and the numbers of infections in the scenarios with interventions.
[c] The percentages prevented was derived by dividing the median estimates of infections in the status quo scenario by the number of infections prevented by the interventions.
[d] The unit impact represents the number of infections prevented per a programme participant.

Figures

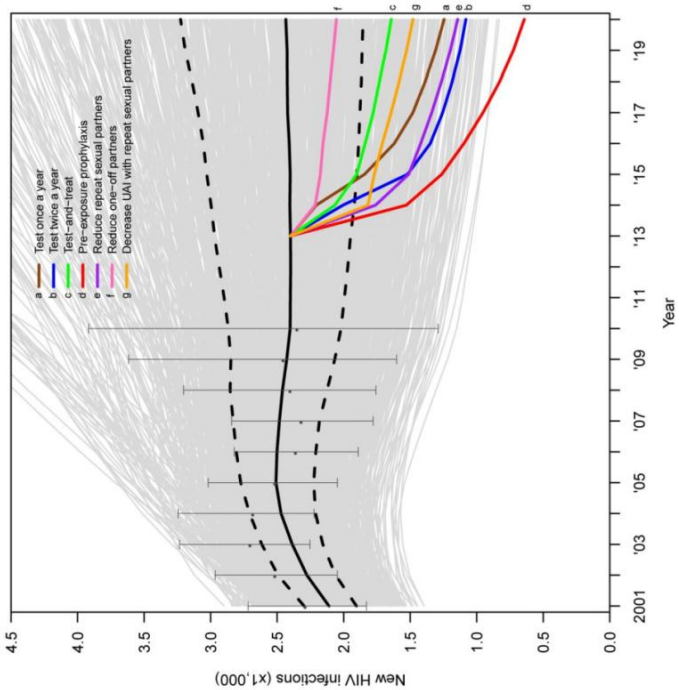

Figure 1: Impact of individual interventions at 100% coverage on the number of new HIV infections

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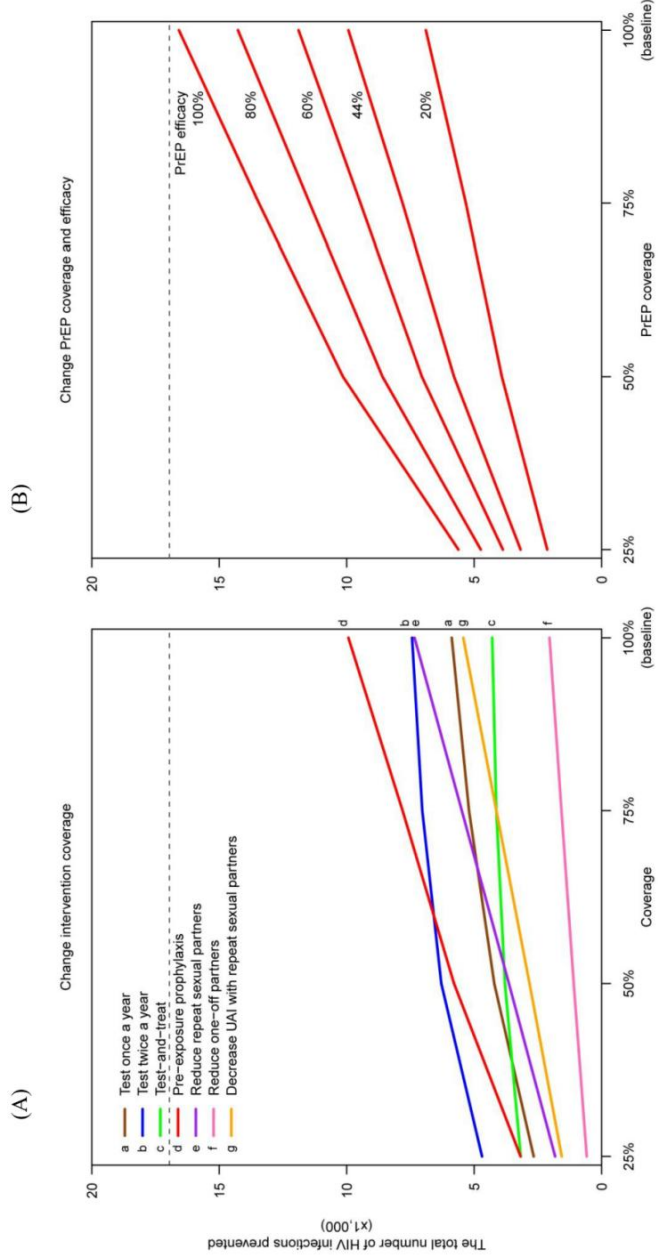

Figure 2: The effect of varying (A) interventions coverage, and (B) PrEP coverage and efficacy, on the number of new HIV interventions prevented over 2014–2020

Figure legends

Figure 1

The estimated numbers of new HIV infections between 2001 and 2020 in the status quo scenario and the intervention scenarios with 100% coverage. The light grey lines show the estimates from 1,093 simulations in the status quo scenario. The black lines show the median estimates (solid line) with interquartile range (dashed lines) from these simulations. The grey dots and error bars show the national estimates in England and Wales during 2001–2010.[2] The average goodness-of-fit of the model is 94.4% which was calculated from the mean of $1-(|O_t - E_t|/O_t)\times 100\%$, where O_t and E_t are the national estimates and the model estimates at time *t*, respectively. The solid lines presented in various colours depict the median estimates of new HIV infections during 2014–2020 in the seven individual intervention scenarios.

Figure 2

Median estimates of the total numbers of HIV infections prevented among MSM in the UK during 2014–2020. The dashed line shows the median estimates of the total number of HIV infections in the status quo scenario. (A) The effects of changing interventions coverage. For HIV testing programs, coverage excluded MSM that already tested at least once a year in the status quo scenario. For test-and-treat, the coverage is the proportion of MSM diagnosed with HIV at CD4≥350 cells/μL and exclude MSM that have already have been treated in the status quo scenario. (B) The effects of various combinations between coverage and efficacy of PrEP.

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Appendix

Potential impact of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the United Kingdom: a mathematical modelling study

Table of contents

1. HIV transmission model

The detailed information about the mathematical model and modelling techniques used in this study are provided extensively in our previous paper.[1] Here, we only describe briefly the HIV transmission model and focus on providing information about some specific components that were extended from the previous model.

1.1 Overview of the HIV transmission model

We adopted and extended the previously published mathematical model of the HIV transmission dynamics among men who have sex with men (MSM) aged 15-64 in the United Kingdom.[1] The flow diagram of the model according to HIV stages and diagnosis status is illustrated in Figure S1, showing a total of 15 different compartments. The main modifications were made to facilitate the implementation of pre-exposure prophylaxis (PrEP) intervention. All key model assumptions and defined terms of the previous model were still applied. The structure of the model and baseline values of model parameters remained unchanged. We used 1,093 sets of accepted parameters values obtained from the previous study[1] to estimate the effects of the potential HIV interventions during the intervention period between 2014 and 2020.

1.2 Model equations

The model used here was constructed based on a set of 1,980 ordinary differential equations and can be described by the 87 equations listed below. The model flow diagram is shown in Figure 1 in the main text. All MSM in the model were stratified

into single (X) and those currently in relationship with a repeat sexual partner (P). The single MSM were further divided into current (Y) and past MSM (Z). Let $Y_{j,k,h}$ and $Z_{j,k,h}$, respectively, be the number of current and past MSM in age group j (j=1 for age group 1, j=2 for age group 2), sexual activity group k (k=1 for low-activity group, k=2 for high-activity group), and HIV infection stages h ($h = 1,\ldots,15$ according to 15 HIV stages: 1=susceptibles, 2=undiagnosed PHI, 3=diagnosed PHI, 4=undiagnosed CD4≥500, 5=diagnosed CD4≥500, 6=undiagnosed CD4 350-499, 7=diagnosed CD4 350-499, 8=undiagnosed CD4 200-349, 9=diagnosed CD4 200-349, 10=undiagnosed CD4<200, 11=diagnosed CD4<200, 12=on treatment, 13=susceptibles on PrEP, 14=undiagnosed PHI on PrEP, and 15=PHI diagnosed while on PrEP). Let $P_{j,k,h}^{m,n,r}$ be the number of pairs where one repeat sexual partner is in age group j, sexual activity group k, and HIV stages h and another in age group m, sexual activity group n, and HIV stages r. We noted that $P_{j,k,h}^{m,n,r} = P_{m,n,r}^{j,k,h}$. All parameters are summarised in Table S1. The model time step was one day (δ=1/365=0.0027) and multiplying any per-year rates by δ will result in the corresponding rates per time-step. The appendix of the previous study[1] provided detailed description of the model.

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We noted that $[j,k] \neq [m,n]$ in all equations below, and the $\{condition\}$ denotes a specific condition that must be satisfied to enable the corresponding term.

Current single MSM

$$\frac{dY_{j,k,1}}{dt} = \nu_{j,k}\{j=1\} - \eta_{j,k,1}\{k=1\} + \sigma_{j,k}(P_{j,k,1}^{j,k,1} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,1}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,1}\{j=2\} - (\alpha_j + \mu_{j,1} + \rho_{j,k}^{rep} + \lambda_{Y,j,k}^{one} + \kappa_{j,k}^{on})Y_{j,k,1} + \kappa_{j,k}^{off}Y_{j,k,13} \quad (1)$$

$$\frac{dY_{j,k,2}}{dt} = \sigma_{j,k}(P_{j,k,2}^{j,k,2} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,2}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,2}\{j=2\} + \lambda_{Y,j,k}^{one}Y_{j,k,1} - (\alpha_j + \mu_{j,2} + \gamma_2 + \phi_{j,k,2} + \rho_{j,k}^{rep})Y_{j,k,2} \quad (2)$$

$$\frac{dY_{j,k,3}}{dt} = \sigma_{j,k}(P_{j,k,3}^{j,k,3} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,3}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,3}\{j=2\} + (1-s_k)\phi_{j,k,2}Y_{j,k,2} + s_l\phi_{j,l,2}Y_{j,l,2}\{l \neq k\} - (\alpha_j + \mu_{j,3} + \gamma_3 + \rho_{j,k}^{rep})Y_{j,k,3} \quad (3)$$

$$\frac{dY_{j,k,h}}{dt} = -\eta_{j,k,h}\{k=1\} + \sigma_{j,k}(P_{j,k,h}^{j,k,h} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,h}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,h}\{j=2\} + \gamma_{h-2}Y_{j,k,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,h} + \rho_{j,k}^{rep})Y_{j,k,h} \quad \text{for } h = 4, 6, 8, 10. \quad (4)$$

$$\frac{dY_{j,k,h}}{dt} = -\eta_{j,k,h}\{k=1\} + \sigma_{j,k}(P_{j,k,h}^{j,k,h} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,h}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,h}\{j=2\} + (1-s_k)\phi_{j,k,h-1}Y_{j,k,h-1} + s_l\phi_{j,l,h-1}Y_{j,l,h-1}\{l \neq k\} + \gamma_{h-2}Y_{j,k,h-2} + \gamma_{15}Y_{j,k,15}\{h=5\} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h + \rho_{j,k}^{rep})Y_{j,k,h} \quad \text{for } h = 5, 7, 9, 11. \quad (5)$$

$$\frac{dY_{j,k,12}}{dt} = -\eta_{j,k,12}\{k=1\} + \sigma_{j,k}(P_{j,k,12}^{j,k,12} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,12}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,12}\{j=2\} + \sum_{g \in s}\tau_g Y_{j,k,g} - (\alpha_j + \mu_{j,12} + \rho_{j,k}^{rep})Y_{j,k,12} \quad \text{where } s = 5, 7, 9, 11. \quad (6)$$

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$$\frac{dY_{j,k,13}}{dt} = \sigma_{j,k}(P_{j,k,13}^{j,k,13} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,13}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,13}\{j=2\} - (\alpha_j + \mu_{j,13} + \rho_{j,k}^{rep} + \varpi\lambda_{Y,j,k}^{one} + \kappa_{j,k}^{off})Y_{j,k,13} + \kappa_{j,k}^{on}Y_{j,k,1} \quad (7)$$

$$\frac{dY_{j,k,14}}{dt} = \sigma_{j,k}(P_{j,k,14}^{j,k,14} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,14}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,14}\{j=2\} + \varpi\lambda_{Y,j,k}^{one}Y_{j,k,13} - (\alpha_j + \mu_{j,14} + \phi_{j,k,14} + \rho_{j,k}^{rep})Y_{j,k,14} \quad (8)$$

$$\frac{dY_{j,k,15}}{dt} = \sigma_{j,k}(P_{j,k,15}^{j,k,15} + \sum_{m=1}^{2}\sum_{n=1}^{2}\sum_{r=1}^{12} P_{j,k,15}^{m,n,r}) + \alpha_{j-1}Y_{j-1,k,15}\{j=2\} + (1-s_k)\phi_{j,k,14}Y_{j,k,14} + s_l\phi_{j,l,14}Y_{j,l,14}\{l \neq k\} - (\alpha_j + \mu_{j,15} + \rho_{j,k}^{rep})Y_{j,k,15} \quad (9)$$

Past MSM

$$\frac{dZ_{j,1,1}}{dt} = \eta_{j,1} + \alpha_{j-1}Z_{j-1,1,1}\{j=2\} - (\alpha_j + \mu_{j,1})Z_{j,1,1} \quad (10)$$

$$\frac{dZ_{j,1,2}}{dt} = \eta_{j,2} + \alpha_{j-1}Z_{j-1,1,2}\{j=2\} - (\alpha_j + \mu_{j,2} + \gamma_2 + \phi_{j,1,2})Z_{j,1,2} \quad (11)$$

$$\frac{dZ_{j,1,3}}{dt} = \eta_{j,3} + \alpha_{j-1}Z_{j-1,1,3}\{j=2\} + \phi_{j,1,2}Z_{j,1,2} - (\alpha_j + \mu_{j,3} + \gamma_3)Z_{j,1,3} \quad (12)$$

$$\frac{dZ_{j,1,h}}{dt} = \eta_{j,h} + \alpha_{j-1}Z_{j-1,1,h}\{j=2\} + \gamma_{h-2}Z_{j,1,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,1,h})Z_{j,1,h} \quad \text{for } h = 4, 6, 8, 10. \quad (13)$$

$$\frac{dZ_{j,1,h}}{dt} = \eta_{j,h} + \alpha_{j-1}Z_{j-1,1,h}\{j=2\} + \phi_{j,1,h-1}Z_{j,1,h-1} + \gamma_{h-2}Z_{j,1,h-2} - (\alpha_j + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h)Z_{j,1,h} \quad \text{for } h = 5, 7, 9, 11. \quad (14)$$

$$\frac{dZ_{j,1,12}}{dt} = \eta_{j,12} + \alpha_{j-1}Z_{j-1,1,12}\{j=2\} + \sum_{g \in s}\tau_g Z_{j,1,g} - (\alpha_j + \mu_{j,12})Z_{j,1,12} \quad \text{where } s = 5, 7, 9, 11. \quad (15)$$

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Paired MSM

Susceptible (HIV stage no.1) – Susceptible (HIV stage no.1)

$$\frac{dP_{j,k,1}^{j,k,1}}{dt} = \psi_{j,k,1}^{rep,j,k,1}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,1}\{j=2\} - (2\alpha_j + 2\mu_{j,1} + \sigma_{j,k} + 2\lambda_{P,j,k}^{one})P_{j,k,1}^{j,k,1} \tag{16}$$

$$\frac{dP_{j,k,1}^{m,n,1}}{dt} = \psi_{j,k,1}^{rep,m,n,1}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,1}\{j=2\} + \alpha_{m-1}P_{m-1,n,1}^{j,k,1}\{m=2\} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,1} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{P,m,n}^{one})P_{j,k,1}^{m,n,1} \tag{17}$$

Susceptible (HIV stage no.1) – Susceptible on PrEP (HIV stage no.13)

$$\frac{dP_{j,k,1}^{j,k,13}}{dt} = \psi_{j,k,1}^{rep,j,k,13}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,13}\{j=2\} - (2\alpha_j + \mu_{j,1} + \mu_{j,13} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \varpi\lambda_{P,j,k}^{one} + \kappa_{j,k}^{off})P_{j,k,1}^{j,k,13} + 2\kappa_{j,k}^{on}P_{j,k,1}^{j,k,1} \tag{18}$$

$$\frac{dP_{j,k,1}^{m,n,13}}{dt} = \psi_{j,k,1}^{rep,m,n,13}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,13}\{j=2\} + \alpha_{m-1}P_{m-1,n,1}^{j,k,13}\{m=2\} - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,13} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \varpi\lambda_{P,m,n}^{one} + \kappa_{m,n}^{off})P_{j,k,1}^{m,n,13} + \kappa_{m,n}^{on}P_{j,k,1}^{m,n,1} \tag{19}$$

Susceptible (HIV stage no.1) – Infected (HIV stage no.2-12, and 14-15)

$$\begin{aligned}\frac{dP_{j,k,1}^{j,k,2}}{dt} &= \psi_{j,k,1}^{rep,j,k,2}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,2}\{j=2\} + 2\lambda_{P,j,k}^{one}P_{j,k,1}^{j,k,1} \\ &\quad - (2\alpha_j + \mu_{j,1} + \mu_{j,2} + \gamma_2 + \phi_{j,k,2} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,2} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,2}\end{aligned} \tag{20}$$

$$\begin{aligned}\frac{dP_{j,k,1}^{m,n,2}}{dt} &= \psi_{j,k,1}^{rep,m,n,2}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,2}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,1}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{P,m,n}^{one})P_{j,k,1}^{m,n,1} \\ &\quad - (\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,2} + \gamma_2 + \phi_{m,n,2} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,2} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,2} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,2}\end{aligned} \tag{21}$$

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$$\frac{dP_{j,k,1}^{j,k,3}}{dt} = \psi_{j,k,1}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,3}\{j=2\} + (1-s_k)\phi_{j,k,2}P_{j,k,1}^{j,k,2} + s_l\phi_{j,l,2}P_{j,k,1}^{j,l,2}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,3} + \gamma_3 + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,3} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,3} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,3} \quad (22)$$

$$\frac{dP_{j,k,1}^{m,n,3}}{dt} = \psi_{j,k,1}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,3}^{j,k,1}\{m=2\} + (1-s_n)\phi_{m,n,2}P_{j,k,1}^{m,n,2} + s_l\phi_{m,l,2}P_{j,k,1}^{m,l,2}\{l \neq n\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,3} + \gamma_3 + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,3} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,3} \quad (23)$$

$$\frac{dP_{j,k,1}^{j,k,h}}{dt} = \psi_{j,k,1}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,1}^{j,k,h-2}$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,h} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,h} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,h} \quad \text{for } h = 4, 6, 8, 10. \quad (24)$$

$$\frac{dP_{j,k,1}^{m,n,r}}{dt} = \psi_{j,k,1}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,1}\{m=2\} + \gamma_{r-2}P_{j,k,1}^{m,n,r-2}$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,r} + \gamma_r\{r \neq 10\} + \phi_{m,n,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,r} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,r} \quad \text{for } r = 4, 6, 8, 10. \quad (25)$$

$$\frac{dP_{j,k,1}^{j,k,h}}{dt} = \psi_{j,k,1}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,1}^{j,k,h-2} + \gamma_{15}P_{j,k,1}^{j,k,15}\{h=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,1}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,1}^{j,l,h-1}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,h} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,h} \quad \text{for } h = 5, 7, 9, 11. \quad (26)$$

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$$\frac{dP_{j,k,1}^{m,n,r}}{dt} = \psi_{j,k,1}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,1}\{m=2\} + \gamma_{r-2}P_{j,k,1}^{m,n,r-2} + \gamma_{15}P_{j,k,1}^{m,n,15}\{r=5\}$$
$$+(1-s_n)\phi_{m,n,r-1}P_{j,k,1}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,1}^{m,l,r-1}\{l \neq n\} \qquad \text{for } r = 5, 7, 9, 11. \quad (27)$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,r} + \gamma_r\{r \neq 11\} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,r} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,r}$$

$$\frac{dP_{j,k,1}^{j,k,12}}{dt} = \psi_{j,k,1}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,12}\{j=2\} + \sum_{g\in s}\tau_g P_{j,k,1}^{j,k,g} \qquad \text{where } s = 5, 7, 9, 11. \quad (28)$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,12} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,12} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,12}$$

$$\frac{dP_{j,k,1}^{m,n,12}}{dt} = \psi_{j,k,1}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,10}^{j,k,1}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,1}^{m,n,g} \qquad \text{where } s = 5, 7, 9, 11. \quad (29)$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,12} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,12} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,12}$$

$$\frac{dP_{j,k,1}^{j,k,14}}{dt} = \psi_{j,k,1}^{rep,j,k,14}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,14}\{j=2\} + \lambda_{P,j,k,13}^{one}P_{j,k,1}^{j,k,13} \qquad (30)$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,14} + \phi_{j,k,14} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,14} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,14} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,14}$$

$$\frac{dP_{j,k,1}^{m,n,14}}{dt} = \psi_{j,k,1}^{rep,m,n,14}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,14}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,1}\{m=2\} + \lambda_{P,m,n,13}^{one}P_{j,k,1}^{m,n,13} \qquad (31)$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,14} + \phi_{m,n,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,14} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,14} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,14}$$

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$$\frac{dP_{j,k,1}^{j,k,15}}{dt} = \psi_{j,k,1}^{rep,j,k,15}\rho_{j,k}^{rep}Y_{j,k,1} + 2\alpha_{j-1}P_{j-1,k,1}^{j,k,15}\{j=2\} + (1-s_k)\phi_{j,k,14}P_{j,k,1}^{j,k,14} + s_l\phi_{j,l,14}P_{j,k,1}^{j,l,14}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,15} + \gamma_{15} + \sigma_{j,k} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,15} + \kappa_{j,k}^{on})P_{j,k,1}^{j,k,15} + \kappa_{j,k}^{off}P_{j,k,13}^{j,k,15} \quad (32)$$

$$\frac{dP_{j,k,1}^{m,n,15}}{dt} = \psi_{j,k,1}^{rep,m,n,15}\rho_{j,k}^{rep}Y_{j,k,1} + \alpha_{j-1}P_{j-1,k,1}^{m,n,15}\{j=2\} + \alpha_{m-1}P_{m-1,n,15}^{j,k,1}\{m=2\} + (1-s_n)\phi_{m,n,14}P_{j,k,1}^{m,n,14} + s_l\phi_{m,l,14}P_{j,k,1}^{m,l,14}\{l \neq n\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,1} + \mu_{m,15} + \gamma_{15} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,15} + \kappa_{j,k}^{on})P_{j,k,1}^{m,n,15} + \kappa_{j,k}^{off}P_{j,k,13}^{m,n,15} \quad (33)$$

<u>Susceptible on PrEP (HIV stage no.13) – Susceptible on PrEP (HIV stage no.13)</u>

$$\frac{dP_{j,k,13}^{j,k,13}}{dt} = \psi_{j,k,13}^{rep,j,k,13}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,13}\{j=2\} - (2\alpha_j + 2\mu_{j,13} + \sigma_{j,k} + 2\varpi\lambda_{P,j,k}^{one} + 2\kappa_{j,k}^{off})P_{j,k,13}^{j,k,13} + \kappa_{j,k}^{on}P_{j,k,13}^{j,k,1} \quad (34)$$

$$\frac{dP_{j,k,13}^{m,n,13}}{dt} = \psi_{j,k,13}^{rep,m,n,13}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,13}\{j=2\} + \alpha_{m-1}P_{m-1,n,13}^{j,k,13}\{m=2\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,13} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{P,m,n}^{one}) + \kappa_{j,k}^{off} + \kappa_{m,n}^{off})P_{j,k,13}^{m,n,13} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,13} + \kappa_{m,n}^{on}P_{j,k,13}^{m,n,1} \quad (35)$$

<u>Susceptible on PrEP (HIV stage no.13) – Infected (HIV stage no.2-12, and 14-15)</u>

$$\frac{dP_{j,k,13}^{j,k,2}}{dt} = \psi_{j,k,13}^{rep,j,k,2}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,2}\{j=2\} + \lambda_{P,j,k}^{one}P_{j,k,13}^{j,k,1}$$
$$-(2\alpha_j + \mu_{j,1} + \mu_{j,2} + \gamma_2 + \phi_{j,k,2} + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,2} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,2} \quad (36)$$

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$$\frac{dP_{j,k,13}^{m,n,2}}{dt} = \psi_{j,k,13}^{rep,m,n,2}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,2}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,13}\{m=2\} + \lambda_{P,m,n}^{one}P_{j,k,13}^{m,n,1}$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,2} + \gamma_2 + \phi_{m,n,2} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,2}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,2} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,2} \quad (37)$$

$$\frac{dP_{j,k,13}^{j,k,3}}{dt} = \psi_{j,k,13}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,3}\{j=2\} + (1-s_k)\phi_{j,k,2}P_{j,k,13}^{j,k,2} + s_l\phi_{j,l,2}P_{j,k,13}^{j,l,2}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,3} + \gamma_3 + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,3}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,3} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,3} \quad (38)$$

$$\frac{dP_{j,k,13}^{m,n,3}}{dt} = \psi_{j,k,13}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,3}^{j,k,13}\{m=2\} + (1-s_n)\phi_{m,n,2}P_{j,k,13}^{m,n,2} + s_l\phi_{m,l,2}P_{j,k,13}^{m,l,2}\{l \neq n\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,3} + \gamma_3 + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,3} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,3} \quad (39)$$

$$\frac{dP_{j,k,13}^{j,k,h}}{dt} = \psi_{j,k,13}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,13}^{j,k,h-2}$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,h} + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,h} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,h} \quad \text{for } h = 4, 6, 8, 10. \quad (40)$$

$$\frac{dP_{j,k,13}^{m,n,r}}{dt} = \psi_{j,k,13}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,13}\{m=2\} + \gamma_{r-2}P_{j,k,13}^{m,n,r-2}$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,r} + \gamma_r\{r \neq 10\} + \phi_{m,n,r} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,r} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,r} \quad \text{for } r = 4, 6, 8, 10. \quad (41)$$

$$\frac{dP_{j,k,13}^{j,k,h}}{dt} = \psi_{j,k,13}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,13}^{j,k,h-2} + \gamma_{15}P_{j,k,13}^{j,k,15}\{h=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,13}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,13}^{j,l,h-1}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,h} + \gamma_h\{h \neq 11\} + \tau_h + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,h} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,h} \quad \text{for } h = 5, 7, 9, 11. \quad (42)$$

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$$\frac{dP_{j,k,13}^{m,n,r}}{dt} = \psi_{j,k,13}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,13}\{m=2\} + \gamma_{r-2}P_{j,k,13}^{m,n,r-2} + \gamma_{15}P_{j,k,13}^{m,n,15}\{r=5\}$$
$$+(1-s_n)\phi_{m,n,r-1}P_{j,k,13}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,13}^{m,l,r-1}\{l \neq n\} \qquad \text{for } r = 5, 7, 9, 11. \quad (43)$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,r} + \gamma_r\{r \neq 11\} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,r} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,r}$$

$$\frac{dP_{j,k,13}^{j,k,12}}{dt} = \psi_{j,k,13}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,12}\{j=2\} + \sum_{g\in s}\tau_g P_{j,k,13}^{j,k,g} \qquad \text{where } s = 5, 7, 9, 11. \quad (44)$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,12} + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,12} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,12}$$

$$\frac{dP_{j,k,13}^{m,n,12}}{dt} = \psi_{j,k,13}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,10}^{j,k,13}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,13}^{m,n,g} \qquad \text{where } s = 5, 7, 9, 11. \quad (45)$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,12} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,12} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,12}$$

$$\frac{dP_{j,k,13}^{j,k,14}}{dt} = \psi_{j,k,13}^{rep,j,k,14}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,14}\{j=2\} + 2\varpi\lambda_{P,j,k}^{one}P_{j,k,13}^{j,k,13} \quad (46)$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,14} + \phi_{j,k,14} + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,14}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,14} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,14}$$

$$\frac{dP_{j,k,13}^{m,n,14}}{dt} = \psi_{j,k,13}^{rep,m,n,14}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,14}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,13}\{m=2\} + \varpi(\lambda_{P,j,k}^{one}P_{j,k,13}^{m,n,13} + \lambda_{P,m,n}^{one}P_{j,k,13}^{m,n,13}) \quad (47)$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,14} + \phi_{m,n,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,14}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,14} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,14}$$

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$$\frac{dP_{j,k,13}^{j,k,15}}{dt} = \psi_{j,k,13}^{rep,j,k,15}\rho_{j,k}^{rep}Y_{j,k,13} + 2\alpha_{j-1}P_{j-1,k,13}^{j,k,15}\{j=2\} + (1-s_k)\phi_{j,k,14}P_{j,k,13}^{j,k,14} + s_l\phi_{j,l,14}P_{j,k,13}^{j,l,14}\{l \neq k\}$$
$$-(2\alpha_j + \mu_{j,13} + \mu_{j,15} + \gamma_{15} + \sigma_{j,k} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,15}) + \kappa_{j,k}^{off})P_{j,k,13}^{j,k,15} + \kappa_{j,k}^{on}P_{j,k,1}^{j,k,15} \quad (48)$$

$$\frac{dP_{j,k,13}^{m,n,15}}{dt} = \psi_{j,k,13}^{rep,m,n,15}\rho_{j,k}^{rep}Y_{j,k,13} + \alpha_{j-1}P_{j-1,k,13}^{m,n,15}\{j=2\} + \alpha_{m-1}P_{m-1,n,15}^{j,k,13}\{m=2\} + (1-s_n)\phi_{m,n,14}P_{j,k,13}^{m,n,14} + s_l\phi_{m,l,14}P_{j,k,13}^{m,l,14}\{l \neq n\}$$
$$-(\alpha_j + \alpha_m + \mu_{j,13} + \mu_{m,15} + \gamma_{15} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2} + \varpi(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,15}) + \kappa_{j,k}^{off})P_{j,k,13}^{m,n,15} + \kappa_{j,k}^{on}P_{j,k,1}^{m,n,15} \quad (49)$$

<u>Undiagnosed PHI (HIV stage no.2) – Infected (HIV stage no.2-12, and 14-15)</u>

$$\frac{dP_{j,k,2}^{j,k,2}}{dt} = \psi_{j,k,2}^{rep,j,k,2}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,2}\{j=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2})P_{j,k,1}^{j,k,2}$$
$$-(2\alpha_j + 2\mu_{j,2} + 2\gamma_2 + 2\phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,2} \quad (50)$$

$$\frac{dP_{j,k,2}^{m,n,2}}{dt} = \psi_{j,k,2}^{rep,m,n,2}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,2}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,2}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,2})P_{j,k,1}^{m,n,2} + (\lambda_{P,m,n}^{one} + \lambda_{m,n}^{rep,j,k,2})P_{j,k,2}^{m,n,1}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,2} + 2\gamma_2 + \phi_{j,k,2} + \phi_{m,n,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,2} \quad (51)$$

$$\frac{dP_{j,k,2}^{j,k,3}}{dt} = \psi_{j,k,2}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,3}\{j=2\} + 2\phi_{j,k,2}P_{j,k,2}^{j,k,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,3})P_{j,k,1}^{j,k,3} - (2\alpha_j + \mu_{j,2} + \mu_{j,3} + \gamma_2 + \gamma_3 + \phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,3} \quad (52)$$

$$\frac{dP_{j,k,2}^{m,n,3}}{dt} = \psi_{j,k,2}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,3}\{m=2\} + \phi_{m,n,2}P_{j,k,2}^{m,n,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3})P_{j,k,1}^{m,n,3}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,3} + \gamma_2 + \gamma_3 + \phi_{j,k,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,3} \quad (53)$$

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$$\frac{dP_{j,k,2}^{j,k,h}}{dt} = \psi_{j,k,2}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,2}^{j,k,h-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h}$$
$$-(2\alpha_j + \mu_{j,2} + \mu_{j,h} + \gamma_2 + \gamma_h\{h \neq 10\} + \phi_{j,k,2} + \phi_{j,k,h} + \sigma_{j,k})P_{j,k,2}^{j,k,h} \qquad \text{for } h = 4, 6, 8, 10. \qquad (54)$$

$$\frac{dP_{j,k,2}^{m,n,r}}{dt} = \psi_{j,k,2}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,2}\{m=2\} + \gamma_{r-2}P_{j,k,2}^{m,n,r-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,r} + \gamma_2 + \gamma_r\{r \neq 10\} + \phi_{j,k,2} + \phi_{j,k,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,r} \qquad \text{for } r = 4, 6, 8, 10. \qquad (55)$$

$$\frac{dP_{j,k,2}^{j,k,h}}{dt} = \psi_{j,k,2}^{rep,j,k,h}\rho_{j,k}^{ste}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,2}^{j,k,h-2} + \gamma_{15}P_{j,k,2}^{j,k,15}\{h=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,2}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,2}^{j,l,h-1}\{l \neq k\}$$
$$+(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})P_{j,k,1}^{j,k,h} - (2\alpha_j + \mu_{j,2} + \mu_{j,h} + \gamma_2 + \gamma_h\{h \neq 11\} + \phi_{j,k,2} + \phi_{j,k,h} + \tau_h + \sigma_{j,k})P_{j,k,2}^{j,k,h} \qquad \text{for } h = 5, 7, 9, 11. \qquad (56)$$

$$\frac{dP_{j,k,2}^{m,n,r}}{dt} = \psi_{j,k,2}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,2}\{m=2\} + \gamma_{r-2}P_{j,k,2}^{m,n,r-2} + \gamma_{15}P_{j,k,2}^{m,n,15}\{r=5\}$$
$$+(1-s_n)\phi_{m,n,r-1}P_{j,k,2}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,2}^{m,l,r-1}\{l \neq n\} \qquad \text{for } r = 5, 7, 9, 11. \qquad (57)$$
$$+(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})P_{j,k,1}^{m,n,r} - (\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,r} + \gamma_2 + \gamma_r\{r \neq 11\} + \phi_{j,k,2} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,r}$$

$$\frac{dP_{j,k,2}^{j,k,12}}{dt} = \psi_{j,k,2}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,12}\{j=2\} + \sum_{g \in s}\tau_g P_{j,k,2}^{j,k,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12})P_{j,k,1}^{j,k,12}$$
$$-(2\alpha_j + \mu_{j,2} + \mu_{j,12} + \gamma_2 + \phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,12} \qquad \text{where } s = 5, 7, 9, 11. \qquad (58)$$

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$$\frac{dP_{j,k,2}^{m,n,12}}{dt} = \psi_{j,k,2}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,2}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,2}^{m,n,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12})P_{j,k,1}^{m,n,12}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,12} + \gamma_2 + \phi_{j,k,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,12}$$

where s = 5, 7, 9, 11. (59)

$$\frac{dP_{j,k,2}^{j,k,14}}{dt} = \psi_{j,k,2}^{rep,j,k,14}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{j,k,14}\{j=2\} + \alpha_{j-1}P_{j-1,k,14}^{j,k,2}\{j=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,14})P_{j,k,1}^{j,k,14} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,2})\varpi P_{j,k,2}^{j,k,13}$$
$$-(2\alpha_j + \mu_{j,2} + \mu_{j,14} + \gamma_2 + \phi_{j,k,2} + \phi_{j,k,14} + \sigma_{j,k})P_{j,k,2}^{j,k,14} \quad (60)$$

$$\frac{dP_{j,k,2}^{m,n,14}}{dt} = \psi_{j,k,2}^{rep,m,n,14}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,14}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,2}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,14})P_{j,k,1}^{m,n,14} + (\lambda_{P,m,n}^{one} + \lambda_{m,n}^{rep,j,k,2})\varpi P_{j,k,2}^{m,n,13}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,14} + \gamma_2 + \phi_{j,k,2} + \phi_{m,n,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,14} \quad (61)$$

$$\frac{dP_{j,k,2}^{j,k,15}}{dt} = \psi_{j,k,2}^{rep,j,k,15}\rho_{j,k}^{rep}Y_{j,k,2} + 2\alpha_{j-1}P_{j-1,k,2}^{j,k,15}\{j=2\} + \phi_{j,k,14}P_{j,k,2}^{j,k,14} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,15})P_{j,k,1}^{j,k,15}$$
$$-(2\alpha_j + \mu_{j,2} + \mu_{j,15} + \gamma_2 + \gamma_{15} + \phi_{j,k,2} + \sigma_{j,k})P_{j,k,2}^{j,k,15} \quad (62)$$

$$\frac{dP_{j,k,2}^{m,n,15}}{dt} = \psi_{j,k,2}^{rep,m,n,15}\rho_{j,k}^{rep}Y_{j,k,2} + \alpha_{j-1}P_{j-1,k,2}^{m,n,15}\{j=2\} + \alpha_{m-1}P_{m-1,n,2}^{j,k,15}\{m=2\} + \phi_{m,n,14}P_{j,k,2}^{m,n,14} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,15})P_{j,k,1}^{m,n,15}$$
$$-(\alpha_j + \alpha_m + \mu_{j,2} + \mu_{m,15} + \gamma_2 + \gamma_{15} + \phi_{j,k,2} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,2}^{m,n,15} \quad (63)$$

<u>Undiagnosed PHI failed PrEP (HIV stage no.14) – Infected (HIV stage no.3-12, and 14-15)</u>

$$\frac{dP_{j,k,14}^{j,k,3}}{dt} = \psi_{j,k,14}^{rep,j,k,3}\rho_{j,k}^{rep}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,3}\{j=2\} + \phi_{j,k,2}P_{j,k,14}^{j,k,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k,}^{rep,j,k,3})\varpi P_{j,k,13}^{j,k,3} - (2\alpha_j + \mu_{j,14} + \mu_{j,3} + \gamma_3 + \phi_{j,k,14} + \sigma_{j,k})P_{j,k,14}^{j,k,3} \quad (64)$$

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$$\frac{dP_{j,k,14}^{m,n,3}}{dt} = \psi_{j,k,14}^{rep,m,n,3}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,3}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,3}\{m=2\} + \phi_{m,n,2}P_{j,k,14}^{m,n,2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,3})\varpi P_{j,k,13}^{m,n,3}$$
$$-(\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,3} + \gamma_3 + \phi_{j,k,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,3} \qquad (65)$$

$$\frac{dP_{j,k,14}^{j,k,h}}{dt} = \psi_{j,k,14}^{rep,j,k,h}\rho_{j,k}^{rep}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,14}^{j,k,h-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})\varpi P_{j,k,13}^{j,k,h}$$
$$-(2\alpha_j + \mu_{j,14} + \mu_{j,h} + \gamma_h\{h \neq 10\} + \phi_{j,k,14} + \phi_{j,k,h} + \sigma_{j,k})P_{j,k,14}^{j,k,h} \qquad \text{for } h = 4, 6, 8, 10. \qquad (66)$$

$$\frac{dP_{j,k,14}^{m,n,r}}{dt} = \psi_{j,k,14}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,14}\{m=2\} + \gamma_{r-2}P_{j,k,14}^{m,n,r-2} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})\varpi P_{j,k,13}^{m,n,r}$$
$$-(\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,r} + \gamma_r\{r \neq 10\} + \phi_{j,k,14} + \phi_{j,k,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,r} \qquad \text{for } r = 4, 6, 8, 10. \qquad (67)$$

$$\frac{dP_{j,k,14}^{j,k,h}}{dt} = \psi_{j,k,14}^{rep,j,k,h}\rho_{j,k}^{ste}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,h}\{j=2\} + \gamma_{h-2}P_{j,k,14}^{j,k,h-2} + \gamma_{15}P_{j,k,14}^{j,k,15}\{h=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,14}^{j,k,h-1} + s_l\phi_{j,l,h-1}P_{j,k,14}^{j,l,h-1}\{l \neq k\}$$
$$+(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,h})\varpi P_{j,k,13}^{j,k,h} - (2\alpha_j + \mu_{j,14} + \mu_{j,h} + \gamma_h\{h \neq 11\} + \phi_{j,k,14} + \phi_{j,k,h} + \tau_h + \sigma_{j,k})P_{j,k,14}^{j,k,h} \qquad \text{for } h = 5, 7, 9, 11. \qquad (68)$$

$$\frac{dP_{j,k,14}^{m,n,r}}{dt} = \psi_{j,k,14}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,14}\{m=2\} + \gamma_{r-2}P_{j,k,14}^{m,n,r-2} + \gamma_{15}P_{j,k,14}^{m,n,15}\{r=5\}$$
$$+(1-s_n)\phi_{m,n,r-1}P_{j,k,14}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,14}^{m,l,r-1}\{l \neq n\} \qquad \text{for } r = 5, 7, 9, 11. \qquad (69)$$
$$+(\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,r})\varpi P_{j,k,13}^{m,n,r} - (\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,r} + \gamma_r\{r \neq 11\} + \phi_{j,k,14} + \tau_r + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,r}$$

$$\frac{dP_{j,k,14}^{j,k,12}}{dt} = \psi_{j,k,14}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,12}\{j=2\} + \sum_{g\in s}\tau_g P_{j,k,14}^{j,k,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,12})\varpi P_{j,k,13}^{j,k,12}$$
$$-(2\alpha_j + \mu_{j,14} + \mu_{j,12} + \phi_{j,k,14} + \sigma_{j,k})P_{j,k,14}^{j,k,12} \qquad \text{where } s = 5, 7, 9, 11. \quad (70)$$

$$\frac{dP_{j,k,14}^{m,n,12}}{dt} = \psi_{j,k,14}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,14}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,14}^{m,n,g} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,12})\varpi P_{j,k,13}^{m,n,12}$$
$$-(\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,12} + \phi_{j,k,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,12} \qquad \text{where } s = 5, 7, 9, 11. \quad (71)$$

$$\frac{dP_{j,k,14}^{j,k,14}}{dt} = \psi_{j,k,14}^{rep,j,k,14}\rho_{j,k}^{rep}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,14}\{j=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,14})\varpi P_{j,k,13}^{j,k,14}$$
$$-(2\alpha_j + 2\mu_{j,14} + 2\phi_{j,k,14} + \sigma_{j,k})P_{j,k,14}^{j,k,14} \qquad (72)$$

$$\frac{dP_{j,k,14}^{m,n,14}}{dt} = \psi_{j,k,14}^{rep,m,n,14}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,14}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,14}\{m=2\} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,14})\varpi P_{j,k,13}^{m,n,14} + (\lambda_{P,m,n}^{one} + \lambda_{m,n}^{rep,j,k,14})\varpi P_{j,k,14}^{m,n,13}$$
$$-(\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,14} + \phi_{j,k,14} + \phi_{m,n,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,14} \qquad (73)$$

$$\frac{dP_{j,k,14}^{j,k,15}}{dt} = \psi_{j,k,14}^{rep,j,k,15}\rho_{j,k}^{rep}Y_{j,k,14} + 2\alpha_{j-1}P_{j-1,k,14}^{j,k,15}\{j=2\} + \phi_{j,k,14}P_{j,k,14}^{j,k,14} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,j,k,15})\varpi P_{j,k,13}^{j,k,15}$$
$$-(2\alpha_j + \mu_{j,14} + \mu_{j,15} + \gamma_{15} + \phi_{j,k,14} + \sigma_{j,k})P_{j,k,14}^{j,k,15} \qquad (74)$$

$$\frac{dP_{j,k,14}^{m,n,15}}{dt} = \psi_{j,k,14}^{rep,m,n,15}\rho_{j,k}^{rep}Y_{j,k,14} + \alpha_{j-1}P_{j-1,k,14}^{m,n,15}\{j=2\} + \alpha_{m-1}P_{m-1,n,14}^{j,k,15}\{m=2\} + \phi_{m,n,14}P_{j,k,14}^{m,n,14} + (\lambda_{P,j,k}^{one} + \lambda_{j,k}^{rep,m,n,15})\varpi P_{j,k,13}^{m,n,15}$$
$$-(\alpha_j + \alpha_m + \mu_{j,14} + \mu_{m,15} + \gamma_{15} + \phi_{j,k,14} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,14}^{m,n,15} \qquad (75)$$

Infected except U2 (HIV stage no.3-12) – Infected except U2 (HIV stage no.3-12)

Undiagnosed – Undiagnosed

$$\frac{dP_{j,k,h}^{j,k,r}}{dt} = \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{ste}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2} - (2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 10\} + \phi_{j,k,h} + \phi_{j,k,r} + \sigma_{j,k})P_{j,k,h}^{j,k,r}$$

for h = 4, 6, 8, 10, and r = 4, 6, 8, 10. (76)

$$\frac{dP_{j,k,h}^{m,n,r}}{dt} = \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{r-2}P_{j,k,h}^{m,n,r-2} - (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 10\} + \phi_{j,k,h} + \phi_{j,k,r} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}$$

for h = 4, 6, 8, 10, and r = 4, 6, 8, 10. (77)

Undiagnosed – Diagnosed

$$\frac{dP_{j,k,h}^{j,k,r}}{dt} = \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2}\{r \neq 3\} + \gamma_{15}P_{j,k,h}^{j,k,15}\{r=5\} + (1-s_k)\phi_{j,k,r-1}P_{j,k,h}^{j,k,r-1} + s_l\phi_{j,l,r-1}P_{j,k,h}^{j,l,r-1}\{l \neq k\} - (2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 11\} + \phi_{j,k,h} + \tau_r\{r \neq 3,15\} + \sigma_{j,k})P_{j,k,h}^{j,k,r}$$

for h = 4, 6, 8, 10, and r = 3, 5, 7, 9, 11, 15. (78)

$$\frac{dP_{j,k,h}^{m,n,r}}{dt} = \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,r} + \gamma_{r-2}P_{j,k,h}^{m,n,r-2}\{r \neq 3\} + \gamma_{15}P_{j,k,h}^{m,n,15}\{r=5\} + (1-s_n)\phi_{m,n,r-1}P_{j,k,h}^{m,n,r-1} + s_l\phi_{m,l,r-1}P_{j,k,h}^{m,l,r-1}\{l \neq n\} - (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h \neq 10\} + \gamma_r\{r \neq 11\} + \phi_{j,k,h} + \tau_r\{r \neq 3,15\} + \frac{\sigma_{j,k} + \sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}$$

for h = 4, 6, 8, 10, and r = 3, 5, 7, 9, 11, 15. (79)

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Undiagnosed – On treatment

$$\frac{dP_{j,k,h}^{j,k,12}}{dt} = \psi_{j,k,h}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,12}\{j=2\} + \sum_{g\in s}\tau_g P_{j,k,h}^{j,k,g} - (2\alpha_j + \mu_{j,h} + \mu_{j,12} + \gamma_h\{h\neq 10\} + \phi_{j,k,h} + \sigma_{j,k})P_{j,k,h}^{j,k,12}$$

for h = 4, 6, 8, 10, and s = 5, 7, 9, 11. (80)

$$\frac{dP_{j,k,h}^{m,n,12}}{dt} = \psi_{j,k,h}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,h}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,h}^{m,n,g} - (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,12} + \gamma_h\{h\neq 10\} + \phi_{j,k,h} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,h}^{m,n,12}$$

for h = 4, 6, 8, 10, and s = 5, 7, 9, 11. (81)

Diagnosed – Diagnosed

$$\begin{aligned}\frac{dP_{j,k,h}^{j,k,r}}{dt} &= \psi_{j,k,h}^{rep,j,k,r}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,r}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,r}\{h\neq 3\} + \gamma_{r-2}P_{j,k,h}^{j,k,r-2}\{r\neq 3\} \\ &+ \gamma_{15}P_{j,k,15}^{j,k,r}\{h=5\} + \gamma_{15}P_{j,k,h}^{j,k,15}\{r=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{j,k,r} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{j,k,r}\{l\neq k\} \\ &+ (1-s_k)\phi_{j,k,r-1}P_{j,k,h}^{j,k,r-1} + s_l\phi_{j,l,r-1}P_{j,k,h}^{j,l,r-1}\{l\neq k\} - (2\alpha_j + \mu_{j,h} + \mu_{j,r} + \gamma_h\{h\neq 11\} \\ &+ \gamma_r\{r\neq 11\} + \tau_h\{h\neq 3\} + \tau_r\{r\neq 3,15\} + \sigma_{j,k})P_{j,k,h}^{j,k,r}\end{aligned}$$

for h = 3, 5, 7, 9, 11, 15, and r = 3, 5, 7, 9, 11, 15. (82)

$$\begin{aligned}\frac{dP_{j,k,h}^{m,n,r}}{dt} &= \psi_{j,k,h}^{rep,m,n,r}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,r}\{j=2\} + \alpha_{m-1}P_{m-1,n,r}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,r}\{h\neq 3\} \\ &+ \gamma_{r-2}P_{j,k,h}^{m,n,r-2}\{r\neq 3\} + \gamma_{15}P_{j,k,15}^{m,n,r}\{h=5\} + \gamma_{15}P_{j,k,h}^{m,n,15}\{r=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{m,n,r} \\ &+ s_l\phi_{j,l,h-1}P_{j,l,h-1}^{m,n,r}\{l\neq k\} + (1-s_n)\phi_{m,n,r-1}P_{j,k,h}^{m,n,r-1} + s_u\phi_{m,u,r-1}P_{j,k,h}^{m,u,r-1}\{u\neq n\} \\ &- (\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,r} + \gamma_h\{h\neq 11\} + \gamma_r\{r\neq 11\} + \tau_h\{h\neq 3,15\} \\ &+ \tau_r\{r\neq 3,15\} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,h}^{m,n,r}\end{aligned}$$

for h = 3, 5, 7, 9, 11, 15 and r = 3, 5, 7, 9, 11, 15. (83)

Diagnosed – On treatment

$$\frac{dP_{j,k,h}^{j,k,12}}{dt} = \psi_{j,k,h}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,h} + 2\alpha_{j-1}P_{j-1,k,h}^{j,k,12}\{j=2\} + \gamma_{h-2}P_{j,k,h-2}^{j,k,12}\{h\neq 3\} + \gamma_{15}P_{j,k,15}^{j,k,12}\{h=5\}$$
$$+(1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{j,k,12} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{j,k,12}\{l\neq k\} + \sum_{g\in s}\tau_g P_{j,k,h}^{j,k,g} \qquad \text{for } h = 3, 5, 7, 9, 11, 15 \text{ and } s = 5, 7, 9, 11. \qquad (84)$$
$$-(2\alpha_j + \mu_{j,h} + \mu_{j,12} + \gamma_h\{h\neq 11\} + \tau_h\{h\neq 3,15\} + \sigma_{j,k})P_{j,k,h}^{j,k,12}$$

$$\frac{dP_{j,k,h}^{m,n,12}}{dt} = \psi_{j,k,h}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,h} + \alpha_{j-1}P_{j-1,k,h}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,h}\{m=2\} + \gamma_{h-2}P_{j,k,h-2}^{m,n,12}\{h\neq 3\}$$
$$+\gamma_{15}P_{j,k,15}^{m,n,12}\{h=5\} + (1-s_k)\phi_{j,k,h-1}P_{j,k,h-1}^{m,n,12} + s_l\phi_{j,l,h-1}P_{j,l,h-1}^{m,n,12}\{l\neq k\} + \sum_{g\in s}\tau_g P_{j,k,h}^{m,n,g} \qquad \text{for } h = 3, 5, 7, 9, 11, 15 \text{ and } s = 5, 7, 9, 11. \qquad (85)$$
$$-(\alpha_j + \alpha_m + \mu_{j,h} + \mu_{m,12} + \gamma_h\{h\neq 11\} + \tau_h\{h\neq 3,15\} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,h}^{m,n,12}$$

On treatment – On treatment

$$\frac{dP_{j,k,12}^{j,k,12}}{dt} = \psi_{j,k,12}^{rep,j,k,12}\rho_{j,k}^{rep}Y_{j,k,12} + 2\alpha_{j-1}P_{j-1,k,12}^{j,k,12}\{j=2\} + 2\sum_{g\in s}\tau_g P_{j,k,12}^{j,k,g} - (2\alpha_j + 2\mu_{j,12} + \sigma_{j,k})P_{j,k,12}^{j,k,12} \qquad \text{for } s = 5, 7, 9, 11. \qquad (86)$$

$$\frac{dP_{j,k,12}^{m,n,12}}{dt} = \psi_{j,k,12}^{rep,m,n,12}\rho_{j,k}^{rep}Y_{j,k,12} + \alpha_{j-1}P_{j-1,k,12}^{m,n,12}\{j=2\} + \alpha_{m-1}P_{m-1,n,12}^{j,k,12}\{m=2\} + \sum_{g\in s}\tau_g P_{j,k,12}^{m,n,g} + \sum_{g\in s}\tau_g P_{m,n,12}^{j,k,g} \qquad \text{for } s = 5, 7,9, 11. \qquad (87)$$
$$-(\alpha_j + \alpha_m + \mu_{j,12} + \mu_{m,12} + \frac{\sigma_{j,k}+\sigma_{m,n}}{2})P_{j,k,12}^{m,n,12}$$

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1.3 Modelling pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) is a medication containing antiretroviral agents that, when used before an exposure to HIV, can provide protection against infection.[2] In case of breakthrough infection, PrEP may also affect drug resistance and reduce the infectiousness and disease progression rate throughout the natural history.[3-4] However, in this study, we only focused on the two key benefits of PrEP, which are decreasing the risk of HIV infection in HIV-negative MSM and reducing infectiousness during primary HIV infection (PHI) in failed-PrEP HIV-positive MSM, on the population-level incidence of HIV among UK MSM. We also ignored the benefit of PrEP programme that may induce more undiagnosed HIV-positive MSM to have an HIV test because they want to use PrEP.

We appended three additional compartments to the previous HIV transmission model in UK MSM[1] to explicitly model the effects of PrEP. According to Figure 1, susceptibles (compartment no.1) who take PrEP move to susceptibles on PrEP (compartment no.13) and remain there until they either stop taking PrEP and move to susceptibles (compartment no.1) or become infected with HIV and move to undiagnosed PHI (compartment no.14). The undiagnosed MSM with breakthrough infections then test for HIV and move to the diagnosis stage (compartment no.15). After being diagnosed, individuals progress to the next disease stage of CD4≥500 (stage no.5) and follow the same paths as in the original model.

1.3.1 Key assumptions

The following important assumptions were made to facilitate PrEP modelling.

- PrEP has protective effects against HIV infection from sex between men.[2]
- PrEP is specifically referred to a once-daily pill containing emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) as used in the iPrEX study.[2]
- Every MSM eligible for PrEP has been tested for HIV before PrEP can be prescribed and only HIV-negative MSM are given PrEP.[5]
- Every individual on PrEP is tested for HIV once every 3 month.[5]
- In case of breakthrough infection while on PrEP:
    - All infected individuals will have a substantially lower HIV infectiousness than normal during the period of PHI regardless of whether or not is he still on PrEP.[3]
    - All infected individuals will be diagnosed with HIV in PHI stage.
- PrEP has no effect in any subsequent disease stages after PHI.

1.3.2 PrEP initiation and dropout rate

The rates at which susceptibles start taking PrEP were calculated from the average proportion of susceptibles who adopt PrEP each year. We assumed the events of HIV-negative men taking PrEP to be a Poisson process and, hence, the aforementioned average proportion ($A_{j,k}$) can be described by the cumulative distribution function of exponential distribution:

$$A_{j,k}^{on} = 1 - e^{-\kappa_{j,k}^{on}} \tag{88}$$

where j and k ,respectively, denote the age group and sexual activity group of MSM. Therefore, the PrEP initiation rate was calculated as:

$$\kappa_{j,k}^{on} = -\ln(1 - A_{j,k}^{on}) \tag{89}$$

The rate at which MSM stop taking PrEP was calculated in the same manner.

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The coverage of PrEP intervention was defined as the proportion of HIV-negative MSM who are on PrEP at any specific points of time. This was assumed 100%, the same as the coverage of other inventions. We allowed a period of around one year after the introduction of PrEP before the coverage reaches and remains constant at these levels. We then explored various combinations of the PrEP initiation and dropout rates and found that $\kappa_{j,k}^{on} = 0.025$ and $\kappa_{j,k}^{off} = 2.7 \times 10^{-7}$ satisfied the above conditions. In the sensitivity analysis, these two parameters were varied to assess the effects of PrEP coverage on the HIV prevention of PrEP intervention.

1.3.3 PrEP efficacy

The effectiveness of PrEP against HIV infection was derived from the iPrEX trial among MSM in North and South America, South Africa, and Thailand.[2] This is the only trial thus far that provides an estimate of PrEP efficacy among MSM participants. The study indicated that the once-daily oral antiretroviral drug containing FTC–TDF provided an average 44% reduction in the risk of acquiring HIV infection from sex between men. We, therefore, assumed a reduction factor of PrEP on HIV transmission probability (ϖ) of 0.56 all subgroups of MSM and throughout the modelling period.

1.3.4 Infectiousness reduction

Findings from a PrEP study in macaque monkeys suggested that, during the first few months after infection, the viral load in case of breakthrough infections is roughly 30% lower than the non-PrEP controls.[6] With this result, we used the same equation that describes the relationship between viral load and infectiousness found in our previous study[1] to calculate the reduction factor during PHI (Ω). We obtained a value

of 0.875 which when multiplied to the normal PHI infectiousness provide the infectiousness of failed-PrEP MSM.

1.3.5 HIV diagnosis

According to US CDC guidance on PrEP administration in MSM,[5] individuals on PrEP should be tested for HIV once every 2-3 month and given further instructions according to the test results. In our model, the failed-PrEP HIV-infected men are diagnosed with HIV and consequently move from *U1p* to *D1p* compartment (see Figure 1 in the main text for model flow diagram). We assumed an HIV test is performed every 3 month. For the undiagnosed infected individuals in *U1p* stage, the first half of this period was assumed already spent while they were still uninfected. The other half (1.5 months) was used to calculate the rate at which MSM on PrEP test for HIV ($\phi_{j,k,14}$) which is equivalent to 0.022 per time step.

1.3.6 Disease progression rate

Since we assumed that all failed-PrEP MSM are diagnosed while they are in PHI, we need to subtract the length of PHI in diagnosed stage *D1p* by half the length of PrEP prescription. This in turns translates into the PHI period of 1.5 months which is equivalent to an average progression rate (γ_{15}) of 0.022 per time step. However, the PHI progression rate is the fitted parameter which means that a large number (1,093) of different values of the parameter with the mean of 0.022 will be used in model simulations.

2. Supplementary results

The matrix presenting the list of individual and combined interventions is shown in Table S2. Figure S2 compares the total numbers of new infections prevented as a result of HIV interventions. The trajectory of HIV epidemic among MSM in the UK influenced by the effects of individual and combined interventions is presented in Figure S3. The estimated proportion of MSM living with diagnosed HIV infection receiving ART over 2001–2020 for all scenarios is shown in Table S3.

Sensitivity analysis

We explored the effects of risk compensation—having more sexual partners, increasing unsafe sex, and with less HIV testing—due to an implementation of the individual interventions. In the target groups of interventions, we specifically increased the repeat sexual partner change rates and the proportion of MSM who perform UAI with repeat sexual partners as well as decreasing the HIV diagnosis rates, all by 25%, 50%, 75% and 100%. The sensitivity analysis on risk compensation was conducted only on scenarios with 100% intervention coverage.

The total number of new HIV infections prevented during 2014–2020 was sensitive to sexual risk compensation (Figure S4a & S4b), particularly, an increase in the number of repeat sexual partners. The majority of interventions could tolerate up to 75% or more increase in both risk compensations before the benefits vanished (Figure S4a & S4b). The insensitiveness of test-and-treat was due to the small number of programme participants and low infectiousness of ART-treated men. PrEP was the most robust

intervention with less than a 3,000 increase in new infections if unsafe sex increased by 100% (Figure S4b). The benefit of reducing one-off sexual partnerships, on the other hand, dropped at the fastest rate and was completely negated at less than 25% increased risks (Figure S4a & S4b).

The sensitivity of the model outcomes to decreasing frequency of HIV testing was relatively less pronounced compared to the sexual risk compensation. However, its effects expanded exponentially as testing frequency declined (Figure S4c). This is especially noticeable in the test-and-treat programme that depended heavily on the number of diagnoses (Figure S4c). Overall, any individual intervention would still be beneficial if MSM consequently test no lower than 25% less often (Figure S4c).

Supplementary tables

Table S1: Model parameters

Parameter	Definition
$N_{j,k,h}$	Total number of MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$X_{j,k,h}$	Total number of single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$Y_{j,k,h}$	Number of current single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$Z_{j,k,h}$	Number of past single MSM in age group *j*, sexual activity group *k*, and HIV stage *h*
$P_{j,k,h}^{m,n,r}$	Number of pairs between an individual of age group *j*, sexual activity group *k*, and HIV stage *h* and an individual of age group *m*, sexual activity group *n*, and HIV stage *r*
$v_{j,k}$	Influx of new susceptibles in age group *j* (*j*=1), and sexual activity group *k*
$\eta_{j,k}$	Number of current MSM in age group *j*, and sexual activity group *k* (*k*=1) moving to past MSM
α_j	Ageing rate from an individual in age group *j* to next age group or out of the model
$\mu_{j,h}$	Mortality rate of an individual in age group *j* and HIV stage *h*
γ_h	Disease progression rate of an individual in disease stage *h* (*h*=2,...,11,15) to the next stage
$\phi_{j,k,h}$	HIV diagnosis rate of an individual in age group *j*, sexual activity group *k,* and undiagnosed stage *h* (*h*=2,4,6,8,10,14)
s_k	The proportion of MSM in sexual activity group *k* who switch to another sexual activity group after being diagnosed with HIV
τ_h	ART initiating rate of an individual in diagnosed stage *h* (*h*=5,7,9,11)
$\rho_{j,k}^{rep}$	Repeat sexual partnership formation rate of an individual in age group *j*, and sexual activity group *k*
$\sigma_{j,k}$	Repeat sexual partnership dissolution rate of an individual in age group *j*, and sexual activity group *k*
$\psi_{j,k,h}^{rep,m,n,r}$	Chance of an individual in age group *j*, sexual activity group *k,* and HIV stage *h* to acquire a repeat sexual partner of age group *m*, sexual activity group *n,* and HIV stage *r*
$\psi_{j,k}^{one,m,n,r}$	Chance of a susceptible in age group *j*, and sexual activity group *k* to acquire a one-off sexual partner of age group *m*, sexual activity group *n,* and HIV stage *r*

Parameter	Definition
$\lambda_{Y,j,k}^{one}$	Force of infection in a relationship between a one-off sexual partner and a single susceptible individual of age group *j*, and sexual activity group *k*
$\lambda_{P,j,k}^{one}$	Force of infection in a relationship between a one-off sexual partner and a paired susceptible individual of age group *j*, and sexual activity group *k*
$\lambda_{j,k}^{rep,m,n,r}$	Force of infection in a relationship between a repeat sexual partner of age group *m*, sexual activity group *n* , and disease stage *h* (*h*=2,...,1) and a susceptible individual of age group *j*, and sexual activity group *k*
ϖ	Risk reduction of PrEP against HIV infection
$\kappa_{j,k}^{on}$	Rate at which an individual in age group *j* and sexual activity group *k* start taking PrEP
$\kappa_{j,k}^{off}$	Rate at which an individual in age group *j* and sexual activity group *k* stop taking PrEP

Abbreviation:
PrEP: Pre-exposure prophylaxis

Table S2: The individual and combined HIV prevention interventions

1. Individual interventions	2. Combined interventions: 2.1) Test once a year and decrease UAI with repeat sexual partners	2.2) Reduce number of and decrease UAI with repeat sexual partners	2.3) Test once a year and test-and-treat	2.4) PrEP and test-and-treat	2.5) PrEP and decrease UAI with repeat sexual partners	2.6) PrEP and reduce number of repeat sexual partners	2.7) All interventions except test once a year
1.1) Test once a year	●		●				
1.2) Test twice a year							●
1.3) Test-and-treat program			●	●			●
1.4) PrEP program				●	●	●	●
1.5) Reduce number of repeat sexual partners		●				●	●
1.6) Reduce number of one-off sexual partners							●
1.7) Decrease UAI with repeat sexual partners	●	●			●		●

Abbreviation:
PrEP: Pre-exposure prophylaxis
UAI: Unprotected anal intercourse

Table S3: The estimated proportion (%) of MSM living with diagnosed HIV infection receiving antiretroviral treatment over 2001–2020

HIV interventions	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Status quo scenario	75.8	76.3	77.0	77.6	78.2	78.7	79.5	80.3	81.1	81.8	82.6	83.3	83.9	84.5	85.0	85.6	86.0	86.5	86.8	87.1
Individual interventions [a]																				
1.1) Test once a year														78.3	78.4	79.7	81.4	82.9	84.3	85.4
1.2) Test twice a year														75.6	77.3	79.6	81.6	83.2	84.7	85.9
1.3) Test-and-treat program														98.1	98.5	98.6	98.7	98.8	98.8	98.9
1.4) PrEP program														82.5	81.9	82.5	83.6	85.1	86.6	88.0
1.5) Reduce number of repeat sexual partners														84.6	85.6	86.6	87.8	88.9	89.8	90.6
1.6) Reduce number of one-off sexual partners														84.6	85.2	85.8	86.5	87.1	87.6	88.0
1.7) Decrease UAI with repeat sexual partners														84.6	85.5	86.5	87.4	88.3	89.0	89.7
Combined interventions																				
2.1) Test once a year and decrease UAI with repeat sexual partners														78.6	79.3	81.2	83.2	84.9	86.5	87.7

2.2) Reduce number of repeat sexual partners and UAI with repeat sexual partners	84.7	85.9	87.3	88.7	90.1	91.2	92.2
2.3) Test once a year and test-and-treat	96.4	98.3	99.0	99.3	99.4	99.5	99.5
2.4) PrEP and test-and-treat	97.2	98.0	98.5	98.9	99.1	99.3	99.4
2.5) PrEP and decrease UAI with repeat sexual partners	83.2	83.1	84.0	85.5	87.1	88.5	89.9
2.6) PrEP and reduce number of repeat sexual partners	83.3	83.5	84.7	86.4	88.1	89.7	91.2
2.7) All interventions except test once a year	97.0	99.5	99.9	100.0	100.0	100.0	100.0
Practical scenarios							
3.1) PrEP and test once a year	82.6	82.7	83.3	84.2	85.2	86.2	87.0
3.2) More PrEP and test once a year	82.4	82.3	83.1	84.3	85.6	86.7	87.8
3.3) PrEP, test once a year, and test-and-treat	91.2	94.1	95.6	96.5	97.1	97.5	97.8
3.4) PrEP, test once a year, and less repeat sexual partnerships	82.7	82.8	83.6	84.7	85.8	86.8	87.8
3.5) PrEP, test once a year, and less UAI	82.7	82.8	83.5	84.5	85.6	86.6	87.5
3.6) PrEP and test once a year but with (RC) no condom use with repeat sexual partners	82.1	81.5	81.7	82.4	83.1	83.9	84.6
3.7) PrEP and test once a year but with (RC) more repeat sexual partnerships	82.6	82.6	83.2	84.2	85.3	86.2	87.1

3.8) PrEP and test once a year but with (RC) no condom use with repeat sexual partners and (RC) more repeat sexual partnerships	82.6	82.5	83.0	83.9	84.8	85.7	86.6
3.9) Reduce repeat sexual partnerships and test once a year	83.0	83.2	83.7	84.6	85.4	86.3	87.0
3.10) Reduce repeat sexual partnerships, test once a year, and test-and-treat	91.4	94.3	95.7	96.5	97.0	97.4	97.7
3.11) Reduce repeat sexual partnerships and test-and-treat but with (RC) less HIV testing	92.7	95.3	96.2	96.6	96.9	97.1	97.2
3.12) Reduce repeat sexual partnerships and test-and-treat but with (RC) less HIV testing and (RC) no condom use with repeat sexual partners	92.6	95.3	96.2	96.5	96.7	96.9	97.0

Abbreviation:
PrEP: Pre-exposure prophylaxis
UAI: Unprotected anal intercourse
RC: Risk compensation

[a] The estimates for individual interventions in all MSM only

Supplementary figures

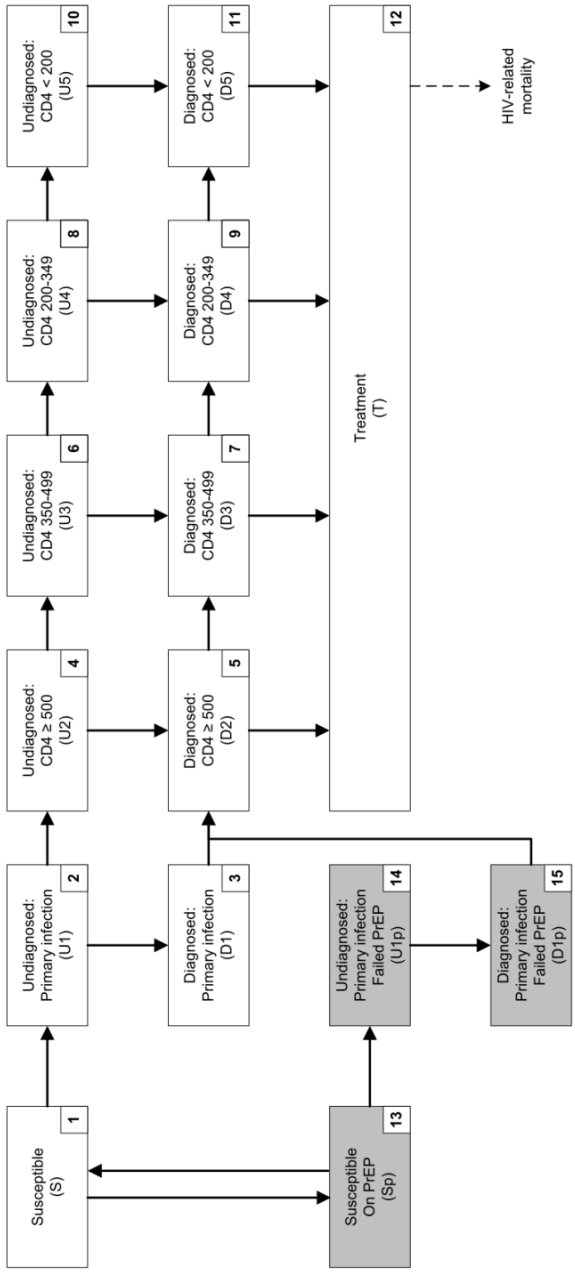
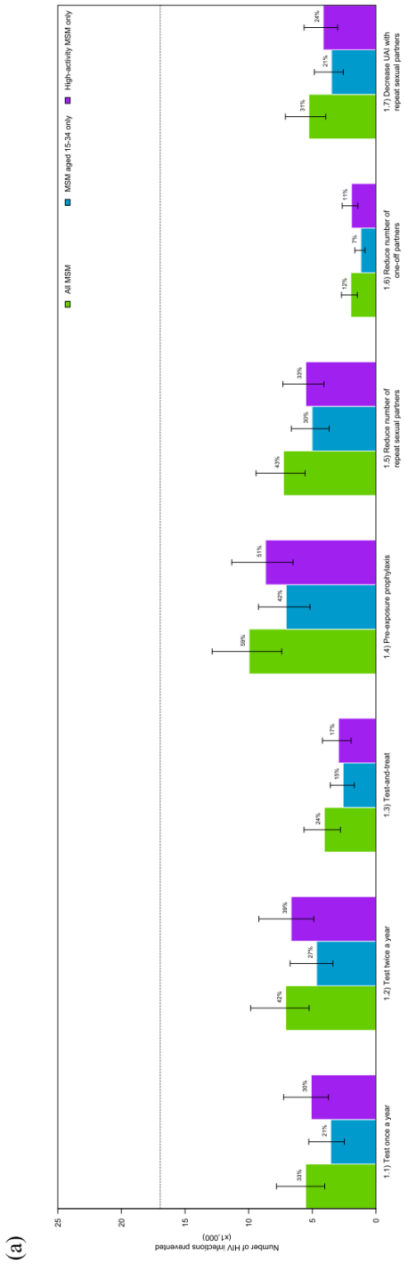
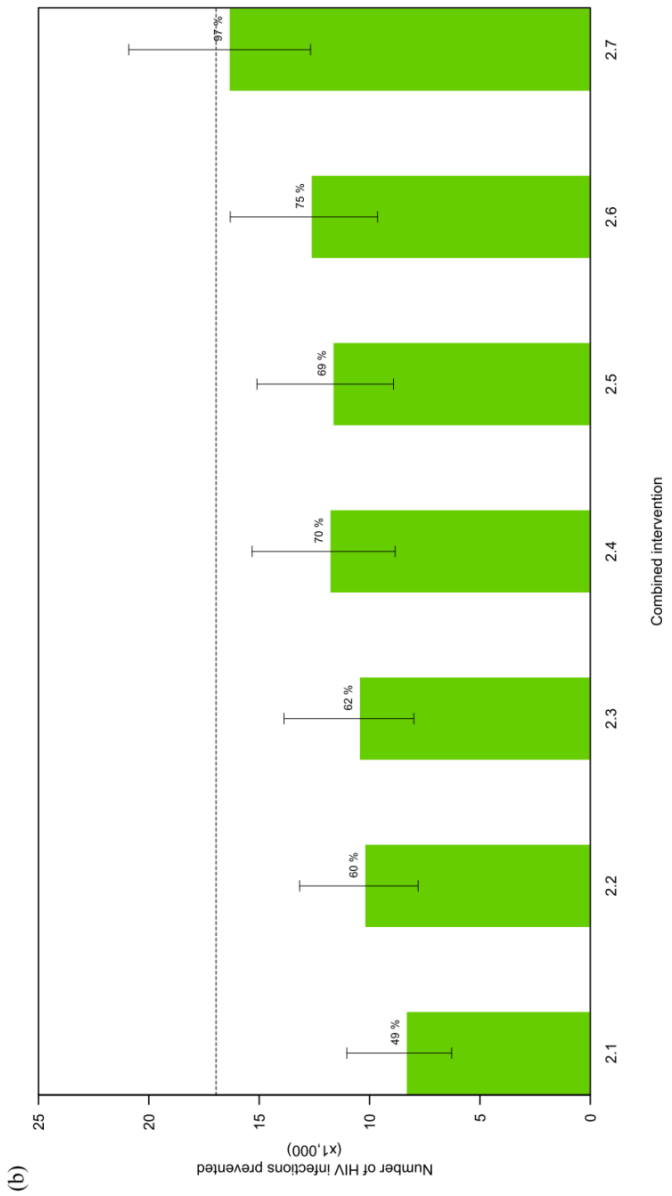


Figure S1: Flow diagram of HIV transmission model for MSM in the UK


(a)
All MSM
MSM aged 15-34 only
High-activity MSM only
Number of HIV infections prevented
(x1,000)
25
20
15
10
5
0
33%
21%
30%
42%
27%
39%
24%
14%
17%
59%
40%
51%
43%
30%
33%
12%
7%
11%
31%
21%
24%
1.1) Test once a year
1.2) Test twice a year
1.3) Test-and-treat
1.4) Pre-exposure prophylaxis
1.5) Reduce number of repeat sexual partners
1.6) Reduce number of one-off partners
1.7) Decrease UAI with repeat sexual partners

32


(b)
Number of HIV infections prevented
(x1,000)
25
20
15
10
5
0
49 %
60 %
62 %
70 %
69 %
75 %
97 %
2.1
2.2
2.3
2.4
2.5
2.6
2.7
Combined intervention

33

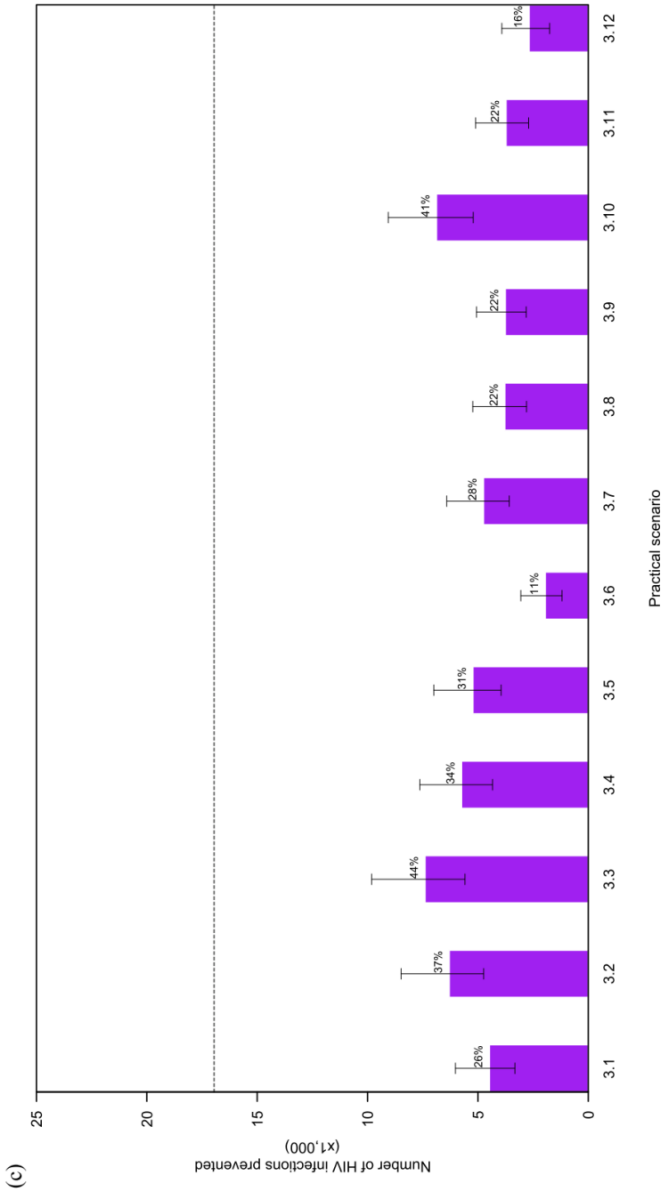
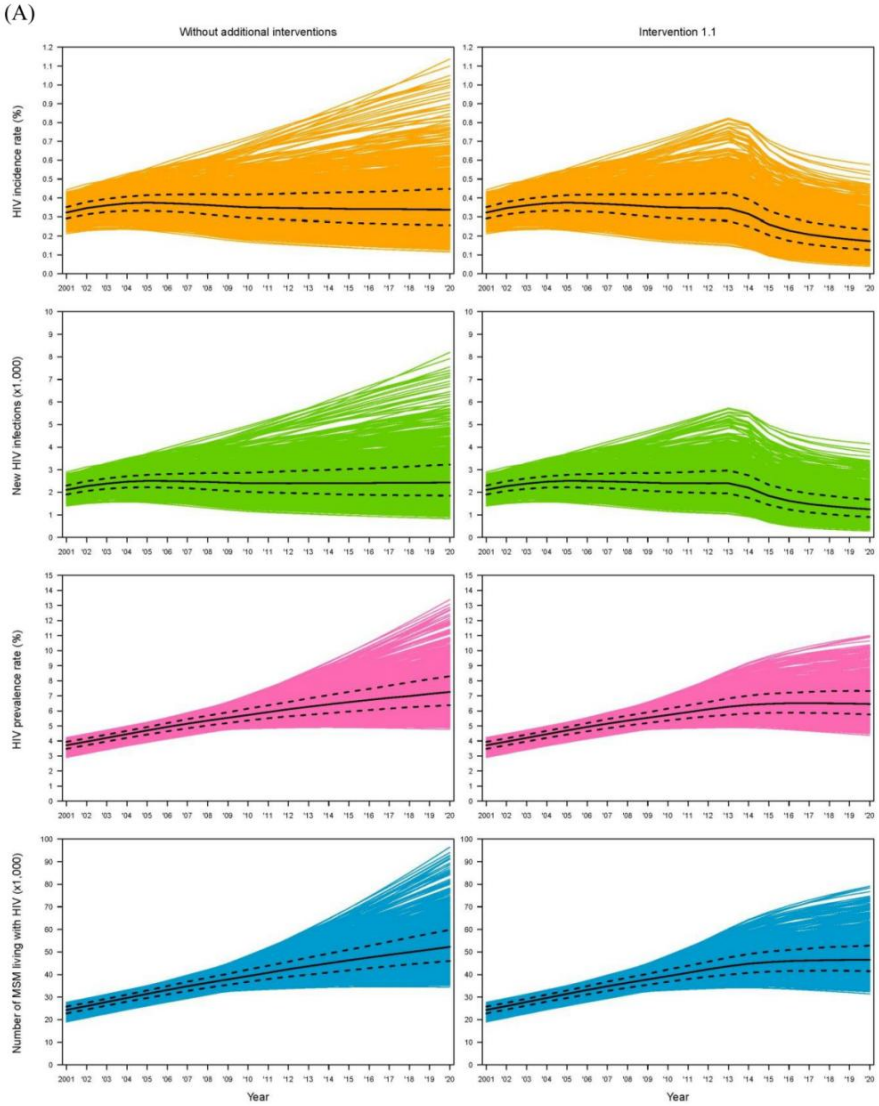


Figure S2: The 2014–2020 cumulative numbers of new infections prevented by HIV interventions

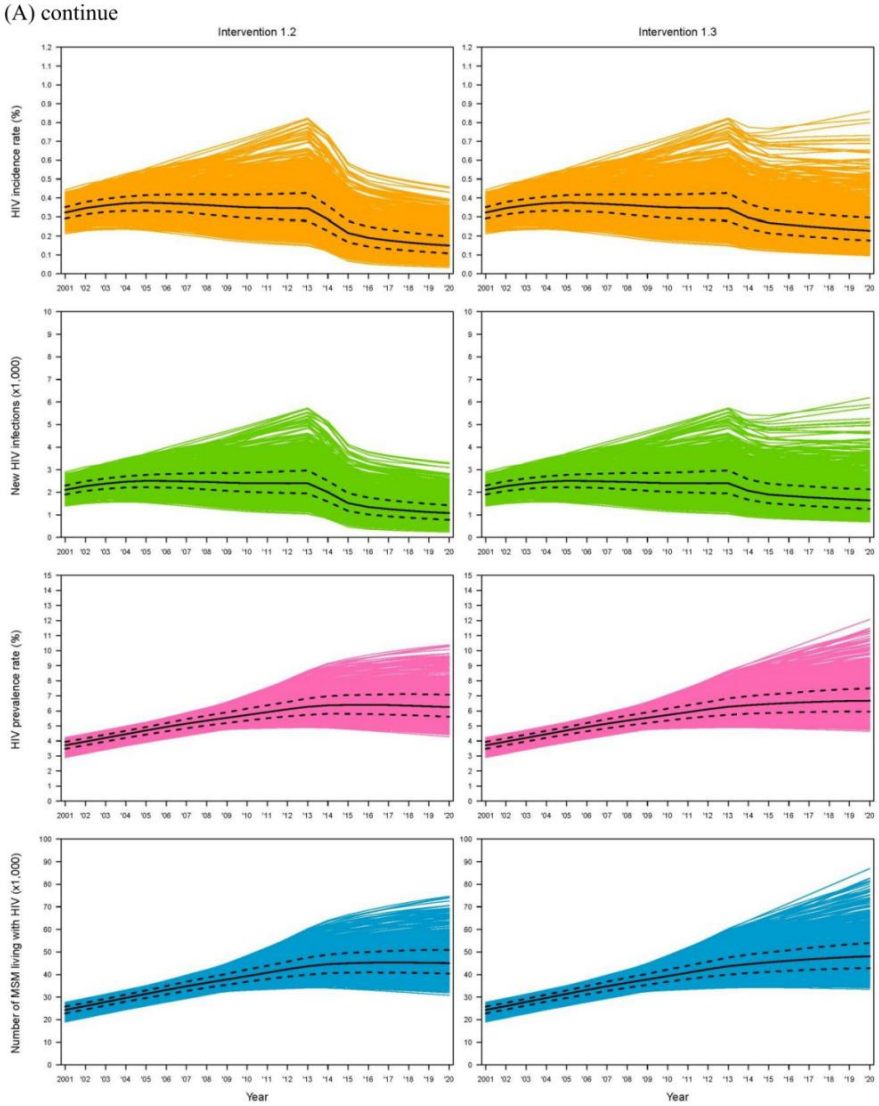
34

(A)


Without additional interventions
Intervention 1.1
HIV incidence rate (%)
New HIV infections (x1,000)
HIV prevalence rate (%)
Number of MSM living with HIV (x1,000)
Year
Year

35

(A) continue



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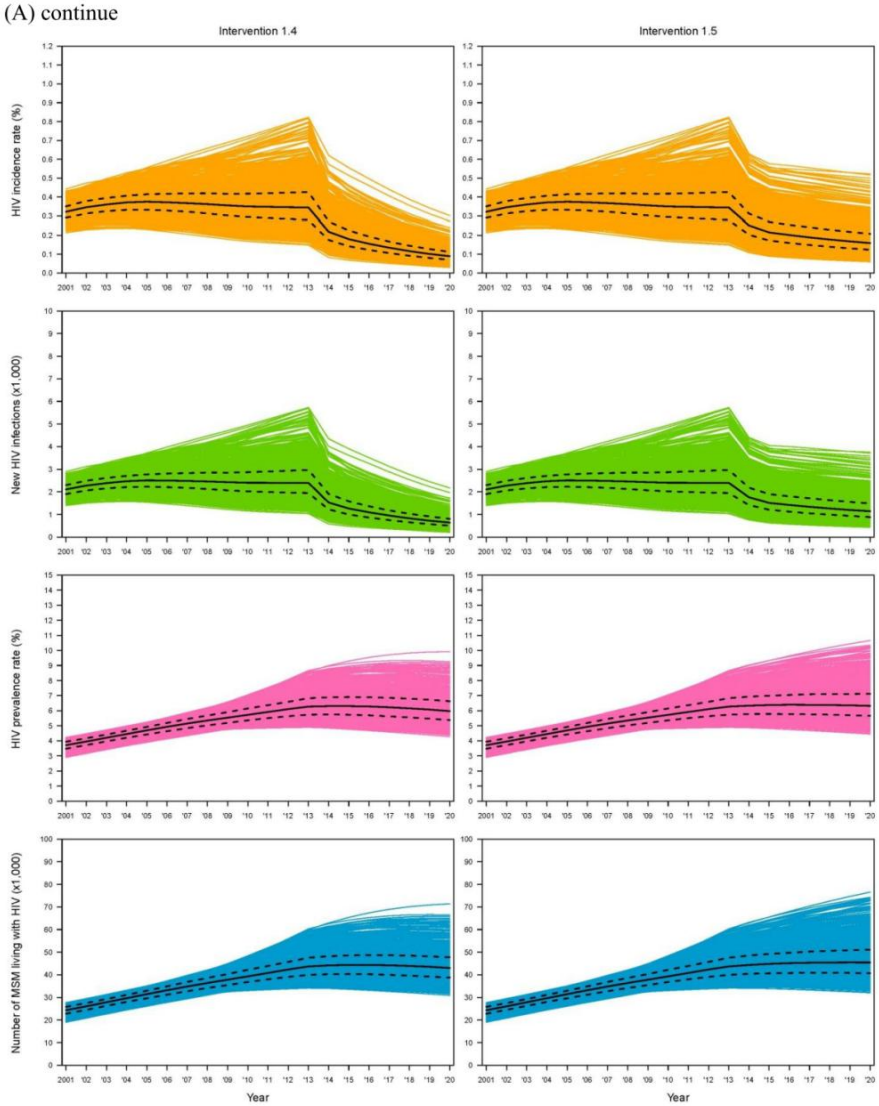
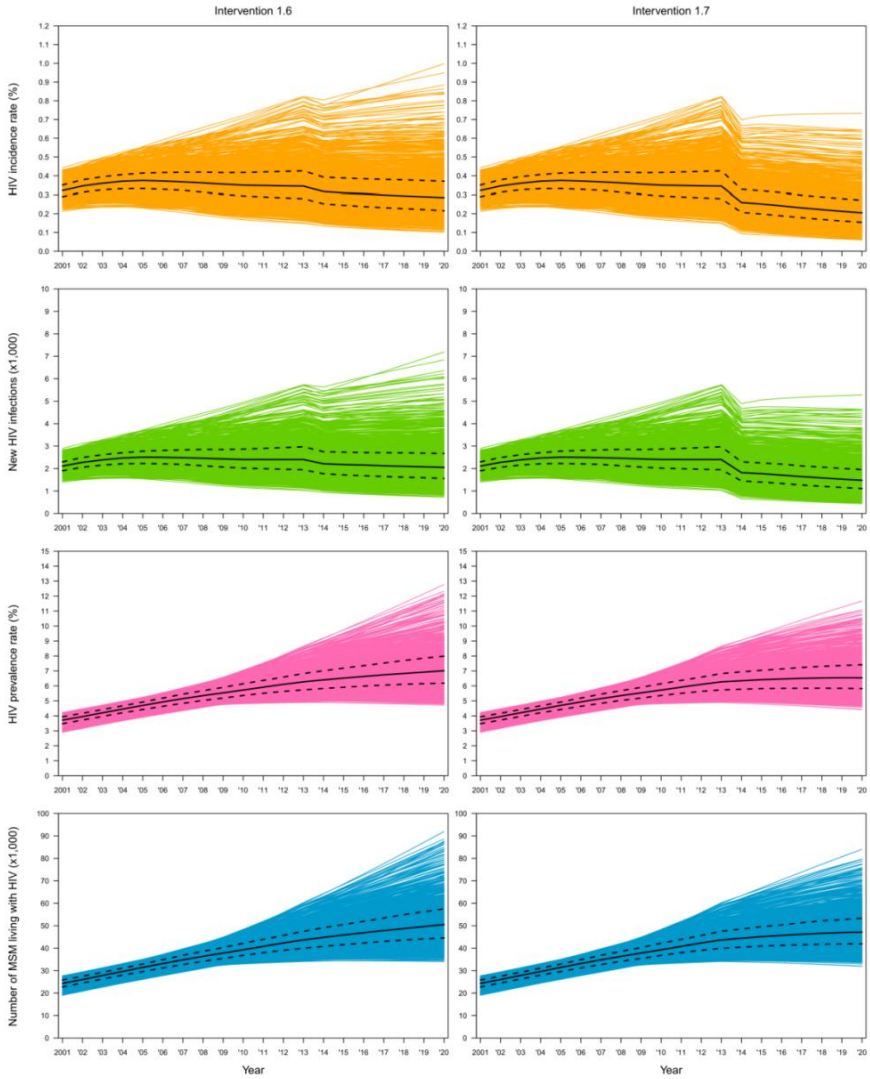
(A) continue



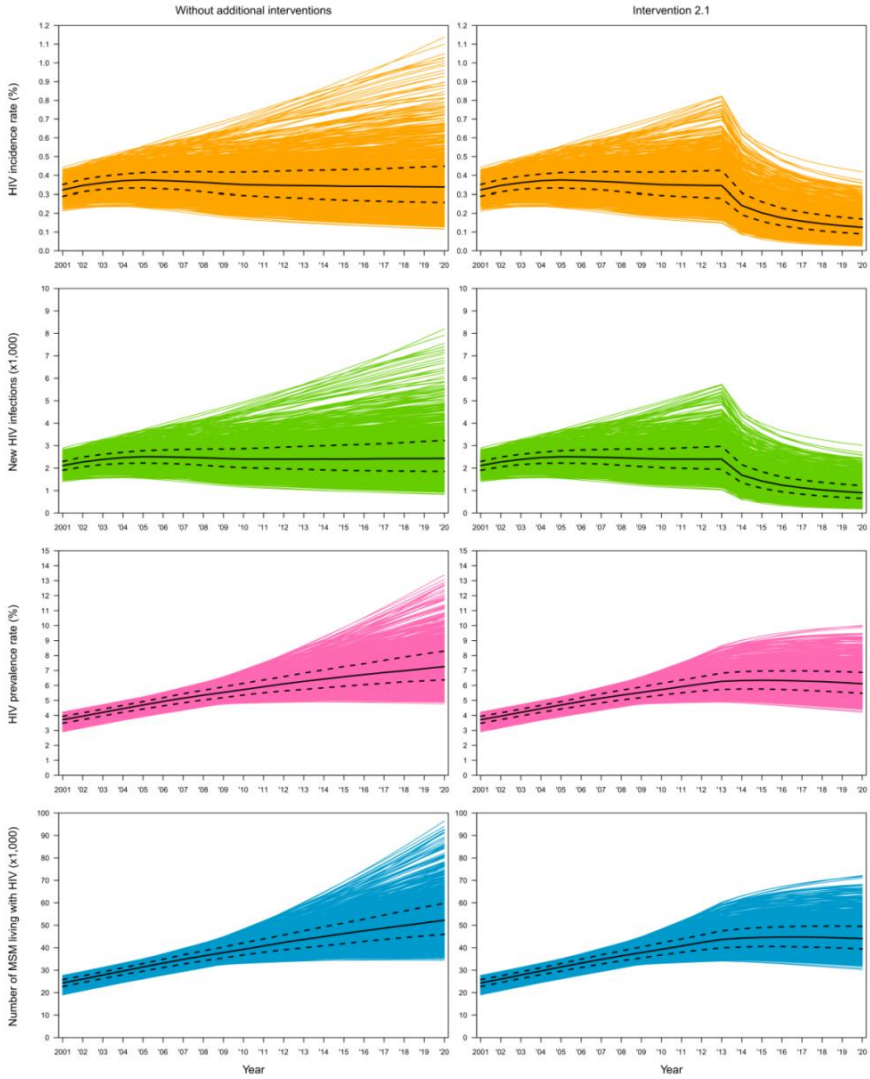
37

(A) continue



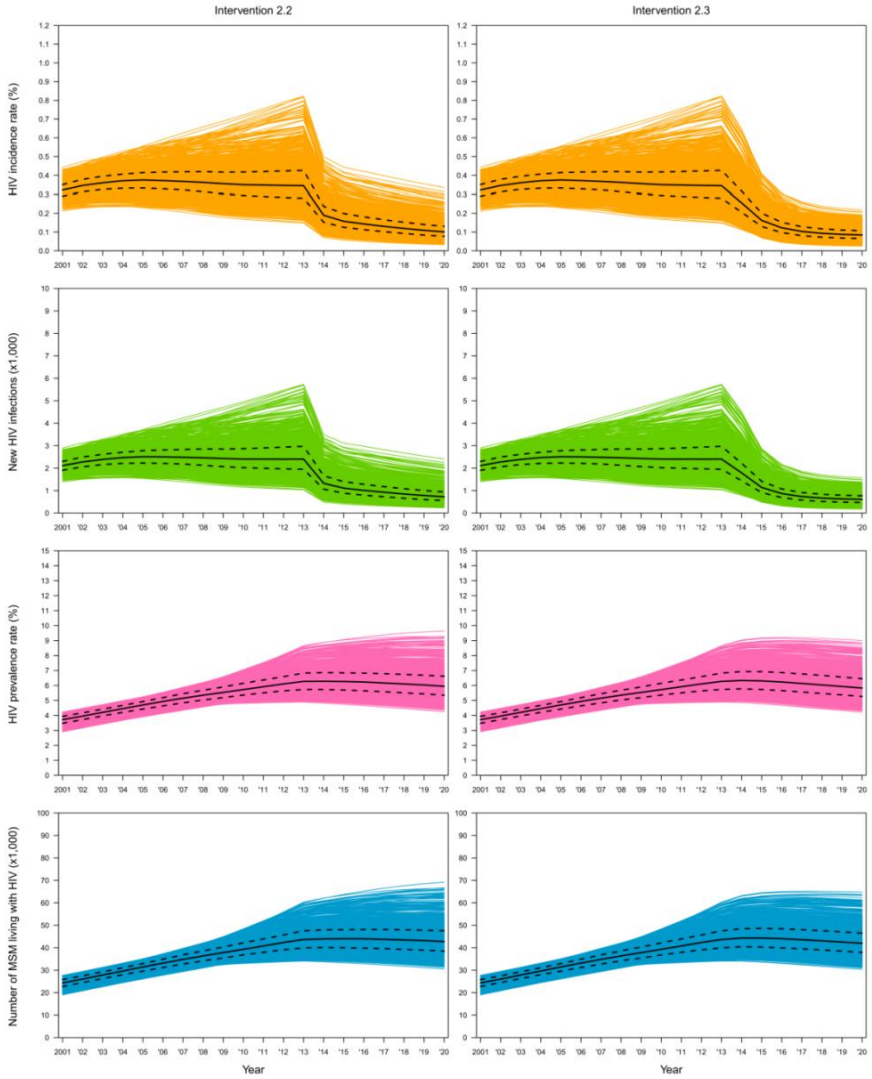
38

(B)


Without additional interventions
Intervention 2.1
HIV incidence rate (%)
New HIV infections (x1,000)
HIV prevalence rate (%)
Number of MSM living with HIV (x1,000)
Year
Year

39

(B) continue



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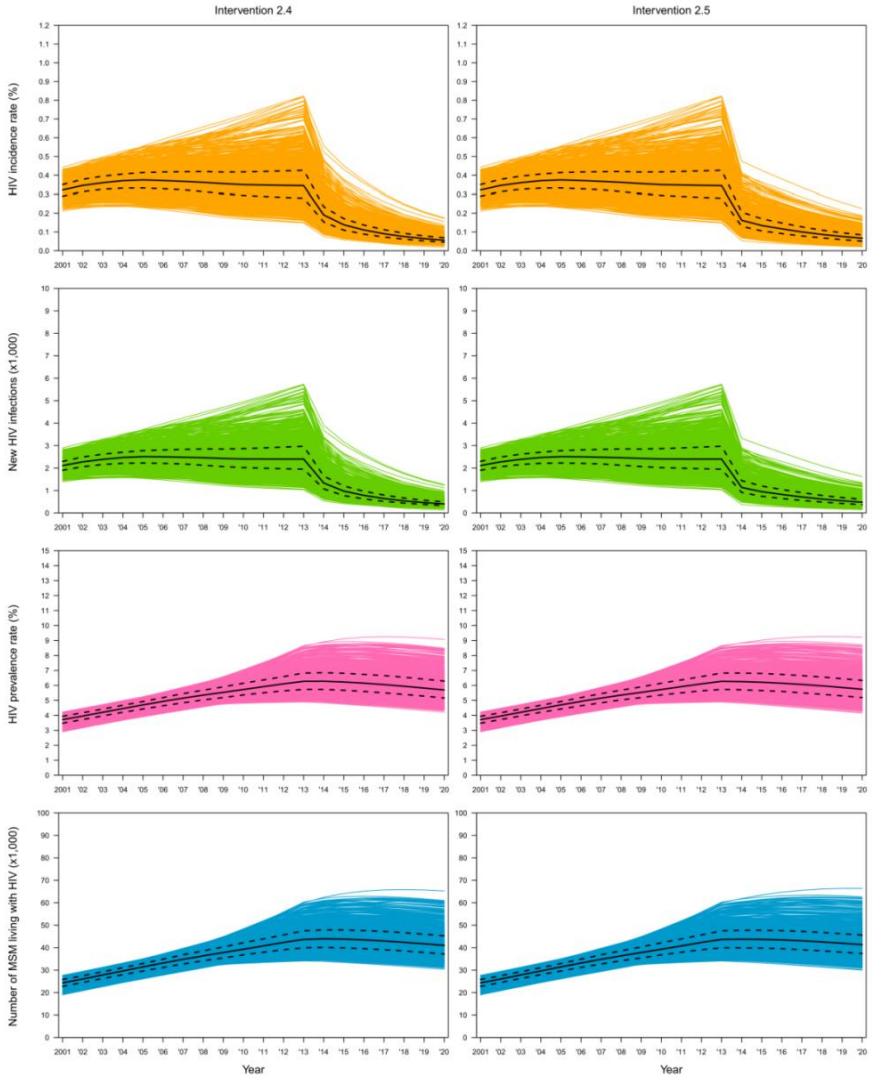
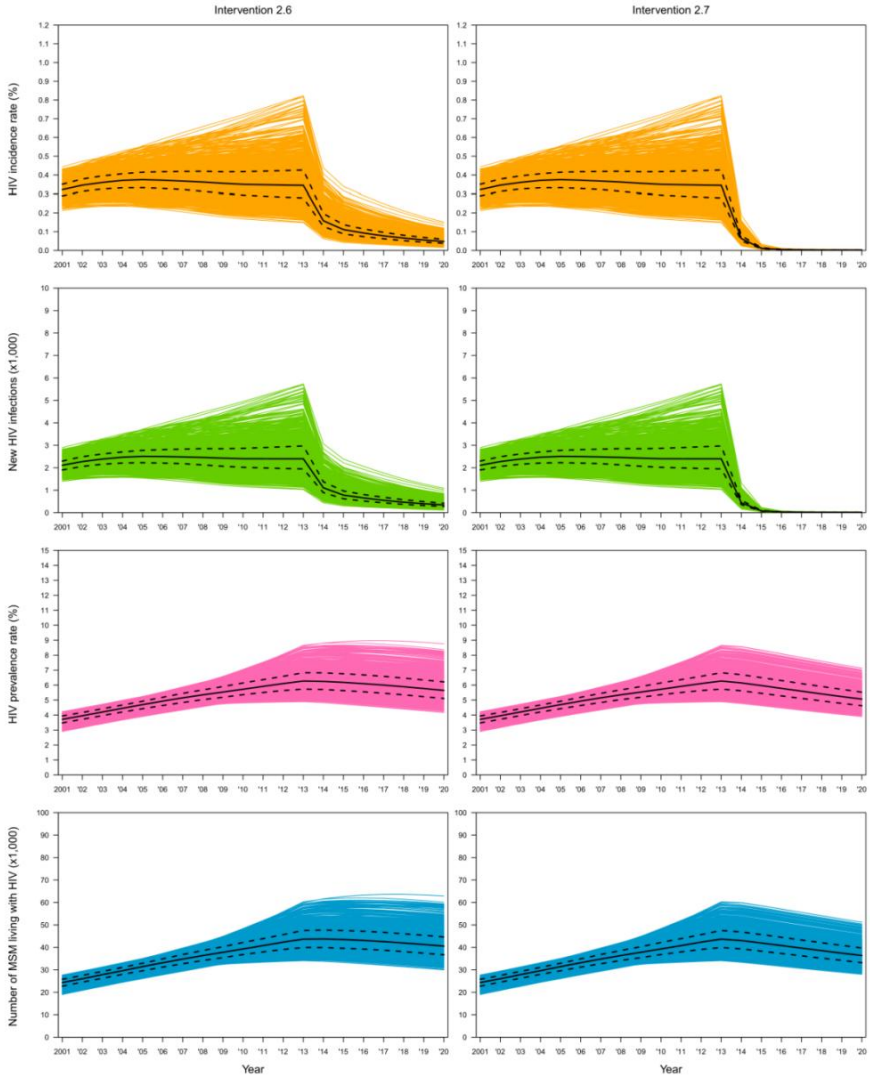
(B) continue



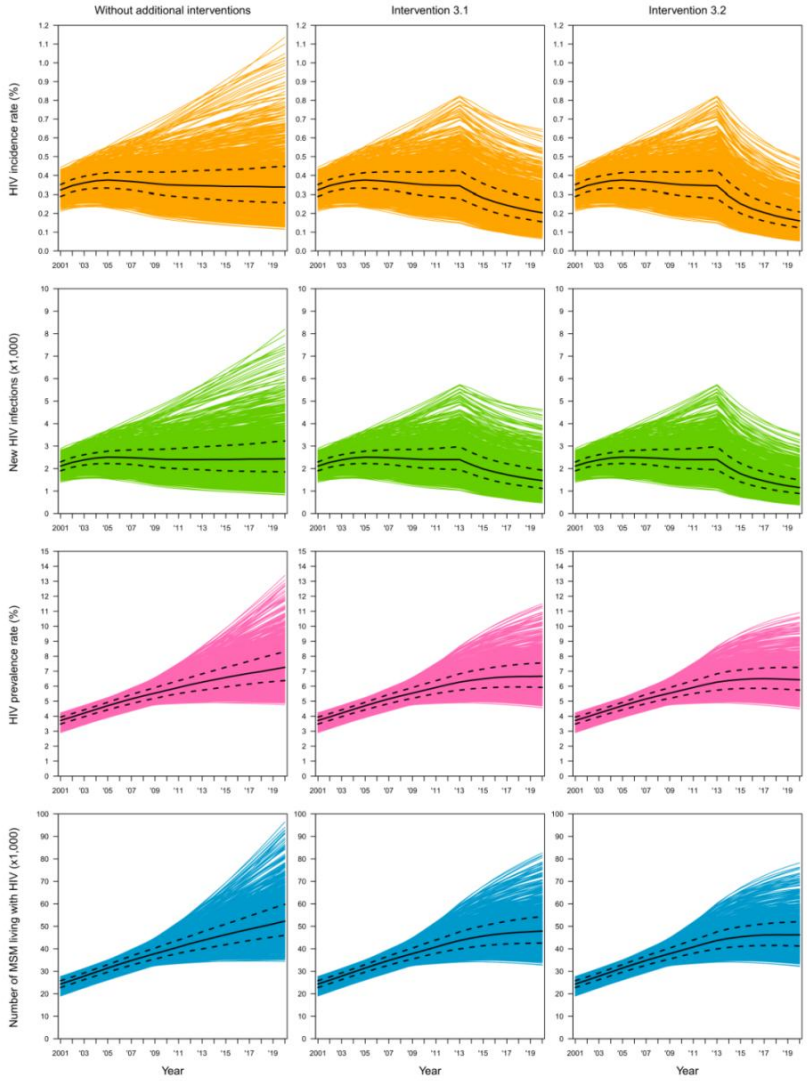
41

(B) continue



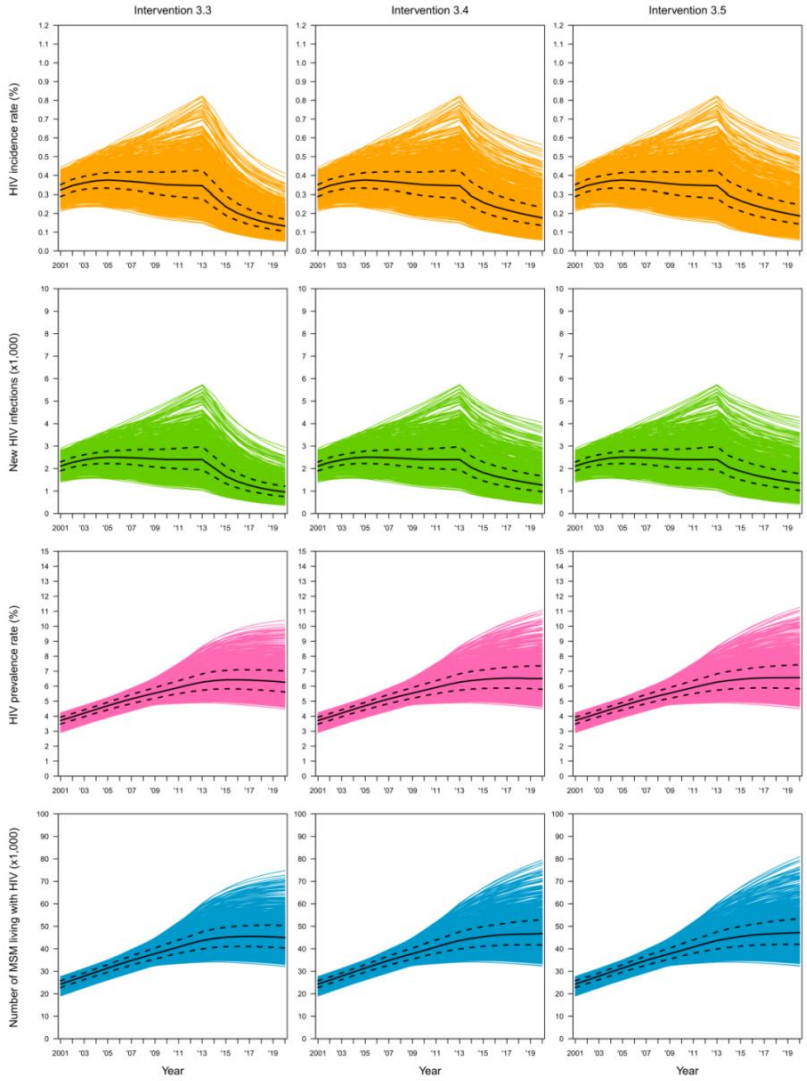
42

(C)


Without additional interventions
Intervention 3.1
Intervention 3.2
HIV incidence rate (%)
New HIV infections (x1,000)
HIV prevalence rate (%)
Number of MSM living with HIV (x1,000)
Year
Year
Year

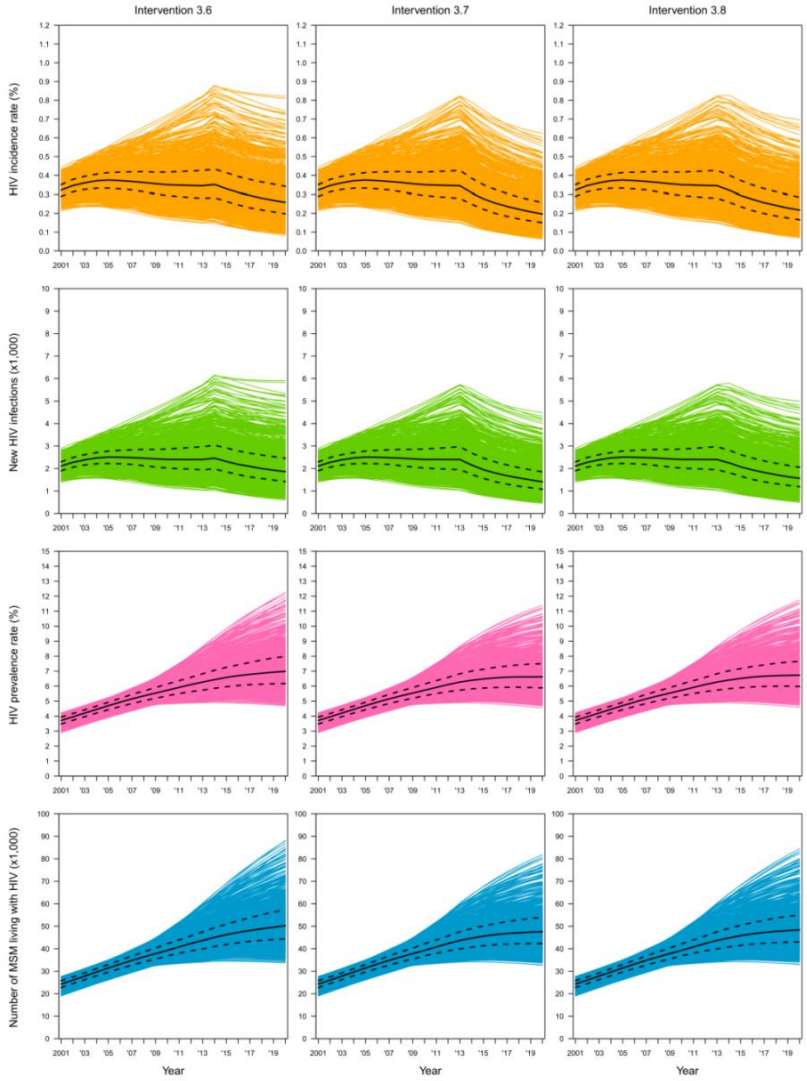
43

(C) continue



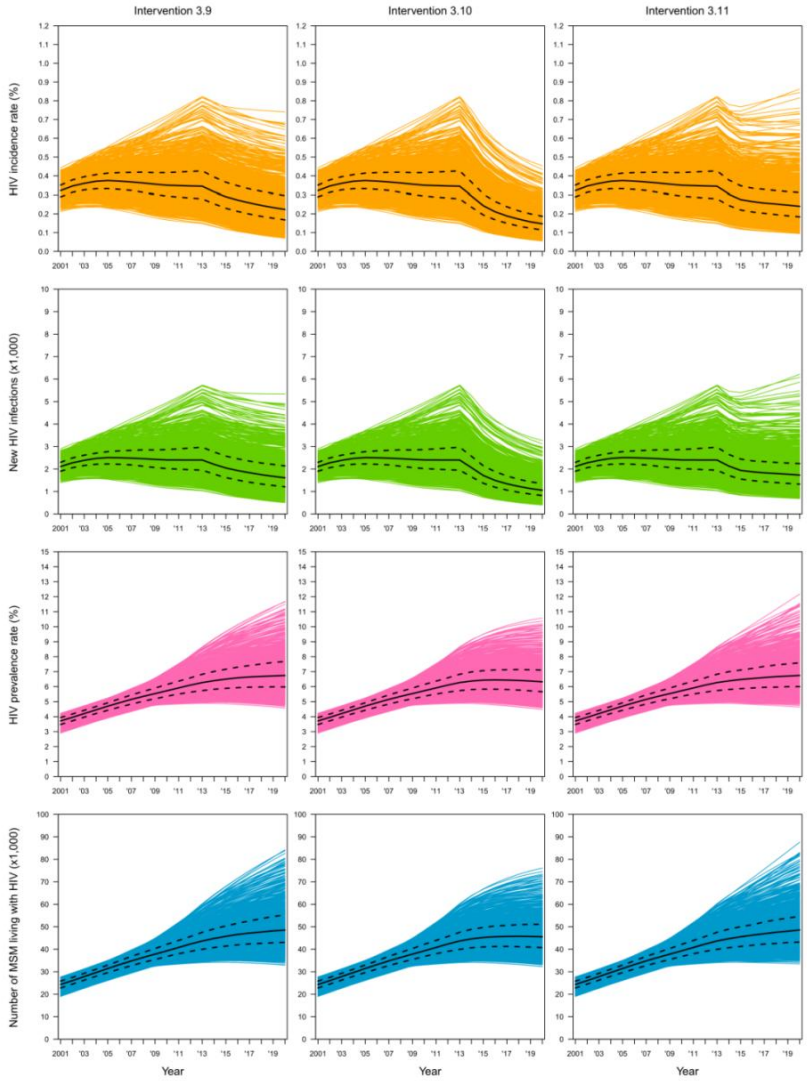
44

(C) continue



45

(C) continue



46

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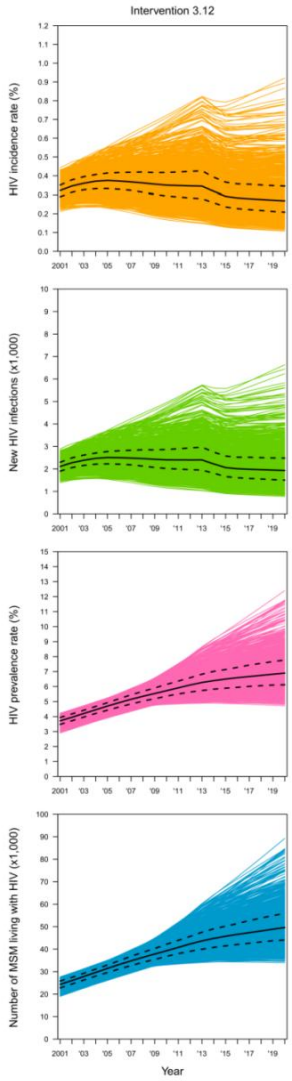

Figure S3: The effects of individual and combined interventions on HIV incidence rates, the numbers of new infections, and the numbers of MSM living with HIV over 2001–2020 in the UK

47

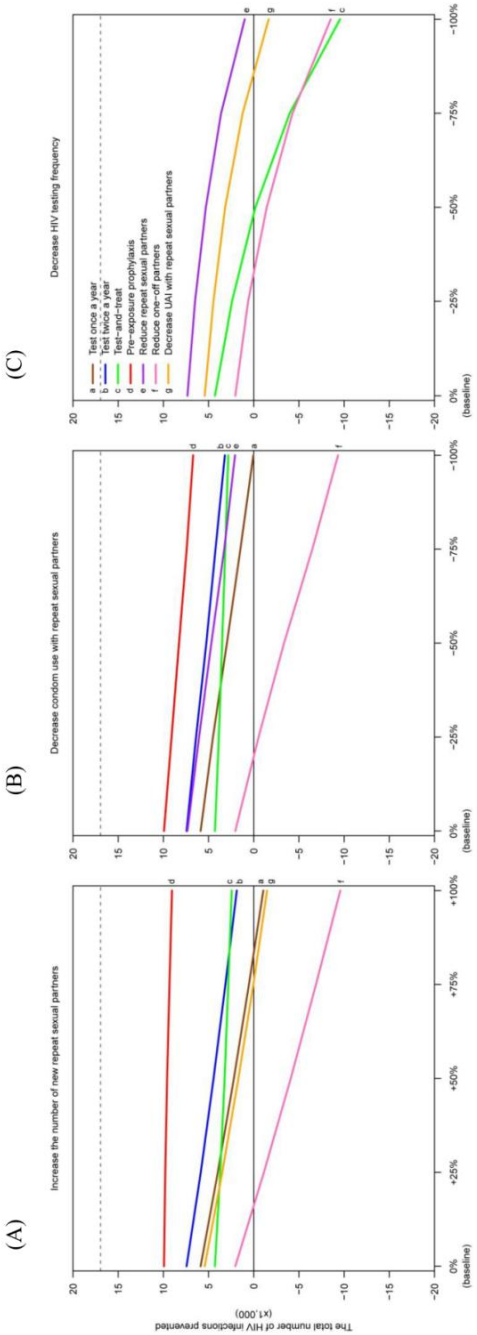

Figure S4: The effects of risk compensation on the effectiveness of the individual interventions

48

Supplementary figure legends

Figure S1

The flow of infection status and disease progression through 15 stages is shown. The disease stages are defined by CD4 cell counts and treatment status. The grey compartments represent additional stages for PrEP intervention. Influx of new MSM into the model and removal of MSM due to death and age above 64 are not shown.

Figure S2

The estimates of the cumulative number of HIV infections prevented between 2014 and 2020 due to (A) individual interventions (B) combined interventions, and (C) practical scenarios compared to the median estimates of the number of infections in the status quo scenario where no additional interventions have been implemented (dashed line). In each individual intervention, the three bars, green, blue, and violet, represent the estimates for intervention implemented in all MSM, MSM aged 15-34, and high-activity MSM, respectively. A percentage of infections prevented are reported on top of each bar. The error bars show the interquartile ranges of the estimates.

Figure S3

The predicted HIV epidemic among MSM on the UK according to (A) the individual interventions, (B) the combined interventions, and (C) the practical scenarios. Each row—the orange, green, and blue plots—represents the model estimates of annual HIV incidence rates, the numbers of new infections, and the numbers of MSM living with HIV during 2001–2020, respectively. Each column represents estimates for the

combined interventions. The first column is for the scenario where no additional interventions have been implemented while the last column is for the scenario where all HIV inventions are applied. The solid lines denote the median and the dash lines illustrate the interquartile ranges of the estimates derived from 1,093 simulations. The estimates before the intervention period (2014–2020) are identical in all scenarios.

Figure S4

The median estimates of the total numbers of HIV infections prevented among MSM in the UK during 2014–2020 are presented. The negative values represent the cases when the estimated total number of new infections is greater than that of the status quo scenario. The dash line illustrates the median estimates of the total number of HIV infections in the status quo scenario. The coverage was assumed 100%. (A) The effects of increasing the number of repeat sexual partners. (B) The effects of increasing the proportion of MSM who have UAI with repeat sexual partners. (C) The effects of decreasing the frequency of HIV testing.

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6.3. Conclusion

The previously developed HIV transmission model was modified and used to investigate the potential effects of HIV prevention interventions in reducing HIV transmission among MSM in the UK. Up until now, all four primary research questions have been addressed and more insights into HIV epidemic in UK MSM have been provided. The final chapter will draw important conclusions from the findings of this study and discuss about its main limitations and future improvements.

Chapter 7

Discussion and conclusion

In this chapter:

Summary of findings

Strengths and limitations of the study

Implication for policy

Future improvements

7.1. Summary of findings

The aim of this research was to provide insight into the contributions of various subpopulations to HIV transmission among men who have sex with men (MSM) in the UK, and evaluate potential effectiveness of a variety of interventions to prevent onward transmission in these populations. The partnership-based mathematical model for HIV transmission and control that has been rigorously calibrated to match the HIV epidemic in UK MSM was used for addressing the aims of the study. Several important issues identified by the review of the literature were taken into account in this study including the lack of recent modelling works on HIV transmission among UK MSM, the lack of studies that used more realistic modelling approaches, and the lack of properly fitted and validated modelling studies.

The model estimated that there were around 44,000 MSM living with HIV in 2013 and, without additional interventions, this number could reach 52,000 by the end of 2020. The number of new HIV infections was estimated at approximately 2,400 cases each year until the end of the decade. The analyses of factor contributions showed that the current epidemic of HIV in UK MSM is sustained primarily by high-activity MSM aged below 35 years, living with undiagnosed HIV in asymptomatic disease stages. The contributions of primary stage (PHI) to new HIV infections among UK MSM were estimated to be small, which is probably due to the relatively short duration of this high infectiousness stage compared to all other subsequent stages. The regression tree analysis confirmed that non-primary HIV infection stages were the most important drivers of the epidemic, while PHI-related parameters were not among them. The findings also suggested that the majority of new infections occurred within a repeat sexual partnership which highlighted an important role of long-term relationships in transmitting HIV.

The analysis on potential impacts of HIV prevention interventions illustrated that pre-exposure prophylaxis (PrEP) could prevent the largest number of infections among all other programs when implemented individually, whereas reducing the number of one-

off sexual partners was shown to be the least effective strategy. Increasing HIV testing frequency could save thousands of MSM from HIV, and substantially more if the test-and-treat program is also implemented. A large number of HIV infections could also be averted by counselling programs that aim at sexual behavioural changes, i.e. reducing the number of repeat sexual partners and unsafe sex with repeat sexual partners, but these programs may be difficult to put into practice.

In a more practical scenario where only relatively small coverage of interventions was achieved, simultaneously offering PrEP, expanding HIV testing, and initiating a test-and-treat program had great potential to become a successful combination. Although risk compensation could adversely affect the overall effectiveness, it is unlikely to completely negate the benefit of the interventions. However, infection eradication was shown not to be realistic over this time frame even after a successful implementation of the most effective combined interventions.

7.2. Strengths

There were a number of the key strengths to this research. First, the partnership-based modelling approach used in this study provided more realistic representation of sexual partnership formation and termination and allowed finite duration of partnerships which resulted in more accurate research outcomes than the non-partnership-based modelling approach.

Second, based on the review in Chapter 2, the HIV transmission model developed and used here was among the most complex MSM models in the literature that incorporated a large number of heterogeneities, including age group, sexual activity level, sexual partner type, partnership status, CD4 stages, diagnosis status, and antiretroviral treatment (ART) status. This allowed the effects of various behavioural and biological factors to be taken into account simultaneously and provided better estimations of HIV transmission and control.

Third, model parameterisation was rigorously carried out using available data from various sources including behavioural surveys, national surveillance databases, and findings from systematic reviews and meta-analysis studies. The model were then fitted to multiple time-series estimates and validated against the datasets that were not used in the model fitting to ensure that the underlying computations in the model resembled closely to the epidemic of HIV among UK MSM.

Finally, the simulation approach adopted here provided a large number of plausible outcomes which allowed uncertainty around the results to be explicitly extracted and investigated. Therefore, all key model outputs in this study were presented with the uncertainty range which was consistent with the recommended principles for good HIV epidemiology modelling [104].

7.3. Limitations

The main limitation of this study concerned issues with the available data used for model parameterisation. First, the lack of required data from behavioural surveys prevented incorporating some important heterogeneities into the model. For example, the partnership types could be stratified into steady partner and causal partner instead of repeat sexual partner and one-off sexual partner as carried out in this study. However, the behavioural data stratified by steady and causal partners, e.g. the number of partners, the frequency of sexual acts, and the duration of relationships, were not available by the time this study was undertaken. Therefore, such stratification of partnership types could not be completed. Second, the completeness and representativeness issue of the data from behavioural surveys, which are among the main sources of uncertainty around all behavioural parameters in the model. For example, NATSAL of the year 2000 was a national-based probability-sampling survey of sexual behaviours that were representative of the UK population. The age range of the surveyed populations of 16-44 years was, however, not compatible with the 15-64 age range in this research. The survey also included only a small number of MSM which made further stratifications not possible. In contrast, GMSHS and GYM studies

were community-based convenience-sampling surveys in London which, without a prior adjustment, would not be suitable for representing MSM populations at the national level. The sample size and age range were, however, sufficiently large for in-depth analyses undertaken throughout this study.

MSM stratification in this study were also limited to only two age groups and two sexual activity levels which may not be sufficiently granulated to capture hidden or unknown heterogeneities that could be important in determining the spread of HIV. This is partly because of the small sample size of MSM in behavioural surveys mentioned earlier, and also because of extra computational burdens that further MSM stratification would add to the model. There were already a total of 1,980 model equations in the PrEP model (Chapter 6) which is considered extremely large in comparison to most HIV transmission models in other studies. Adding a few more subgroups would exponentially increase the number of model equations and time to complete the simulations which was not viable under the time constraint of this study.

Many assumptions made in this study were by necessity a simplification of the real-world situations and may not actually occur. For example, the epidemic projection was based on the assumption that there were no effects of additional interventions and all model parameters remained constant until the end of projection. This may be true only for the near future but unlikely for the long term. However, such projection was meant to provide an indication of the epidemic without additional intervention to emphasise the need of additional HIV prevention efforts rather than to precisely project its future course.

The effects of ART resistance and co-infection with other sexually transmitted diseases on HIV transmission were not explicitly included in this research. However, the model parameters were fitted to the current HIV epidemic among UK MSM and have therefore already taken these factors into account. Unless the prevalence of co-infection and drug resistance strain changes greatly during the intervention period, their effects on the model outputs may be modest.

7.4. Implication for HIV prevention policy

This research suggests that the current epidemic of HIV among MSM in the UK is driven mainly by undiagnosed HIV-positive MSM in the asymptomatic stage aged below 35 years who have high sexual activity levels. Any successful efforts to reduce the number of this high-risk group are likely be an effective HIV control strategy. Reducing the number of sexual partners was shown to be effective against HIV transmission but may be difficult to put into practice. Expanding HIV testing, on the other hand, should be more practical. Offering HIV testing beyond STI clinics, e.g. in routine health checks or when MSM present with other health problems, may help increase HIV testing uptake and provide necessary counselling for HIV-positive men.

Encouraging more HIV testing is also crucial in determining the success of subsequent programs including test-and-treat. This study shows that a test-and-treat program, when implemented without a program to increase HIV testing uptake, has a limited impact against HIV transmission at the population level. With both programs combined, not only the prevention effectiveness increases substantially, but the benefits are also gained from a number of key strengths offered by this combination.

The provision of PrEP could save thousands of lives from HIV within a few years after the introduction. Initiating PrEP would also increase the proportion of diagnosed individuals since it requires HIV testing prior and during treatment administration. However, the main concern lies in the effects of risk compensation that could negate the prevention benefits. It is, thus, important to keep monitoring the level of risk behaviours in PrEP users and continue the research to better understand risk-taking behaviour and PrEP application.

In conclusion, it is clear that, in populations most severely affected by the HIV epidemic such as MSM, a combination of interventions is necessary to bring the epidemic under control. Expanding HIV testing remains the core of the HIV prevention strategy among MSM in the UK. Simultaneously implemented with the

programs to offer immediate ART, and PREP is likely to marked improve the overall effectiveness against HIV transmission and become the key preventive measures for HIV/AIDS in the UK.

7.5. Future improvements

This PhD study highlights a need for further research in several aspects surrounding the modelling of HIV transmission including model structure, parameterisation, data, and analysis.

The use of partnership-based model in this study provided more realistic approach to modelling HIV transmission between sexual partners. However, the number of model equations increases exponentially with the number of subgroups, e.g. age groups, sexual activity levels, and disease stages, and rapidly becomes a computational burden. A method to simplify the modelling process and reduces the number of equations without sacrificing the partnership formation mechanism of the model will thus be very helpful for further application of the model. Such simplification may be achievable by approximating the probability that paired individuals select their partners from each subgroup and calculate the probability of HIV transmission within these partnerships without actually pairing them as done in the original partnership-based approach. This process would then be repeated every modelling time step allowing for changes over time in the size of subgroups, while other model computations remain unaffected. The successful implementation of this approach will greatly reduce the number of model equations, for instance, in Chapter 5 from 1,296 to as small as 120, which will make room for other important heterogeneities to be incorporated into the model, such as STI co-infection, ART resistance, and recreational drug use that has recently been found to have a strong association with unprotected sex among UK MSM [105].

As for model parameterisation, an increasing number of studies have applied a variety of Bayesian approach to parameter estimation in the context of modelling HIV

transmission and other infectious diseases. The key advantage is that the approach can utilise information from multiple sources to simultaneously estimate a number of parameters and incorporates uncertainty analyses in the fitting process [104,106]. For example, a Bayesian melding approach combines beliefs, information, and data on inputs and output of the model using a simulation technique to estimate the model parameters with uncertainty ranges [107]. The approach has recently been used to fit the heterosexual HIV transmission model to HIV prevalence data in Malawi [58], as well as fitting the influenza transmission model to incidence data in Belgium, the Netherlands, and Portugal [108]. Another method under the Bayesian framework called the evidence synthesis has been applied for modelling HIV transmission among MSM in England and Wales to simultaneously estimate various model parameters using information on demographics, sexual behaviours, and sexual contacts [54]. To date, these Bayesian methods have never adopted for parameterising a partnership-based HIV transmission model, and it is thus useful to explore if such approaches can provide more accurate estimates over other methods currently used.

Regarding to the data issues, increasing the availability of more accurate and granulated data is always welcome. The findings from Chapter 5 that showed a clear difference in the level of contribution between repeat and one-off sexual relationships suggested that the future sexual behavioural studies may need to focus on distinguishing between different types of partnerships, e.g. steady and casual, in a more precise manner. Although this PhD study showed that there is a good possibility that steady partnerships also play an important role in driving the UK epidemic, a further study is needed to confirm this finding. If accurate information on the average number of partners, the frequency of sexual acts, the partnership duration, and the partnership concurrency, are made available for each type of partnership, then the model can be reparameterised to assess various aspects of partnership types and help clarify whether HIV transmission within steady or casual partnerships is the main contributor for the ongoing epidemic.

The model-based estimates would also benefit from more accurate data on how UK MSM select their sexual partners based on age, sexual activity, and HIV infection status, as well as other important characteristics that influence the incidence of HIV such as ethnicity and geographic area [109]. This should help with constructing a more precise sexual mixing matrix which may reveal some important patterns in subpopulations. Also, the future research will benefit from the updated information on sexual behaviours and attitudes in UK MSM provided by the next round of the NATSAL survey conducted in 2010–2012 [63]. The survey reports on same-sex activity and expands the sample's age range to 16-74 years which will help resolve this uncertainty and lead to more precise estimates.

The estimates of HIV transmission probability, which was showed in Chapter 5 to be among the most influential parameters in the model, require an update as new evidence becomes available in the future. An empirical study designed to estimate per-act HIV transmission probability among MSM in the UK or other developed countries where ART is widely accessible would be of great importance for improving the accuracy of transmission rates. If ART with a good adherence could substantially suppress HIV transmission through unprotected sex among seroconcordant couples [110], it is highly possible that the future contribution of ART-treated men to new HIV infections will be much less than that estimated in this study.

Finally, including cost-effectiveness analysis for HIV prevention interventions will substantially improve the usefulness of this study. It is possible that any highly effective programmes against HIV transmission suggested here may not be cost-effective in the actual UK setting. Therefore, further economic evaluations are necessary to inform timely and accurate public health decision making. The comprehensiveness of the model also supports further expansion to HIV epidemics in other populations and locations. Depending on the available data, the model could be easily modified to assess the impact of any specific HIV prevention interventions in greater detail. Its flexible structure also allows the future incorporation into the model of other alternative interventions in parallel with those already included in this PhD.

7.6. Final words

This study provided a better overall understanding of the dynamics of the HIV epidemic among MSM in the UK. The development of partnership-based model was expected to emphasise the importance of partnership characteristics in modelling HIV transmission and control. A number of integrated heterogeneities and better use of available data allowed this study to make the most of available knowledge and information that exist in the context of HIV epidemics. The achievement of this study will encourage a greater use of an alternative model and soon it may become one of the standard HIV modelling approaches. The findings from an application to the HIV epidemic in MSM should help inform HIV prevention and control strategies in the UK, which will ultimately bring a benefit to the society as a whole.

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