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Title:
Eliminating hepatitis C in the UK among men who have sex with men during the era of pre-exposure prophylaxis

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ELIMINATING HEPATITIS C IN THE UK AMONG MEN WHO HAVE SEX WITH MEN DURING THE ERA OF PRE-EXPOSURE PROPHYLAXIS

Louis MacGregor

May 2019

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Health Sciences.

45,000 words
Abstract

Globally, over 70 million people are infected with hepatitis C virus (HCV), leading to an estimated 400,000 deaths per year. Co-infection with HIV poses even greater risks due to accelerated rates of HCV related liver damage. Within men who have sex with men (MSM) HCV is more concentrated in those with HIV: in the UK 10% of MSM with HIV are co-infected, whereas HCV prevalence is 1% in HIV negative MSM. Yet reasons for this disparity are not fully clear. To tackle this global epidemic, in 2015 the World Health Organisation (WHO) and the UK National Health Service (NHS) announced their targets to eliminate HCV; by reducing HCV incidence by 90% by 2030 and 2025 respectively.

In this thesis we utilise a compartmental transmission model, parameterized with UK behavioural data and biological factors associated with HIV and HCV co-infection to explore the feasibility of these HCV elimination targets and determine the key factors which may influence their success. This analysis was undertaken accounting for the changing landscape of (1) HCV treatment and prevention initiatives, such as the scale up of direct acting antivirals (DAAs) and (2) the evolution of HIV prevention through the introduction of pre-exposure prophylaxis (PrEP). PrEP use offers individuals an 86% reduced risk of HIV acquisition, but with PrEP’s growing uptake, data is increasingly pointing to the rise of risk compensatory behaviours, including reducing condom usage or changes in sexual mixing.

Our results indicate behavioural and not biological factors are largely accountable for the pattern of HCV infection; specifically preferential mixing by HIV status and heterogeneity in the number of sexual partners between MSM. We projected that HCV elimination in UK MSM is possible by both 2030 and 2025, requiring enhanced HCV screening in all MSM and faster initiation of treatment than in the pre-DAA era. Furthermore, by incorporating this extra screening into routine sexual health appointments, our proposed elimination strategies, for both the 2025 and 2030 targets, are also cost-effective at the willingness to pay threshold of <£20,000 per quality adjusted life-year (QALY) set by the NHS.

In conclusion, HCV elimination within UK MSM is possible whilst being cost-effective, but requires a scale up of HCV screening over all MSM, not just those with HIV co-infection. It is also important to mitigate risk compensatory behaviours associated with PrEP use, as our projections have shown these behaviours to be both drivers of the UK HCV epidemic pattern in MSM, as well as highly influential to the overall cost-effectiveness of implementing our HCV elimination strategies.
Acknowledgements

I would like to express my special appreciation and thanks to my supervisor Peter Vickerman. I have grown so much as a scientist and a researcher under his guidance and support. Throughout this PhD, Peter has spent many hours critiquing and helping to shape my work which have been instrumental to my development and a testament to Peter’s dedication to his work and his students.

I would also like to extend a huge thank everyone who has made suggestions, comments and critical insights to the work presented here; including Matthew Hickman, Zoe Ward, Ford Hickson, Peter Weatherburn, Jane Nichols, Monica Desai and Ayalvadi Ganesh. In particular though, I would like to especially thank Natasha Martin for her support as my adopted supervisor. Natasha’s work has been both an inspiration and a large component of the foundation on which this work stands, as well as Natasha being an unfailing source of knowledge and optimism.

I would also like to thank my colleagues in the infectious diseases mathematical modelling group at the University of Bristol. For their sage advice and patience in watching countless presentation practices and checking my work, but also for making our time at conferences so much more memorable and enjoyable that it would have been without them.

To my family and friends, I earnestly say that we couldn’t have made it through to finishing this work without you. There has been so many ups and downs over the last years, and without your support and love we know that we would never had made it to the finish line. I will always be grateful, and I will always remember the sacrifice and encouragement that my loved ones demonstrated throughout this period.

Lastly, I am also so thankful to the Engineering and Physical Sciences Research Council for funding the work done throughout this PhD, without which I would never have been able to take this opportunity and learn so much about not only sexual transmitted infections, but about myself too.
Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ........................................ DATE: 28/10/19
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<td>ALT</td>
<td>Alanine aminotransferase</td>
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<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>Credibility interval</td>
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<td>Direct acting anti-viral</td>
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<td>Gamma-hydroxybutyrate acid</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<td>HIV</td>
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<td>HR</td>
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<td>NAT</td>
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<td>OR</td>
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<td>PCR</td>
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<td>PEP</td>
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<td>Pre-exposure prophylaxis</td>
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Below is a list of publications that have arisen from research undertaken throughout this PhD along with my contribution to each publication (as printed in the publication):


**Author Contributions**
P.V. and N.K.M. designed the study. C.M. undertook preliminary model analyses. L.M. undertook the statistical analyses, model development, simulations and analyses. P.V., N.K.M. and L.M. wrote the first draft of the article. L.M., C.M., F.H., P.W., M.H., N.K.M. and P.V. interpreted the data, edited the article and approved the final version.

Also under review with the Lancet’s open access journal EClinicalMedicine at the time of final submission:

Louis MacGregor, Monica Desai, Natasha K Martin, Jane Nichols, Ford Hickson, Peter Weatherburn, Matthew Hickman, Peter Vickerman. ‘Scaling up screening and treatment for elimination of hepatitis C among men who have sex with men in the era of HIV pre-exposure prophylaxis’.

**Author contributions**
P.V. and L.M. designed the study. L.M. undertook the statistical analyses, model development, simulations and analyses with supervision from P.V. L.M. and P.V. wrote the first draft of the article. L.M., F.H., P.W., M.D., J.N., M.H., N.K.M. and PV interpreted the data, edited the article, and approved the final version.

These articles are attached as additional material at the end of the thesis.
Chapter 1 Introduction

Epidemiology as a discipline is concerned with the understanding and control of infectious diseases. Work in this area is key to health policy, implementing effective interventions to combat disease and the assignment and optimisation of budgets in order to maximise and improve public health.\(^\text{220}\) From one of the first applications of an epidemiological intervention involving inoculation of smallpox in 1796,\(^\text{248}\) to the vast array of modern day interventions ranging from country wide vaccination programmes to policies encouraging routine disease screening, breakthroughs in epidemiology are synonymous with extending and improving the quality of human life.\(^\text{220}\)

The way in which we approach the study of epidemiology is varied, with work being done in clinical settings at the front lines of disease management, in laboratories that uncover the genetics and traits of diseases and using theoretical tools. Amongst these theoretical tools is the application of mathematical modelling, that can be used to establish the main mechanisms of disease spread, in order to predict future courses of outbreaks and evaluate strategies to help in controlling epidemics. This can be in the form of estimating the resources needed, planning interventions or understanding how complex risk factors may contribute to the observable pattern of disease spread. This is all critical work, as death by disease remains one of the largest contributors to human mortality despite the knowledge we now possess allowing many diseases to be preventable. Pushing the forefront of this discipline is beneficial to not only our continued success as a species but to individual quality of life and personal prosperity.

One important subsection of epidemiology focuses its attention on sexually transmitted infections (STIs), which are by definition: bacterial or viral infections characterised by their presence in and transmission between the tissues and fluids of the sexual organs. Most STIs are now easily treated in high income settings, with prognosis of these infections often being very good. There are however notable exceptions to this; one of the most infamous STIs of recent history in this category being Human Immunodeficiency Virus (HIV). HIV leads to the onset of Acquired Immune Deficiency Syndrome (AIDS), a condition which over time suppresses immune system function and leads to death
from secondary opportunistic infections.\textsuperscript{116,161} Whilst anti-retroviral treatments and lifestyle changes can prolong the lifetime of individuals with HIV to near that of those uninfected,\textsuperscript{332} the infection remains ultimately fatal, with dire consequences occurring if diagnosis is made late\textsuperscript{183} or if individuals with HIV prove resistant to forms of treatment.\textsuperscript{346}

Along with HIV, hepatitis C virus (HCV) is another serious virus which can be transmitted sexually. HCV poses great risks to health by causing liver damage over time, often in the form of cirrhosis and liver cancer.\textsuperscript{290} Damage accumulates until liver function becomes so impaired that individuals with HCV face risk of death.\textsuperscript{290} Although treatment outcomes for HCV are generally good thanks to modern direct acting antivirals (DAAs),\textsuperscript{350} HCV can go unnoticed for long periods and the damaged done to the liver during the course of infection is difficult to reverse.\textsuperscript{290} Also due to the fact that HIV and HCV can remain asymptomatic for long periods of time, there is a greater chance of onward transmissions, and the presence of both diseases in one individual (known as co-infection) poses greater combined risk than either infection presents individually.\textsuperscript{286}

Due to the varied nature of sexual intercourse, some individuals find themselves more vulnerable to HIV and HCV than others. Traditionally in high income settings and as a subpopulation; people who inject drugs (PWIDs) are at highest risk of both HIV and HCV co-infection.\textsuperscript{233} However, this is not mainly due to sexual activity, but to the sharing of injecting equipment and thus direct blood-to-blood exposure. More recently, men who have sex with men (MSM); who have historically always been burdened greatly by the HIV epidemic;\textsuperscript{20,21} are now facing a high prevalence of HCV co-infection.\textsuperscript{225} MSM’s history of a greater burden of HIV holds true especially in high income settings. For example despite accounting for only approximately 1% of the UK population,\textsuperscript{144} MSM harbour just under half of all UK HIV infections.\textsuperscript{238} More recently however, a HCV epidemic has also emerged in this population, concentrated amongst HIV positive individuals. This, although not as high as rates of co-infection in PWIDs, is of significant concern and estimated to be around 10% in the UK.\textsuperscript{179} Largely MSM without HIV infection remain with HCV prevalence akin to background levels at 1%,\textsuperscript{232} yet amongst MSM who use PrEP higher prevalences of HCV have been observed. Prevalence of HCV being 4.8% amongst a cohort of PrEP users in Amsterdam\textsuperscript{125} and observations of incidence increasing more than 10-fold between 2014 and 2017 in Prep users in a French study.\textsuperscript{242} This pattern is found both within the UK and globally in high income settings.\textsuperscript{225}

Although many reasons have been put forward for the emergence of HCV infection in the MSM population,\textsuperscript{63,310} the exact contribution of and interaction between these behaviours and biological
factors remain largely unknown. The large skew between HCV infection in those with and without HIV infection has also not fully been explored. The current landscape of HIV prevention in MSM is also evolving rapidly with the introduction of pre-exposure prophylaxis (PrEP), a pre-emptive medication used to prevent the acquisition of HIV. Further to this, treatments for HCV have also advanced dramatically in recent years with the introduction of DAAs which have large success rates, yet are incredibly expensive. With the introduction of these new elements, there is likely to be shifts in attitudes towards safe-sex and sexual behaviours, which will be important to understand from a disease-spread perspective. Paired with the introduction of DAAs, effectively targeting treatment and screening for HCV are key challenges.

This work aims to further clarify the level of contribution from the multitude of biological and behavioural factors linking the HIV and HCV co-epidemic found in the MSM community, in order to understand the main drivers of the skewed epidemic pattern. Using these findings we then aim to predict the impact that PrEP could have on both these behaviours and biological vulnerabilities and thus on the HIV and HCV co-epidemic. Furthermore, both the World Health Organisation (WHO) and the UK national health service (NHS) aim to reduce HCV incidence by 90% by 2030 and 2025 respectively in high risk populations, which includes MSM. On this basis, we also aim to inform the levels of screening scale-up needed in UK MSM paired with using new highly effective HCV antiviral drugs to reach HCV elimination targets. Once we establish these strategies, we then finally aim to use an additional cost-effectiveness analysis to project the required resource needed to reach these targets, to discover a cost-effective way to reach the elimination targets.

What our work does not do, is aim to fully recreate the historical trends of the HIV and HCV epidemics. We instead make use of current epidemic trajectories, using these as a basis for examining epidemic patterns and planning intervention strategies. We approach our aims with a combination of detailed parametrization and deterministic epidemiological modelling. This approach allows us insight into the impact of individual parameter assumptions as well as rate of infection spread and epidemic size. Further to this, modelling provides opportunity for forecasting of intervention impacts and/or implications of changing behaviours within our target population.

Chapter 2 begins this thesis with a background and overview of the natural history of HIV and HCV and the complexities involved with co-infection. This is subsequently supplemented with an overview of the specific sexual behaviours of MSM, and a history of the HCV epidemic in this group, while describing in detail the placement in the existing literature into which the work in this thesis adds
value. Chapter 2 ends with the introduction to mathematical modelling concepts which are key to the methodology and analysis of the results based chapters 3, 4 and 5.

Within chapter 3 we examine a range of known and theorised contributors to the HIV and HCV co-epidemic pattern within MSM. We aim to expose the main behavioural and biological factors which drive the high prevalence of HCV in HIV diagnosed MSM, while examining the sensitivity of the epidemic to fluctuations or changes in key parameters. Chapter 3 finishes with a brief exploration of the benefits of treatment as prevention (TasP) amongst HIV diagnosed MSM with HCV DAAs given varying patterns of HCV spread over the entire MSM population.

In chapter 4 we build on our work, and the model which we used in chapter 3. Specifically, we introduce PrEP into the model, along with associated risk compensatory behaviours, such as reduced condom use driven by confidence in PrEP to provide sufficient protection from forward transmission of HIV infection. We briefly explore the expected impact of PrEP on HIV, while looking more in depth at its impact on the pattern of HCV. Under this setting, we examine the feasibility of the HCV elimination targets under interventions which span over the entire MSM population.

Within chapter 5 we consider the cost-effectiveness of our interventions which we proposed in chapter 4. We explore both the individual efficiency of each screening strategy over sub-populations as well as the overall cost-effectiveness of the strategies needed to reach the WHO and NHS HCV elimination targets.

Chapter 6 forms our discussion of these results and gives our recommendations for reaching the HCV elimination targets within MSM. We explore avenues for future work which would either improve our understanding of the HIV and HCV co-epidemic in MSM, or facilitate easier and more accurate modelling, while analysing the main strengths and weaknesses of the work done in this thesis.

This thesis’s original contribution to knowledge is firstly providing evidence that behavioural factors, especially preferential mixing of MSM by HIV status and risk heterogeneity are mainly driving the HCV epidemic patterns, rather than biological complications of the two pathogens. Secondly we find that in the era of PrEP, without risk compensation, we expect HCV prevalence to remain fairly steady, but will be concentrated within PrEP users, as well as remaining high in those with HIV. We also find that it is possible to reach both the WHO and NHS HCV elimination targets, but that this will require higher
levels of screening amongst all MSM, yet at rates that are lower than or consistent with current UK sexual health check-ups in MSM, leading us to conclude that the HCV elimination targets are indeed feasible. In the case of risk compensation however, HCV prevalence can increase over all sub-populations of MSM, with PrEP users and HIV positive MSM affected the most. Risk compensation however does not have an affect so great that it can prevent the HCV elimination targets from being reached with adequate screening. Thirdly, our proposed screening strategies are found to be cost effective by a time horizon as close as 2030, and can be cost-saving by 2050.

The work in chapter 3 was produced in collaboration with Peter Vickerman, Natasha Martin, Matthew Hickman, Chris Muldivari, Ford Hickson and Peter Weatherburn and is published in the Journal of Infectious Diseases. The work in chapter 4 was produced in collaboration with Peter Vickerman, Monica Desai, Natasha Martin, Jane Nicholls, Matthew Hickman, Ford Hickson and Peter Weatherburn and currently under review by the Lancet’s open access journal EClinicalMedicine. The work in chapter 5 was produced in collaboration with Peter Vickerman, Zoe Ward, Monica Desai, Natasha Martin, Jane Nicholls, Matthew Hickman, Ford Hickson and Peter Weatherburn. My contribution to each chapter was inclusive of the design of the studies, the statistical analyses, model development, simulations and analyses along with input and guidance from co-authors. Within chapter 5, we utilised previous parametrisation of the costs and QALYs associated with HCV screening, treatment and care constructed by Dr. Zoe Ward and developed from her cost-effectiveness paper concerning PWID HCV interventions in Scotland, adapting them for use within my thesis.
Chapter 2  - Background and literature review

2.1 Introduction

This thesis firstly builds on our understanding of the epidemiological patterns of HCV and HIV within the MSM population in high income settings, with a focus on the UK. Secondly, using this understanding, we assess the requirements and cost-effectiveness of reaching current HCV elimination targets for MSM in the UK. Set by the World Health Organisation (WHO) and NHS-England, these targets aim to ambitiously reduce HCV incidence by 90% overall by 2030 and 2025, respectively. Throughout our work, we use mathematical modelling to gain insight into how complexities in the sexual behaviours among MSM could affect the benefits of scaling up HCV treatment. This research, by necessity, also considers the potential effect that pre-exposure prophylaxis (PrEP) for pre-emptive prevention of HIV transmission may also effect the impact of HCV treatment.

This chapter reviews crucial aspects of the literature that feed into this PhD thesis. The chapter divides the current literature into seven main sections: the first three explore the natural history of HIV, HCV, and the interactions between HIV and HCV during co-infection. The fourth section explores sexual behaviours specific to MSM; with the fifth exploring how these behaviours have shaped the current MSM HCV epidemic. The sixth section explores the range of prevention and treatment interventions that are commonly used to control the HIV and HCV epidemics among MSM, while the final section briefly explores the application of mathematical modelling in epidemiology contexts, focusing on the models implored in this work.
2.2 Human Immunodeficiency Virus (HIV)

2.2.1 Introduction

HIV is a retrovirus in the genus Lentivirus of the family Retroviridae. HIV infection targets a range of cells within the immune system, most notably and importantly causing the number of CD4 T lymphocyte cells (CD4 cells) to decline as HIV both attacks these cells and causes them to be overactive, leading to increased CD4 cell death. The immune system is gradually weakened, eventually leading to acquired immunodeficiency syndrome (AIDS), at which point immune system deterioration creates an environment for opportunistic infections and ultimately leads to death. Untreated, the survival period for HIV is, on average, between 9 to 11 years from initial HIV infection, but this largely depends on HIV subtype.

HIV exists with two main genotypes, HIV-1 and HIV-2, although there are a multitude of genetic subtypes within each main genotype due to the virus' rapid mutation rate. HIV-1 is highly infective in comparison to HIV-2 and is estimated to comprise >95% of all HIV infections globally. For example, the chance of transmission from breastfeeding for HIV-2 infected mothers is under 4% compared to over 24% for HIV-1 infected mothers. Geographically, HIV-2 is also largely contained to West Africa, which is attributed to its lower transmission rates.

HIV is transmitted as a single-stranded, enveloped RNA virus, with infection occurring by exchange of bodily fluids including: blood; semen; vaginal fluid; pre-ejaculate; or breast milk. The most common routes of HIV infection are sexual transmission as well as vertical transmission from mother to child.

Since the origin of the HIV epidemic, WHO statistics indicate that there have been over 70 million HIV infections and about 35 million individuals have died due to HIV related causes. This significant toll is due to widespread HIV infection around the world, mainly because of a long asymptomatic incubation period enabling HIV to be unknowingly transmitted to others before being detected, and its high mortality rate if untreated. The development of antiretroviral therapy (ART) was a significant milestone, both dramatically increasing the life expectancy of those infected with HIV, and in reducing ongoing HIV transmission. Indeed, a world-wide scale-up has resulted in annual AIDS related deaths halving over the period 2005-2016. ART acts to reduce HIV viral load and increase CD4 count, vastly increasing life expectancy and reducing HIV infectivity. However, despite ART scale-up, 36.7 million [30.8–42.9 million] individuals were still HIV positive at the close of 2016. This is estimated at 0.8% [0.7-0.9%] of all adults aged between 15 and 49 worldwide. This is however partly...
due to the success of ART in improving the life expectancy of HIV positive individuals. The majority of all HIV infections reside in sub-Saharan Africa, which despite accounting for only 12% of the global population, is burdened with 71% of all global HIV infections.\textsuperscript{94,140} In high income settings the prevalence of HIV tends to be lower than in resource constrained countries,\textsuperscript{94} partly due to increased access to healthcare information. The UK is reflective of this trend with an overall HIV prevalence of 0.16%.\textsuperscript{238}

2.2.2 Natural History

Pre-AIDS HIV infection has four distinct phases.\textsuperscript{194} Once infected, individuals experience primary or acute infection, which is characterised by mild symptoms in 25-65% of cases, while more severe symptoms much more rarely.\textsuperscript{194} During this initial period of infection, which lasts for approximately 3 months,\textsuperscript{121} HIV has a high replication rate, with viral loads at a relative high compared to those experienced during the subsequent phase of infection, resulting in acutely infected individuals being highly infectious;\textsuperscript{194} with a longitudinal study in Uganda estimating that they are 26 times more HIV infectious than in the following asymptomatic phase.\textsuperscript{121} CD4 cell counts also decrease by 80-90%, compared to the usual CD4 count of 400-1600 cells per mm\textsuperscript{3} range found in healthy HIV negative individuals.\textsuperscript{194} Following acute infection, HIV progresses to an asymptomatic phase where the immune system fights back.\textsuperscript{194} The asymptomatic phase can last for up to 10 years and during this period CD4 cell counts are found to be within normal ranges, yet lower than the individual’s pre-HIV infection count.\textsuperscript{194}

The third stage is characterised by persistent generalised lymphadenopathy; swelling of the lymph glands for three or more months, in two or more sites on the body (excluding the groin) which are attributed to HIV infection.\textsuperscript{194} The final phase before the progression to AIDS is symptomatic HIV. In this pre-AIDS stage symptoms include skin and mouth health issues and haematological disorders.\textsuperscript{194} These result in a decrease in immune competence occurring due to increased replication of HIV in previously latent sites and falling CD4 cell counts.\textsuperscript{61,194} In late stage HIV progression, we therefore also observe a rise in infectivity due to increased viral load, where individuals are calculated to be approximately 7 times more infectious than during the asymptomatic phase.\textsuperscript{121}

The progression to AIDS is ultimately declared when CD4 cell count falls below 200 cells per mm\textsuperscript{3}, or alternatively, development of diseases and/or cancers associated with HIV infection: referred to as opportunistic infections.\textsuperscript{194} Once progressing to AIDS, life expectancy is only 1 or 2 years.\textsuperscript{116,161}
2.2.3 Transmission of HIV

Sexual transmission

Sexual transmission is the most common route of all new HIV infections,\(^{304}\) despite the probability of sexual transmission routes being lower (with the exception of anal intercourse)\(^{219,255}\) than through other major routes such as vertical transmission and injecting drug use. Heterosexual vaginal intercourse has an estimated rate of HIV transmission of 0.08\% per act,\(^{27}\) whereas anal intercourse is much higher, with receptive partners having the greatest risk, estimated at 1.4\% per act.\(^{11}\) This puts subgroups such as MSM, who more frequently have anal intercourse, at higher risk of sexual HIV transmission.\(^{11}\)

This is reflected by the pattern of HIV infections which are universally higher in the male homosexuals than in heterosexuals,\(^{20}\) with 12\% of all new HIV infections attributable to MSM globally.\(^{305}\) In a high income country such as the UK, with progressive LGBT+ rights and legislation allowing MSM to not be culturally or behaviourally suppressed,\(^{20}\) data from 2016 estimated that just under 50\% of new HIV infections were within the MSM community.\(^{78}\)

As with all routes of HIV transmission, the probability of becoming infected through sexual transmission is reduced by consistent ART treatment use\(^{56,96}\) of the HIV infected sexual partner, with evidence suggesting that no transmission occurs if the HIV infected sexual partner has an undetectable HIV viral load.\(^{252}\) However, if detectable, then the probability of sexual transmission is also complicated by a range of individual-based factors: being higher in individuals with common STIs,\(^{91}\) such as herpes-simplex virus\(^ {90,162}\) and syphilis\(^ {247}\) or history of genital ulcer disease;\(^ {27}\) or for individuals who participate in higher risk sexual practices. We will describe in detail the exact risks associated with these factors later in section 2.5.

Vertical transmission

Vertical transmission (from mother to child) is the second largest contributor to HIV transmission. In the absence of ART and other interventions, there is a 15-45\% chance that HIV will be passed on from a HIV positive women to their children during pregnancy.\(^ {149,335}\) After the birth of a child, breastfeeding poses further risk, with transmission rates of 8.9 per 100 person-years.\(^ {32}\) Use of ART greatly reduces both of these risks, so that the risk of vertical transmission is less than 5\% over the entire period until the child is fully weened,\(^ {335}\) this has directly resulted in approximately 1.6 million averted HIV infections in children under 15 since ART use scaled up in 1995.\(^ {304}\)
ART however is not widely available in all countries (especially in lower income countries), meaning that vertical HIV transmission still represents a significant route of transmission,\textsuperscript{305} with the overall global vertical transmission rates still meaning one in ten of all new HIV infections occurs in children under 15.\textsuperscript{305}

**Medical procedures**

Blood transfusions involving HIV infected blood have over 90% chance of HIV transmission.\textsuperscript{10} However, within high income countries, blood is routinely screened, mitigating this risk factor of HIV transmission almost entirely. Indeed, current tests for HIV anti-bodies and nucleic acid testing (NAT), reduce transmission risk to approximately 1 per 1.5 million units of blood transfused.\textsuperscript{102}

Further to this, contaminated medical injections and needle stick injuries carry a risk of HIV infection of around 0.25-0.32\% per incident.\textsuperscript{10,15} However due to diligent protocols around medical supply manufacture and disposal, these risk are minimized in most high income settings with incidents being rare.\textsuperscript{15}

**Injecting drug use**

Injection of drugs using unsterilized equipment (which is frequently shared between injectors) is also a major transmission route for HIV infection, with approximately an 0.8\% chance of HIV transmission per act.\textsuperscript{70} As such, globally 19\% of people who inject drugs (PWID) are infected with HIV,\textsuperscript{70} accounting for approximately 10\% of all new HIV infections.\textsuperscript{70}

The population of PWID can prove challenging to treat for HIV as drug use is often criminalised and/or stigmatised.\textsuperscript{304} Within MSM populations, there is cross-over between drug use and sexual transmission of HIV, with practices such as ‘slamming’, where recreational drugs such as crystal meth, methedrone and gamma-hydroxybutyrate acid (GHB) are injected to enhance sexual experiences, and where the combination of injecting and sexual transmission can elevate risk levels further\textsuperscript{63,100} which we explore more fully in section 2.6.3.
2.2.4 Treatment of HIV

HIV currently has no known cure so the emphasis of treatment is on managing the condition. Antiretroviral therapy (ART), which commonly consists of a combination of multiple antiretroviral drugs aims to control and subdue HIV infection whilst avoiding resistant mutations of HIV arising, so that HIV becomes a chronic condition which may never progress to AIDS in the course of a normal lifetime. ART is recommended to anyone who is HIV positive to reduce the impact of the infection and slow progression of the virus, plus to help prevent further HIV transmissions, achieved primarily by reducing HIV viral loads. In the acute phase (which lasts from 1.7-6 months after HIV infection) HIV viral loads are often higher and symptoms are more likely than the following latent period. Studies have shown that being treated during this phase may have better results in terms of reducing likelihood of progression to AIDS and suffering from HIV related illnesses.

2.3 Hepatitis C Virus (HCV)

2.3.1 Introduction

HCV is a single stranded RNA virus in the genus Hepacavirus within the family Flaviviridae. HCV targets and damages liver cells, over time causing cirrhosis and liver cancer. Worldwide, HCV causes around a quarter of all cases of cirrhosis cases and hepatocellular carcinoma. In 2015 WHO estimates indicated that viral hepatitis caused 1.3 million deaths, even more than HIV, which led to 1.1 million. There are 6 genotypes of HCV, but as with HIV, HCV has a high mutation rate, resulting in each genotype having many subclasses. Overall, the most common is genotype 1, comprising 46% of all cases globally, however different regions of the world have localised clustering which makes given strains more prevalent region by region. For instance, genotype 4 accounts for 97.6% of the HCV infections in Central sub-Saharan Africa. Interestingly, HCV also clusters within human networks as well as by geographical region. For example, genotypes 1 and 3 are the most common in the UK, with data from 2015 indicating that these genotypes accounted for 47% and 41% of all countrywide infections respectively, however within MSM in the UK, infections are more commonly the historically hard to treat genotypes 1 and 4.

Global HCV prevalence is currently estimated to be 3%, although this again varies significantly from country to country, with higher prevalence of HCV generally being associated with lower income within a country. The greatest prevalence, at 10% of the population, is in Egypt. In the UK, chronic HCV prevalence is estimated at 0.33%.
2.3.2 Natural History

HCV has four main stages of infection: the first stage being acute HCV, which by clinical definition lasts for a maximum of six months.\textsuperscript{290} Individuals at this stage of infection are often undiagnosed due to this stage’s widely asymptomatic nature; with symptoms occurring in only 20%-30% of those infected.\textsuperscript{187} For this minority, symptoms usually present between 3 weeks to 3 months after infection and can include malaise, anorexia, weakness, jaundice, a loss of appetite, fatigue, nausea, muscle or joint pains, and weight loss,\textsuperscript{326} however progression to liver failure at this stage is extremely rare.\textsuperscript{85} At 2-8 weeks after infection, the levels of alanine aminotransferase (ALT) which is an enzyme associated with liver cirrhosis, are one order of magnitude higher than found in a healthy individual\textsuperscript{287}. The concentrations of HCV RNA increase steeply in the initial few weeks following infection, at which point the HCV RNA becomes detectable, with HCV RNA levels reaching their maximum just before the peak of ALT levels and the subsequent development of symptoms.\textsuperscript{86} In around 20-30% of acute HCV cases, individuals are able to clear the disease before it can reach the next, chronic stage of HCV infection. This is known as “spontaneous clearance”.\textsuperscript{206} A recent meta-analysis calculates that spontaneous clearance rates were 19.8% (95% CI: 2.6-47.5%), 27.9% (95% CI: 17.2-41.8%), 36.1% (95% CI: 23.5-50.9%), and 37.1% (95% CI: 23.7-52.8%) within 3, 6, 12, and 24 months of HCV infection respectively.\textsuperscript{4} Chances of spontaneous clearance however largely vary,\textsuperscript{123,193} depending on factors such age, gender, ethnicity and genotype of HCV.\textsuperscript{41}

The remaining 70-80% who do not spontaneously clear their infection progress to the second stage; chronic HCV infection,\textsuperscript{193,206} defined as detectable viral replication for over six months. Chronic HCV is largely asymptomatic, although one common symptom is fatigue. Individuals generally remain in the second stage of chronic asymptomatic infection for decades post initial infection. Estimates indicate between 15-20% of chronically infected patients will suffer from liver cirrhosis after 20 years since initial infection,\textsuperscript{285} although the time over which liver fibrosis develops is influenced by factors including levels of alcohol consumption, age at infection, gender and HIV co-infection.\textsuperscript{89,285}

This marks progression to the third stage of HCV, defined as cirrhosis of the liver or liver cancer.\textsuperscript{254} Liver cirrhosis causes high blood pressure in the portal vein system, excess fluid in the abdomen, easier bruising and bleeding, varices, jaundice, cognitive impairment and ascites.\textsuperscript{213,347} At this stage of disease progression, there is also a 1-7% annual risk of developing hepatocellular carcinoma and a 2-6% annual risk of developing hepatic decompensation.\textsuperscript{290,325} Finally end-stage HCV occurs when the liver is severely damaged and can no longer fully perform its function, leading to grave health consequences, including liver failure, end-stage liver cancer, and eventually the need for a liver transplant or death.\textsuperscript{254}
2.3.3 Transmission of HCV

Vertical transmission

Vertical transmission comprises one of the primary routes of HCV infection,\textsuperscript{16,28} with an average of 5.8% probability of transmission from HIV negative women to their children,\textsuperscript{17} but with HCV viral load playing a large role in determining the risk.\textsuperscript{294} Indeed higher viral loads are commonly found in women who transmitted the virus\textsuperscript{181,276} and there is strong evidence that RNA-negative mothers have very little chance of transmitting their infection.\textsuperscript{17,230} Once children are born however, future risk of transmission is minimised, as there is no evidence that breast milk is able to transmit HCV.\textsuperscript{58}

Medical procedures

HCV when present in blood used for a transfusion has a very high rate of infection,\textsuperscript{231} with 75% of patients testing positive for HCV 15 years after receiving transfused blood containing HCV.\textsuperscript{231} However, in many high income countries, the introduction of effective screening practices has seen the chances of HCV transmission related to blood transfusions decrease substantially,\textsuperscript{50} so that this is no longer a main route of transmission in high income settings.\textsuperscript{77,292} A US study has found that the risk of transmission is only around 1 per 2 million units of blood transfused.\textsuperscript{73}

This is supplemented in high income countries by reductions in HCV transmission due to contaminated needles and medical equipment, which is uncommon due to the careful treatment and disposal of medical equipment.\textsuperscript{15} Although needle-stick injuries when they do occur have a non-negligible rate of transmission per occurrence of 1.3-3%.\textsuperscript{48}

Injecting drug use

PWID are the single highest contributing group to new HCV infections in high income settings.\textsuperscript{264} For example, within the UK and Australia greater than 90% of new infections are attributable to PWID,\textsuperscript{67,244} while a recent modelling study estimates that 43% of all new HCV infections could be prevented between 2018-2030 if the heightened HCV risk associated with injection drug use was removed.\textsuperscript{296}

This group is put at such high risk of HCV through the sharing of needles and syringes,\textsuperscript{215,228} and other injecting equipment.\textsuperscript{228} HCV is extremely infectious when people are exposed to sharing injecting equipment, with HCV being around 10 times more transmissible than HIV through the same means.\textsuperscript{10,299,316} This is partially attributable to the fact that HCV can survive for long durations in syringes\textsuperscript{2,214} and survive high temperatures,\textsuperscript{52,76} so that HCV may still be transmittable after drug preparation\textsuperscript{114} and still present on syringes between uses.
Sexual transmission

Although HCV can be transmitted as a result of sexual intercourse, the exact routes of transmission are not akin to common STIs, due to HCV being a blood-borne virus, and thus requiring direct blood to blood contact. It is therefore likely to be necessary that sexual transmission occurs through traumatic sexual practice which is resultant in blood exchange, rather than sexual intercourse itself. For this reason, HCV transmission through sexual contact is largely inefficient amongst heterosexual couples. One study that distinguished between transmissions through heterosexual HCV serodiscordant partners and transmissions from other individuals (using phylogenetic analysis), found that of the 4% of individuals who became infected with HCV, only 0.6% of these infections could be attributed to transmission from their serodiscordant partners; of which only a proportion would be due to sexual activity. In the presence of co-infections and amongst MSM, however, sexual HCV transmission can be substantially more likely. Indeed, sexual transmission is efficient enough in MSM to lead to an HCV epidemic in this group and indeed motivating the work in this thesis. HCV incidence amongst HIV positive MSM is calculated as just over 4 times greater than in HIV negative MSM (in which HCV incidence is similar to back-ground population levels), with incidences of 6.08 and 1.48 per 1000py, respectively. Further details on the mechanisms behind this epidemic and the specifics behind sexual transmission of HCV between MSM specifically will be covered in section 2.6.

2.3.4 Treatment of HCV

There are two main tests that establish the presence of hepatitis C. The antibody test establishes whether you have ever been exposed to the hepatitis C virus and a polymerase chain reaction (PCR test), which establishes whether the virus is still active through detection of HCV RNA. The two tests require a blood sample, with the HCV antibody test normally completed first, detecting the presence of antibodies to the virus generated by the immune system. Unfortunately, it usually takes between six and twelve weeks after HCV infection for these antibodies to develop, and on rare occasions it can take up to six months. Upon positive results for an antibody test, it is possible that there has been clearance of a previous HCV infection. Therefore, if an antibody test is positive, the PCR test, also known as an RNA test, will check if the virus is still present. Test results for the RNA test are generally reported as either “undetectable” or “detectable”. Results which detect HCV RNA are often accompanied by a measure of viral load. It is usually not possible to tell from these tests however if the individual’s HCV infection
is in the acute or chronic stage. In fact generally, there is not a universally used criteria for categorising an acute versus chronic HCV infection at the point of testing.

If an individual is currently HCV infected, as confirmed by a positive RNA test, then the next step is often treatment. Treatment aims for a sustained virological response (SVR), defined as “a patient having an undetectable HCV viral load 6 months after finishing their course of treatment.”

Over the last five years, the treatment landscape for HCV has changed significantly. Older treatments usually comprised of a combination of pegylated interferon alpha and ribavirin, which could be over a course of 24 or 48 weeks, dependent on the specific genotype of the infected person. This approach produces an SVR in 70-80% of patients for genotype 2 and 3, and 45-70% for the other genotypes, with treatment during the acute phase with these medications often being more likely to produce a SVR than the chronic phase. Side effects to these older treatments are common and include suffering from flu like symptoms or emotional issues, which for many meant that treatment courses were not completed.

Notably, since 2013 a stream of other new drugs came on to the market. These drugs have much higher efficacy, less side effects and lower treatment durations, including among HIV positive patients, who had lower efficacy of treatment with the older treatments. They are also an effective choice for those who had failed previous treatment plans. Sofosbuvir, which was one of the first new DAAs is estimated to have an efficacy of 90% when used to treat genotype 1, 4, 5, or 6 disease and requires only a 12 week course when paired with Ledipasvir. Sofosbuvir, with only ribavirin is also estimated to be around 93% effective in genotypes 2 in a 12 week course and 85% in genotype 3 over a 24 week course, although less effective in those who already had liver cirrhosis. The leading treatments using Ledipasvir and Sofosbuvir, commonly referred to as Harvoni has an SVR of around 93-99%, although competitive combinations such as Sofosbuvir and Velpatasvir (commonly referred to as Epclusa) have similar success rates and are also popular choices. In 2016, driven partly by the success of these new DAAs, the World Health Organisation (WHO) set targets to eliminate viral hepatitis. These targets aim for an overall 90% reduction in HCV incidence by 2030.

Despite the high efficacies of these drugs, their market price remains very high at around £40,000 per 12-week treatment with Sovaldi, Harvoni or Epclusa. Although this is being driven down by recently emerging alternatives including Zepatier at £36,000 or a combination of Viekirax and Exviera at £34,000 per 12-week treatment duration. However generic versions of these drugs are also likely to
drive down price further. Sofosbuvir and Daclatasvir are currently being produced generically at a “good quality” at prices as low as $256 per patient per treatment, and set to fall further as manufacturing costs reduce.

2.4 HIV and Hepatitis C Co-infection

2.4.1 Introduction

HIV and HCV co-infection represents a major health burden. The main complication of co-infection occurs due to the acceleration of HCV based liver damage caused by HIV infection, which vastly increases overall mortality. What is more, these infections are commonly found in tandem both amongst PWID and increasingly among MSM, largely due to common transmission routes previously described. Within HIV infected individuals globally, the HIV-HCV co-infection prevalence is 2.4%. However, the co-infection prevalence is higher in HIV positive MSM, at 6.4%, and 82.4% among HIV infected PWIDs. Within high income settings, liver disease has developed to be one of the main contributors to mortality rates in HIV infected individuals, however treatment and prevention of both diseases is in a state of revolution, through increasing access to HCV DAAs and pre-exposure prophylaxis (PrEP), giving health care professionals the tools they need to tackle co-infection over the next few decades.

2.4.2 Changes to the natural course of HIV and HCV disease progression

A number of intra-host factors alter the way in which HCV and HIV progress or function under the circumstance of co-infection. Whilst infected with HIV, individuals have reduced chances of spontaneously clearing HCV, with a recent meta-analysis finding an odds ratio (OR) of 0.50 (95% CI: 0.37-0.67) compared with HIV uninfected individuals. However, another important factor significantly associated with HCV clearance is gender, with males having an OR of 0.68, (95% CI: 0.59-0.81) of spontaneous clearance compared with females. When combined within HIV positive MSM specifically, spontaneous clearance rates can be very low, occurring in only 13-15% of cases.

Under investigation of the mechanisms behind these lower spontaneous clearance rates, it was observed that there is a strong correlation between lower CD4 cell counts and higher HCV viral load, with higher HCV viral loads reducing the chance of clearing HCV spontaneously. Additionally, in patients with acute HCV, higher levels of HCV genomic diversity increased the probability of that individual progressing to a chronic HCV infection.
Most importantly though, individuals who are co-infected also show an accelerated course of liver cirrhosis and more rapid progression to complications such as hepatocellular carcinoma, ultimately leading to a higher probability of death. This faster progression can be reduced by initiation of ART; with those not on ART having a 2.5 factor increase in HCV progression, while among those on ART it is reduced to a 1.7 factor increase. HIV co-infection increases liver disease progression due to accelerated fibrosis which in turn is due to higher rates of HCV virus replication, compounded immune dysregulation, and irregularities in the liver’s self-repair mechanisms, which ART plays a role in slowing. It is not clear if HIV progression is affected by HCV infection other than increased mortality, although CD4 count can be decreased by HCV treatments temporarily, but they return to pre-treatment levels afterwards.

2.4.3 Changes to transmission

There is evidence to suggest that there are higher HCV viral loads found in those with HIV, leading to greater HCV infectivity in co-infected individuals, although there is currently no direct way to ascertain the relationship between higher viral loads of HCV and HCV transmission risk. However, it is clear that concentrations of HCV viral load are influenced significantly by aspects of HIV-status: one study found a median plasma viral load of 7.19 log10 IU/ml (international units per millimetre) in HIV positive individuals and 6.73 log10 UI/ml in HIV negative individuals (translating to 2.88 times more viral load). Although these findings pre-date indiscriminatory prescription of ART regardless of CD4 levels. Indeed a more recent study found that in HIV-positive MSM, treatment with ART reduced HCV viral load by 0.3 log10 UI/ml. While other studies found that HCV viral loads remained similar, or even increased compared to other HIV-positive individuals not on ART.

Furthermore, a study on needle-stick injuries and subsequent risk of HCV infections, stratified by HIV-status of the source, found a potential but uncertain increased HCV infectiousness of between 0.4-2.1 for needles with an HIV positive source. Other studies have also looked at the increased chance of vertical transmission between mother and child, with one study finding a 2.82 (1.78-4.45 95% CI) greater risk if the mother was HIV positive. A recent systematic review also found almost double the chance of vertical transmission within HIV positive women, with transmission rates of 5.8% in HIV negative women compared to 10.8% in HIV positive women, with data drawn largely from high income settings where ART would have been available to individuals with lower CD4 cell counts. There is also however very limited data suggesting that the chance of vertical transmission for HIV-positive women may decrease if they are on ART, highlighting a potentially protective effect of ART on HCV
transmission. Although these results concern non-sexual transmission routes, they are likely to indicate increased HCV transmission in this scenario, although this assumption must be applied with due caution.

A further justification for HIV positive males having increased HCV infectiousness is that males co-infected with HIV and HCV have been found to be more likely to have small amounts of HCV in their semen. One study found this to be 37.8% of those with HIV versus 18.4% of those without. The presence of HCV in seminal fluid could facilitate per mucosal transmission of HCV, especially during unprotected anal intercourse. Interestingly, one study found HCV shedding into semen in HIV-positive MSM, with higher HCV viral loads present in semen significantly correlated with higher HCV viral loads in the blood and with more recent HCV infection. Furthermore, HCV viral shedding was also observed in roughly half of rectal fluid samples from HIV-positive MSM, again with higher rectal fluid HCV viral loads being correlated to higher HCV viral loads in the blood. These may all be mechanisms by which positive HIV-status increases HCV infectiousness. It must be noted however that the very low viral loads found in semen and rectal fluids compared to blood may mean that HCV transmission through semen could be negligible.

2.4.4 Treatment and diagnosis for co-infection

Treatment of co-infected patients has changed quite significantly in recent years, as DAAs have proven extremely effective at treating HCV with upwards of 90% efficacy, regardless of HIV-status and specific genotype. This is compared to the old HCV drug regimens, which were significantly varied in their efficacy by HCV genotype and HIV co-infection. Furthermore, concerns about hepatotoxicity caused by the combination of ART and non-DAA based HCV drug regimes meant that HCV treatment for HIV or HCV would need to be delayed. HCV treatment regimens for all patients are now often equivalent regardless of HIV-status, although there are special considerations, such as potential drug-drug interactions. More historically there were concerns of overlapping hepatotoxicity, (especially among those with advanced cirrhosis or end-stage liver disease), although these concern have also recently been highly alleviated by the introduction of current DAAs which are much less taxing on the liver than previous HCV drug regimes. Despite these advances, remaining challenges exist in patients with high levels of cirrhosis and the small percentage of individuals who do not respond to treatment. Also, HIV positive MSM suffer from high HCV reinfection rates and above average relapse rates following treatment, which could be alleviated with more personalised treatment approaches in this group such as additional counselling.
As previously stated in 2.4.2, one other positive benefit of ART in those with co-infection is the reduction in the rate of HCV disease progression. However, rates are still higher than expected in mono-infected individuals.\textsuperscript{342,324} Thus, for most co-infected patients, ART remains beneficial despite concerns of the medication damaging the liver through potential excess hepatoxicity. Therefore ART is now widely initiated for most HIV/HCV co-infected patients, no matter what level their current CD4 count.\textsuperscript{38}

2.5 Sexual behaviours in Men who have Sex with Men

2.5.1 Introduction

MSM’s sexual landscape is vastly different to that of heterosexual couples, which impacts on epidemiology of STIs in this group.\textsuperscript{189} This includes a greater likelihood of anal sex,\textsuperscript{219} higher number of sexual partners,\textsuperscript{101} higher chances of risky sexual practices such as ano-brachial insertion (fisting),\textsuperscript{63} HIV-status related choices around sexual partners\textsuperscript{78,138} and more common use of recreational drugs to enhance sexual intercourse.\textsuperscript{63} It is important to have a deep understanding of these practises and specialised modelling approaches to encompass this complexity and accurately capture HIV and HCV patterns in this group.

2.5.2 Anal intercourse and fisting

One of the key drivers of blood-borne STIs in MSM is the increased propensity of anal sex. As previously discussed in section 2.2.3, anal intercourse has very high transmission rates for HIV,\textsuperscript{261} second only to injecting drug use, needle-stick injuries or blood transfusions,\textsuperscript{219} due to the fact that anal intercourse is much more likely to result in semen-blood and blood-blood contact than for vaginal intercourse.\textsuperscript{261}

Further to the increased propensity for anal intercourse, fisting (also known as ano-brachial insertion, where the hand is inserted into the anus) is more common amongst MSM\textsuperscript{63} than heterosexual couples. Fisting can lead to high levels of trauma to the rectum, which causes anal bleeding.\textsuperscript{54} This can lead to a significant level of blood-blood contact, especially where the insertive partner does not use a glove for protection.\textsuperscript{54} The chance of HIV acquisition in MSM who have participated in receptive fisting in last 12 months has an OR of 3.10 (95% CI 1.46-6.60),\textsuperscript{145} while HIV acquisition from participation in insertive fisting in the last 12 months has an OR of 1.58 (95% CI 0.85-2.95).\textsuperscript{145} Similarly, HCV acquisition
from participation in receptive fisting in last 12 months has an OR of 4.75 (2.14-10.57 95% CI),$^{63}$ while HCV acquisition from participation in insertive fisting in last 12 months has an OR of 5.53 (95% CI 2.59-11.81).$^{63}$

**2.5.3 Condom use**

Anal intercourse is more risky when condoms are also not used. Unprotected anal intercourse (UAI) is a significant contributor to the chances of both HIV and other STIs, including HCV infection.$^{219}$ However, due to both imperfect technique and a higher chance that anal intercourse can cause condom breakage compared with vaginal intercourse, the protection offered is lower than might be expected. One study finds that this protective chance is around 70% (95% CI, 60-80%) within MSM.$^{270}$ Encouragingly however, MSM tend to use condoms more consistently than heterosexual couples.$^{101}$ One study found that compared to consistent condom use, or UAI where both partners are known to be HIV negative, that insertive UAI had an OR of 1.22 (0.30-4.99 95% CI) for HCV infection and any (insertive or receptive) UAI had an OR of 7.65 (3.59-16.31 95% CI).$^{314}$

**2.5.4 Number of sexual partners**

Compounding the higher chance of blood-borne STIs per sexual act is the higher number of sexual partners had by MSM.$^{101}$ One study amongst young MSM, found that the overall number of sexual partners was a strong predictor for HIV infection:$^{308}$ using 1-4 sexual partners as a reference, 5-19 partners had an OR of 2.5 (1.7-3.7 95% CI) for acquiring HIV infection within their lifetime while 20 or more partners had an OR of 5.0 (3.4-7.3, 95% CI).$^{308}$ Another study highlighted that in the general MSM population, the number of sexual partners in the last six months could be used as an indicator for the risk of HIV acquisition:$^{314}$ with 0-1 partners as the reference, 2-3 partners had a hazard ratio (HR) of 1.58 (0.89-2.81 95% CI), 4 to 9 a HR of 2.84 (1.72-4.69 95% CI) and 10 or more a HR of 5.23 (3.26-8.40, 95% CI). These results are mirrored for the acquisition of HCV, one study finding that: with no casual partners as the reference; 1-9 partners had an OR of 2.39 (0.97-5.93 95% CI), 10-19 had an OR of 2.95 (1.13-7.70 95% CI), 20-49 partners had an OR of 7.62 (2.72-21.29 95% CI), and more than or equal to 50, had a HR of 6.00 (1.62-22.16 95% CI).$^{314}$
2.5.5 Recreational drug use

In general, MSM are found to be more likely to use recreational drugs than non-MSM. This has links to sexual risk taking, in the form of: reduced chance of condom use; and improper condom use; and more traumatic anal intercourse. One study cites increased HRs for HIV acquisition for use of the following substances in the last 6 months: marijuana 1.91, (1.49-2.45 95% CI), poppers 2.46 (1.92-3.45 95% CI), amphetamines 3.98 (3.05-5.18 95% CI), hallucinogens 2.06, (1.59-2.68 95% CI) and cocaine/crack 2.24 (1.72-2.93 95% CI), whereas the use of drugs or alcohol generally before sex yielded an HR of 2.54 (1.83-3.53 95% CI).

In addition to these risks, as previously mentioned in sections 2.2.3 and 2.3.3, there is heightened risk of HIV and HCV infection when undertaking the practice of injecting drugs. In MSM this can occur due to nonsexual motivation (as a subset of the general population of PWID will be MSM), or commonly in MSM this can be sexually motivated. This activity is coined “slamming”, which is used to describe “injecting drugs before or during sexual intercourse”, which some use to facilitate more enjoyable sexual intercourse. However, findings have shown the added risk of HIV acquisition from injecting drugs in last 12 months has an OR of 2.23 (1.49-3.33 95% CI), and similarly for HCV an OR of 2.05 (0.72-5.82).

2.5.6 Group sex

Individuals who participate in group sex, defined as “sexual behaviour involving more than two participants”, are likely to have a greater number of sexual partners than those who don’t, while there is also a reported decrease in condom use and increased exposure to drug taking behaviours or other high risk activities compared to binary partnerships. Indeed, a study found MSM who participated in group sex were more likely to also participate in other high risk activities including: receptive and insertive UAI and receptive and insertive relative to the study controls. The results concluded that the ORs for HCV infection associated with performing at least two or at least three of these sexual practices whilst participating in group sex were 9.16 (3.51–23.90 95% CI) and 23.50 (9.47–58.33 95% CI), respectively compared to those who hadn’t. Another study found that participation in sexual intercourse with 2 partners simultaneously had an increased HCV acquisition rate OR of 1.74 (0.69-4.40 95% CI), while if they had three of more partners simultaneously then they had an increased HCV acquisition rate OR of 4.39 (2.34-8.26 95% CI).
2.5.7 Serosorting behaviours

Serosorting is the practice in which “MSM modify their sexual behaviours due to their own perceived HIV-status, and/or that of their partners.” The rational for doing so include reducing the risk of acquiring HIV, or to protect sexual partners from exposure to HIV, or conversely if both partners are HIV positive, using less protection in order to have more enjoyable sexual experiences. Although serosorting is a broad category of behaviours, three main behaviours dominate:

(1) One such behaviour is to use condoms only when engaging in sexual activity with an assumed serodiscordant partner and forgo them with an assumed seroconcordant partner. Within HIV negative MSM, one study found this practice had been adopted at some time by 45.1% of individuals, while in HIV positive MSM this practice had been adopted by 55.1% of individuals. Another study reported that 36.5% of MSM answered “yes” to “will only have anal sex without a condom, with a man who has the same HIV-status as we do”. A further study found that 29% of HIV negative and 27% of HIV positive individuals only used a condom if they believed their partner was serodiscordant. A systematic review looking at HIV acquisition discovered that serosorting based around forgoing condoms led to 79% increased HIV transmission relative to consistent condom use. Conversely, relative with no condom use, condom based serosorting lowered the chances of HIV transmission by 53%. Another US based trial equally found that condom based serosorting could lead to a modest reduction in HIV transmission with an OR of 0.88 (0.81–0.95 95% CI) compared to the alternative of no preventative strategy.

(2) Another common serosorting practice extends to abstaining from sex with partners who are perceived or known to be HIV serodiscordant. A study found that within HIV negative and positive MSM this practice has been used by 12.6% and 37.2% of individuals respectively, with another study finding this proportion to be 24.7% and 19.5%.

(3) The last main serosorting behaviour is seropositioning or “strategic positioning” where the HIV positive partner in a serodiscordant relationship preferentially chooses to be the receptive partner during unprotected anal intercourse (UAI). This is due to the much lower chance of HIV transmission for the insertive partner compared with the receptive partner.

In an analysis covering a range of MSM studies, between a quarter and three quarters of respondents confirmed use of at least one of the three described seroadaptive strategies, with between quarter and a half saying reporting that they “only had condomless anal sex with MSM of the same HIV-status” and up to a third reporting that they had utilised strategic positioning.
Although serosorting has been shown in some cases to be more effective than no HIV prevention strategy, it is consistently shown to be inferior to consistent condom use.\textsuperscript{138} The main complication and limitation to the effectiveness of serosorting is the assumption concerning an individual’s own HIV-status, and that of their partner’s.\textsuperscript{42,138,327} Assumptions may be incorrect due to a multitude of factors. For instance, commonly the disclosure of HIV-status may not have occurred, plus many HIV infections go undiagnosed for long periods of time. For example, approximately 25% of HIV infections in the UK amongst MSM are undiagnosed.\textsuperscript{200} A meta-analysis of serosorting studies found that for serosorting to be an effective stratagem, it is necessary for “quality-assured HIV testing, high frequency of repeat HIV testing, and the existence of legal and social environments supportive of HIV testing and serostatus disclosure” such as is found in high income settings world.\textsuperscript{138}

Overall, serosorting leads to more like-with-like mixing between seroconcordant MSM, and higher risk sex between them. Due to this, serosorting is thought to play a role in the pattern of spread of other STIs.\textsuperscript{297} Indeed, one study found that compared with consistent condom use, serosorting resulted in an OR of 1.6 (1.44–1.83 95% CI) of acquiring gonorrhoea, syphilis or chlamydia,\textsuperscript{103} but the impact on HCV is largely unknown and is something we address in subsequent work in this thesis.

Serosorting also plays an important role in increasing the opportunity of an individual acquiring multiple strains of HIV, which is also known as HIV superinfection.\textsuperscript{227} Subsequently, leading to increased viral loads, greater rates of drug resistance, and could ultimately lead to the failure of treatment.\textsuperscript{227,267}
2.6 The HCV epidemic in MSM

2.6.1 Introduction

The HCV epidemic amongst MSM is a relatively recent phenomenon, with estimates indicating that it began in the mid 1990’s, unfolding in high income settings, primarily in HIV positive MSM. This skew of infection towards HIV positive MSM is theorized as the consequence of both biological and behavioural heterogeneities in the MSM population, as discussed in section 2.5. This leads to “core groups” with significantly elevated risk, and thus greater HCV and HIV prevalence. Although there exists a wealth of research helping to pin-point the exact causes of the pattern of the HCV epidemic (which we explore in detail in this section), the exact contribution and importance of each factor still remains uncertain. In chapter 3 of this thesis, we aim to add to the discussion, and highlight the main drivers from those proposed throughout the literature found in our work. Recent global estimates indicate that MSM co-infected with HIV however have a higher prevalence of HCV at 8.3% (6.7-9.9%). Reflective of this, in the UK, most recent estimates of HCV prevalence amongst HIV positive MSM from 2011 indicate 9.9% were co-infected within the UK Collaborative HIV Cohort and 7.7% (4.2%-12.9%) were co-infected within a London based study.

2.6.2 Historical progression of the HCV epidemic

Since 2000, HCV infections have been noticed more commonly among HIV positive MSM. With rising prevalence and incidence sign-posted throughout Europe. UK incidence data from 2002-2006 found rising incidence amongst HIV positive MSM, but not within HIV negative MSM. Beyond the UK, similar patterns were also seen between 2001-2004 in France, while between 2000-2004 HIV positive MSM in the Switzerland (as part of the Swiss Cohort Study) were also found to have significantly raised incidence of HCV, which was linked to engaging in unsafe sexual practices, even without history of injecting drugs. A subsequent study from the Netherlands in the period 2007-2008 also found significant amounts of risk for HCV associated with HIV positive MSM when there was evidence of injecting drugs, fisting or use of the recreational substance GHB. One of the earliest studies which examined UK HCV patterns between 1999-2005 also indicated that rather than a genetic mutation to the HCV virus, sexual behaviours amongst MSM was to blame.
Critically, phylogenetic analysis indicated a high degree of HCV genetic clustering amongst HIV positive MSM with these risk factors, when compared to isolates taken from other MSM between 2000 and 2007. Using phylogenetic data from across Europe, the presence of an international HCV network among MSM was revealed. This network was discovered to also be sexual in nature, comprising of greater than 80% of common circulating strains belonging to HCV genotypes 1 and 4 (which notably were hard to treat before the era of DAAs). Another international study examining HCV DNA sequences from England, the Netherlands, France, Germany, and Australia supported the finding that an HCV transmission network had formed in HIV positive MSM, stating that “the shorter genetic distance of the HCV isolates suggested that sexually acquired virus circulating within the HIV positive population was of recent origin and had expanded rapidly.” Using molecular clock analysis this study dated the emergence of the epidemic to be around 1996, despite the delay in its detection until the early 2000s. One other supporting study used data from multiple cohorts from Europe to estimate both the incidence and timeline of the MSM HCV epidemic using data containing the dates of HIV seroconversions from the previous two decades, finding that the increases in HCV occurred in HIV positive MSM from the middle of the 1990s, with the main growth of the epidemic occurring from around 2002.

Despite the main body of early evidence coming from Europe, similar findings were reported shortly after from the USA in 2005, Taiwan in 2001, Hong Kong in 2009-2014 and Australia, indicating a global epidemic in high income countries. Interestingly, simultaneous to the start of this HCV epidemic, was the introduction of widespread ART (also introduced in the mid-1990s). In this period, risk behaviours increased, and those with HIV infection had largely extended lifespans due to the high efficacy of these new HIV treatments. It is therefore plausible that ART had a significant role in triggering the widespread HCV epidemic we now experience in HIV positive MSM.

A recent global review spanning across 38 high income countries and compiling estimates between 2000-2015 found overall HCV prevalence to be 8.3% (95% CI: 6.7-9.9) in HIV positive MSM and 1.5% (95% CI 0.8-2.1) in HIV negative MSM. However, reporting of HCV prevalence estimates was more frequently documented in HIV positive MSM. Within the UK, one of the most recent estimates of HCV prevalence from the 2011 UK Collaborative HIV Cohort found 9.9% of HIV positive MSM were co-infected with HCV, while another 2012 London based study found 7.7% (4.2%-12.9% 95% CI) of HIV-positive MSM were co-infected. The London study also estimates the HCV prevalence among HIV negative MSM to be 1.15% (95% CI 0.58%-2.06%). Comparatively, recent estimates show approximately 5.9% of MSM are HIV-positive in the UK overall, hence approximately 0.25%-0.75% of all UK MSM suffer from HIV-HCV co-infection.
One other important feature of the emergent high risk European sexual network\textsuperscript{309} and of high risk sexual networks generally, is that they are able to form a foundation for sexual transmission, where sexual contact has not historically been a viable route of transmission,\textsuperscript{174} which may explain the previous lack of observations of sexually driven HCV epidemics. The identification and investigation of this network however, has allowed an understanding of how HCV has managed to out-break over such a large number of locations whilst become de-localized geographically.\textsuperscript{174}

\subsection*{2.6.3 The contribution of recreational drug use and the formulation of chemsex}

One main contributor to the high risk behaviours needed to create the MSM HCV epidemic is postulated to be sex involving recreational drug use, or as it has been coined, “chemsex.”\textsuperscript{63} As previously described in section 2.5.5, MSM have a propensity to use drugs recreationally around sexual intercourse. Administration of substances can be through injection, snorting or oral use, with each method carrying associated risks.\textsuperscript{314} In regard to specifically injecting drugs, one study found that HCV acquisition had an OR of 2.05 (0.72-5.82 95% CI)\textsuperscript{145} for those that have ever injected a substance, with a global review finding that HCV prevalence was significantly higher in MSM who reported injecting drug use at 34.8% (26.9-42.7 95% CI) relative to those who did not 3.5% (2.4-4.5 95% CI).\textsuperscript{134}

However, there have also been studies which have linked non-injecting drug use to increased chances of HCV transmission. One study stated that compared to no drug use, oral drug use had an OR of 1.59 (0.49-5.15 95% CI) for HCV acquisition; snorting without shared snorting equipment had an OR of 3.18 (1.42-7.11 95% CI); and snorting with shared equipment had an OR of 7.87 (3.48-17.80 95% CI).\textsuperscript{314} Additionally, the ASTRA study based in the UK examined HIV diagnosed MSM and explored the risk factors for prevalent HCV co-infection. Once adjusted for sexual health clinic and age, the odds of HCV were 4.6 (3.1-6.7 95% CI) for methamphetamine use, 6.5 (3.5-12.1 95% CI) for injection of drugs, 2.3 (1.6-3.4) for use of gamma-hydroxybutyrate acid (GHB) and 1.6 (1.3-2.0) for use of amyl nitrites (commonly referred to as poppers) in the last year.\textsuperscript{65} Furthermore, within a study of acute HCV infections specifically related to chemsex, those with HCV were more likely than controls to use methamphetamines (crystal meth); ketamine; GHB; amyl nitrites; ecstasy/MDMA and LSD, or to have previously shared equipment for both nasal and rectal routes of substance use.\textsuperscript{63}
2.6.4 The contribution of high risk sex and serosorting

Another feature of MSM sexual networks is the high rate of sexual partners and comparatively risky sex as covered in section 2.5. A UK based clinical study found that equally, under univariate analysis, more than 30 partners in the previous year was significantly associated with HCV infection, along with unprotected anal intercourse, rimming, fisting and use of sex toys. Under multivariate analysis, fisting remained as the only significantly associated factor. The ASTRA study also explored risk factors for prevalent HCV co-infection in HIV diagnosed MSM. After adjustment for clinic and age, for more than 10 new sexual partners in the past year ORs for HCV were 1.7 (1.5–2.0) for all UAI, 2.0 (1.6–2.5) for group sex, 1.5 (1.2–1.9). Group sex is also much more common amongst those who developed HCV infections, and has been linked to higher chances of fisting and unprotected anal intercourse, which raises the likelihood of HCV infection in their own right.

Associated with high risk behaviours, and as previously discussed in section 2.5.7, increases in serosorting stemming largely from advances in communication technology (largely the internet) in the last few decades, allow MSM to search for partners of the same HIV-status for UAI. Yet because of the increased biological vulnerability that HIV positive MSM have to HCV, this means that the transmission of HCV amongst HIV seroconcordant partnerships is significantly higher. For example within the ASTRA study based in the UK, which examined HCV infection risk factors for HIV diagnosed MSM, ORs for HCV were 2.1 (1.7–2.5 95% CI) for UAI in HIV seroconcordant and 1.3 (0.9–1.9 95% CI) for UAI in HIV serodiscordant partnerships, compared to no UAI in the previous 3 months.
2.7 HIV and HCV prevention in men who have sex with men

2.7.1 Introduction

HIV prevention has proven difficult within MSM due to the high transmission risk of anal intercourse, high frequency of sexual activity, historically fewer tailored services for MSM, and co-existing challenges including mental health and substance use. The control of HCV widely suffers from the same risk landscape and challenges, but with the added difficulty of occurring mainly as a co-infection in HIV positive individuals, with whom sexual risk behaviours tend to be greater and the primary mechanisms by which HCV spreads are less well known.

Historically, HIV prevention interventions focused on changing high risk behaviours, which although beneficial, were unable to provide sufficient influence to curb the epidemic. Behavioural interventions include any methods which lower the inherent risk of STI transmission through influencing sexual decision-making processes. This can relate to changes to the number of sexual partners, the choices of sexual activity (anal, fisting etc.), consistency of condom use or other protection, plus use of recreational drugs to enhance sexual intercourse. As medications have been developed to combat HIV’s natural course of infection these have also been used as an intervention tool.

In addition to the short-term efficacy of interventions, we also have to consider the feasibility and longevity of interventions within the MSM community. This applies mainly to behavioural interventions which can lose momentum easily, though it should be noted that treatment based and behavioural interventional approaches have complementary roles in a tackling HIV prevention in MSM.

2.7.2 Promoting consistent condom use

As we have discussed, UAI is at the epicentre to the transmission and patterns of HIV infection in MSM. It therefore follows that the use of condoms is also central to HIV related interventions. Indeed, from the 1980s, condom use has been known to contribute significantly to HIV prevention among MSM. Encouragement to use condoms was originally driven by community initiatives. In 2011, an international meta-analysis performed by the WHO
found that consistent condom use resulted in reducing HIV transmission by 64%, while also reducing the transmission of other STIs by 43%. Not only is condom use effective, but the use of condoms is widely accepted allowing condom based interventions to become established within MSM communities.

One method of encouraging condom use historically was peer-led group interventions, defined as “interactive group activities where a trained peer facilitates promotion of precautionary behaviours for HIV” which included consistent condom use, amongst other advice. A systematic review of peer-led interventions found them to be significantly effective, with reductions in UAI ranging from 13% to 33%. Similarly, peer outreach interventions, which comprise of trained members of the MSM community approach other MSM in their communities to both provide HIV related information and support. These initiatives achieved on average about a one third reduction in UAI, with data showing high uptakes and acceptance of peer led intervention within Europe.

Condom use however is not as high as it could be, and worryingly HIV sero-sorting has led to large decreases in condom use in couples or groups of HIV positive MSM, which leaves this group more vulnerable to HCV infection. Amongst MSM, behavioural interventions to prevent HCV spread are linked to interventions for HIV and other STIs, but there are no studies to date that have measured the direct impact of behavioural interventions for reducing HCV specifically in MSM.

2.7.3 Screening and STI testing

Screening for HIV and HCV plays a critical role in not only leading to treatment, but also as a preventative measure for reducing ongoing infections. The reason for the latter is due to a reduced propensity for high risk behaviours being noted immediately following the diagnosis of HIV infection due to both fear of forward transmission and the general education provided through counselling post-diagnosis.

The NHS advises that MSM should be screened for STIs, including HIV, every six months to a year. However, the average rate of HIV testing amongst MSM in the UK was back calculated as 3.2 years in a study from 2010, although a recent re-estimation from 2016 suggests it has reduced to 2.3 years. Interestingly, a recent UK report suggests that approximately 27% of MSM in the UK have never been screened for HIV.
In contrast to HIV, the general MSM population is not routinely screened for HCV due to the low prevalence of HCV in non-high risk groups. High risk groups include PWIDs, those suspected of needle stick injuries, HIV positive MSM, medical staff or others deemed to have a high chance of exposure. Therefore the majority of HIV negative MSM who have HCV are unaware of their infection due to the generally asymptomatic nature of HCV before cirrhosis or other signs of liver damage occur at which point diagnosis usually takes place. Conversely people who have HIV infection are advised to be tested for HCV annually in the UK, increasing to 6-monthly in the presence of relevant elevated risk behaviours, with those diagnosed with HCV now being put on to HCV treatment rapidly. Guidelines both in Europe and the USA also agree with the recommendation that individuals newly diagnosed with HIV are to be tested for HCV antibody upon HIV diagnosis.

Whether routine HCV screening should be implemented in HIV negative MSM remains controversial. There is evidence that HCV infection risk is rising amongst HIV negative MSM, but few HIV negative MSM populations have been screened as of yet. However, one systematic review concluded that screening within HIV negative MSM could be an effective public health measure. we address this question in this thesis, both in regards to the WHO and NHS HCV elimination targets in chapter 4, and its cost-effectiveness in chapter 5.

Another important factor in preventing HIV spread, is that screening and treating other STIs is also important in reducing HIV transmission. STIs can increase the infectiousness of HIV-positive individuals, as they trigger a local immune response within the genital areas, leading to increases in the concentration of HIV infected cells in key transmission sites. Additionally, STIs can lead to increased chances of HIV infection through the addition of symptoms such as open sores and damage to protective tissues. For example, infection with herpes-simplex 2 virus increases the HR of HIV acquisition by 1.7 (1.2-2.4 95% CI) in MSM and syphilis has a HR of 4.4 (3.0-6.7 95% CI) after adjustment for known risk factors. Due to the similar transmission routes of HCV, it is possible that the presence of other STIs could play a role in increasing the ease of HCV infection.
2.7.4 Treatment-as-prevention

ART was historically started when CD4 counts reached a critical thresholds to offset the higher risk of opportunistic infections after further CD4 count decline. These thresholds increased over time (from 200 cells/μl to 350 cells/μl to 500 cells/μl), with there being a recent move away from judging the initiation of ART based on CD4 count, to treating all HIV positive individuals on diagnosis. This is in part because ART’s impact on suppressing viral load vastly reduces the chance someone with an HIV infection transmits that infection to another individual, paired with evidence from the START trial that initiating ART earlier results in improved health and lifespans of HIV-positive individuals.

A pivotal randomised controlled trial (RCT) published in 2012 found that the level of HIV transmission amongst serodiscordant couples reduced by 96% with earlier initiation of ART relative to delaying therapy. However, only a small proportion of this sample were homosexual males (37 of 1763), so this estimate could not readily be applied to MSM. Evidence for MSM has improved substantially recently with results from the PARTNER trial which suggested that MSM with suppressed HIV viral loads due to ART treatment will also not be able to transmit HIV.

For HCV, the mechanism is slightly different given that HCV treatment results in a cure. Thus, for every person cured by HCV treatment, there is one less infected person that can transmit to others and so if the number of infections treated exceed that of reinfections, a net prevention benefit will be achieved. Recent modelling has shown that treatment as prevention in MSM for HCV is not only beneficial, but that it could be greatly curbing the number of ongoing infections in HIV diagnosed MSM and would be necessary for reaching the 2030 elimination targets in both PWID and MSM. Convincing governments to adopt this policy however can be challenging, as the cost of new DAA drugs is high, and reinfection rates can be significant. The initial high expense and economic impact of treatment as prevention need to be considered, especially in regards to elimination targets. This thesis contributes to the discussion of cost-effectiveness of treatment as prevention (TasP) in regards to HCV elimination in chapter 5 of this thesis.
2.7.5 Circumcision

A less commonly cited HIV prevention method is circumcision, which has been shown to reduce the chance of HIV transmission by 60% in three RCTs among largely heterosexual African populations.\textsuperscript{319} This benefit is postulated to be due to physiological differences incurred by the process.\textsuperscript{280} The effectiveness of circumcision among MSM was examined by a systematic review of 21 studies in 2011, which found that among circumcised men having primarily or exclusively insertive anal sex, there was a 73% (OR of 0.27; 95% CI 0.17–0.44) decrease in HIV infection.\textsuperscript{329} However, despite this large decrease in the chance of becoming HIV-positive when circumcised (if the individual is mainly an insertive partner), this intervention may not be feasible at the MSM population level in high income settings due to the necessary shift in social perceptions around voluntary circumcision. Circumcision may therefore remain primarily rooted in geographical and cultural aspects, despite its documented benefits.\textsuperscript{329}

The impact of circumcision on HCV is not known as no studies have examined the relationship between these factors. It is also the case that there is no evidence to suggest a biological reason that HCV transmission processes might be impacted specifically by circumcision.

2.7.6 Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) involves the use of a short 28 day course of ART treatment started within 72 hours of being potentially exposed to HIV, to reduce the likelihood of HIV transmission.\textsuperscript{36} PEP is primarily used as an emergency option rather than a consistent HIV prevention method.\textsuperscript{36} This is partially due to the efficacy of PEP not being fully understood because of the ethical restrictions of withholding a potentially effective treatment.\textsuperscript{36} Due to this necessary limitation, the efficacy of PEP in MSM has only been explored by findings from two retrospective studies, both of which only reported one subsequent HIV infection.\textsuperscript{165,274} However, in non-human primates, results from a systematic review indicate an 89% reduction in HIV infections where PEP was administered.\textsuperscript{130} Use of PEP is also notably low, possibly both due to the difficulty in accessing PEP and its position as an emergency measure.\textsuperscript{36}
2.7.7 Pre-exposure prophylaxis

HIV prevention methods have been revolutionised recently by the emergence of pre-exposure prophylaxis (PrEP). PrEP is a pre-emptive anti-retroviral medication, similar in nature to ART, which lowers the acquisition chance of new HIV infections. Randomized trials within MSM indicate high levels of HIV incidence reduction: iPrEx observing a 44% (15-63% 95% CI) reduction, IPERGAY an 86% (40-96% 95% CI) reduction and PROUD a 86% (64-96% 90% CI) reduction (with the range in efficacy of PrEP largely attributed to adherence).

Despite these promising results from clinical trials, there were concerns about the introduction of widespread PrEP, as seen during treatment optimism from ART. These include changes in behaviours and sexual risk taking which could significantly increase the incidence of STIs. Initially evidence for reduced condom use was mixed from the controlled PrEP trials, with findings from PROUD indicating a small reduction in condom use while engaging in receptive anal intercourse, iPrEx not finding a significant difference in condom use and IPERGAY finding an increase in condomless sex from 77% to 86% over 18 months. However these clinical trials were not fully equipped to measure the full range of risk compensatory behaviours, plus having the limitation of observing use of PrEP MSM in an artificial setting. More recent evidence from a meta-analysis, discovered that outside clinical trials, PrEP users have an 11-15 times higher incidence of STIs than non-PrEP users. Although this result is not necessarily indicative of risk compensation as there is higher baseline risk among PrEP users, other recent studies seem to give a consistent picture that the incidence of STIs is increasing following initiation of PrEP. One study found a 1.72 (1.22-2.41 95% CI) increased rate of STI acquisition 12 months after PrEP initiation compared to the 12 months before and within a 2018 systematic review there was found to be an OR of 1.24 (0.99-1.54 95% CI) for STI diagnoses in PrEP users versus non-PrEP users, with a trend towards higher ORs for more recent studies. It has also been postulated that beyond changing behaviours observed in PrEP users themselves, HIV negative MSM who aren’t using PrEP may even increase propensity for UAI, due to individual perceptions around HIV and increasing ‘herd immunity’.

Compared to other high income settings, the UK was fairly late in prescribing PrEP for widespread use. Although PrEP is now prescribed by NHS services in Scotland and in Wales (through the PrEPARED trail), currently the only way to access PrEP for MSM in England through the NHS is by enrolment in the currently running IMPACT trial. The IMPACT trial has a limited number of 13,000 participants (though this may be increased) over its 3 year duration (having started in October 2017). It is
possible, however, to also access PrEP through private health care providers or by ordering PrEP online. In contrast, the US has approved PrEP prescriptions since 2012, under criteria which are met by those at high risk of HIV infection, including MSM who have had an STI in the last 6 months or not used a condom as part of anal sex in the last 6 months. Australia has similarly adopted guidelines amongst MSM since 2017. Eligibility guidelines from NHS England target the use of PrEP for individuals who have substantial, higher-than-average risk of contracting HIV. Eligibility for the current IMPACT trial include: forgoing condom use at least once in the previous 3 months with high likelihood to do so in the next 3 months; having an HIV positive partner; or any activities which put individuals at similar levels of risk.

In the UK, NHS prescribed PrEP-users are required to be screened every three months for most STIs alongside HIV itself. Using this frequent clinical contact as a foundation, in chapter 5 of this thesis we examine the question of, “How often should PrEP-users be screened for HCV in the UK to be cost-effective?” This high frequency of contact also allows for rapid identification of HIV infection and subsequently early HIV treatment initiation.

However, considering PrEP’s role as an anti-viral and it’s close similarity to ART treatment, if individuals with HIV infection are using PrEP then we might expect to observe impacts of this medication on their HIV infection. Evidence suggests that PrEP extends the time taken to reach notable milestones of HIV progression known as Fiebig stages, with PrEP-users reaching Fiebig stage 6 21 days later than the 49 days average. This is combined with evidence showing that the viral loads of HIV infected PrEP-users compared to HIV infected MSM not using PrEP are $2/3\log_{10}$ lower (after adjusting for the time between progression between Fiebig levels).

PrEP’s impact on chronic HIV is unclear, but PrEP is not intended to be used in treatment of this stage of HIV, and due to the process of screening for HIV before prescribing PrEP and the three-monthly PrEP follow up appointments, it is likely to be a rare case that someone with chronic HIV is prescribed PrEP.
2.8 Mathematical Modelling

2.8.1 Introduction

Epidemiology poses the challenge of understanding a range of complex phenomena which comprise of many interacting factors, including the setting, the exposed population, and the intra/inter-dynamics of the population or disease vectors. The role of modelling in infectious disease epidemiology includes capturing the establishment and spread of pathogens using mathematical frameworks, as well as estimating the importance of factors contributing to the epidemic. In this section, we firstly cover the basics behind the three main modelling structures used in infectious disease epidemiology, providing key information about their formulation, strengths and limitations. We secondly give an overview and rational of the critical tools used in the analysis of results relevant to work in this thesis. Further detailed information specific to the models used for this thesis are found in chapters 3, 4 and 5, over which our model evolves in order to reach the sophistication needed to address the entire range of research questions tackled in this thesis.

2.8.2 Compartmental modelling

One of the first epidemic models proposed was a deterministic compartmental model by Kermack and McKendrick in 1927. General assumptions made for this type of compartmental model include splitting the population into non-intersecting classes. One of the simplest scenarios is an ‘SIR’ model where three classes are defined. Firstly, a class of individuals is included who may contract the disease, known as the susceptible population. The number of people in this class, (referred to as the size,) is usually denoted by $S$. Secondly, a class of individuals is included who are currently infected with the pathogen, known as infected individuals, denoted by $I$, and lastly the class of individuals who have recovered from the pathogen after being infected are included. These individuals are assumed to not be able to become infected with the disease again, and are called recovered individuals, denoted $R$.

The size of these classes can change with time, hence we can denote the classes as functions of time $t$, $S(t)$, $I(t)$, and $R(t)$. At a given time, the total population size $N = S + I + R$ is the sum of the sizes of all three classes. When formulating a model, actual disease dynamics are simplified using assumptions which capture key features of the disease progression without over-bearing detail. For example in the Kermack and McKendrick model, infected individuals are assumed to be infectious and the total population size remains constant. In this example, we have new members of the population
\( \theta \) move into the susceptible class at the same speed as the death rate for each compartment \( \mu \). Therefore \( \theta = \mu S + \mu I + \mu R \). It is however common for disease models to drop many of these assumptions, by including many different complexities such as a class of infected individuals who are not infectious, or to allow the total population to vary in size.\(^\text{8,185}\)

Regardless of these details in modelling choice, the heart of compartmental models is that they consist of systems of ordinary differential equations (ODEs) or difference equations that describe the dynamics of each class, which in essence governs the rates at which individuals move between these classes. For example, when a susceptible individual has “contact” with an infectious individual, there is a probability that the susceptible individual will become infected; this individual then moves from the susceptible class into the infected class. “Contact” can be any mechanism from physical proximity to sexual intercourse and is highly dependent on the pathogen being modelled.

Simultaneously, the class of infected individuals increases by the same number of newly infected individuals removed from the susceptible class. Through this approach, we are assuming that the number of members in a compartment is a differentiable function of time and that the epidemic process is completely deterministic.

If we assume that the number of contacts made by one infectious individual is proportional to the total population size with per capita contact rate \( c \), then that infectious individual forms \( cN \) contacts per unit of time. If we denote \( S_N \) as the probability that the contact is with a susceptible individual, then \( cNS_N \) is the number of contacts with susceptible individuals that one infectious individual makes per unit of time. Under the assumption of equal chances of mixing between all individuals, known as perfect mixing, \( S_N = \frac{S}{N} \). If we suppose \( p \) is the probability that a contact with a susceptible individual results in transmission, (as not every contact with a susceptible individual necessarily leads to transmission) then \( pcS \) is the number of susceptible individuals who become infected per unit of time per infectious individual. We then let \( \beta = pc \), where \( \beta \) is known as the transmission rate constant. This then means that \( \beta SI \) is the number of individuals who become infected per unit of time, which is referred to as the incidence of the infection.

If we define \( \lambda(t) = \beta I \), then the number of individuals who become infected per unit of time is equal to \( \lambda(t)S \), where the function \( \lambda(t) \) is known as the force of infection. Furthermore, at any given time, the proportion of infected individuals in the population \( I(t) \) is known as the prevalence of the disease.
In the Kermack and McKendrick model, individuals who recover leave the infected class at a constant probability per unit of time \( r \), known as the recovery rate. That is, \( rI \) is the number of infected individuals per unit of time who recover from infection. Individuals who recover leave the infectious class and move to the recovered class at rate \( \gamma(t) = rI \). Using this structure, we can represent the model using a system of ODEs:

\[
\begin{align*}
\frac{dS}{dt} &= \theta - \beta IS - \mu S \\
\frac{dI}{dt} &= \beta IS - rI - \mu I \\
\frac{dR}{dt} &= rI - \mu R
\end{align*}
\]

This system is equipped with initial conditions (when \( t = 0 \)), plus due to the dependent variables in the model denoting population sizes, it is also required that solutions start from non-negative initial conditions and remain non-negative for all time.\(^{139}\) For the Kermack and McKendrick model we also note an extra condition due to a stable size of population. We denote by \( N \) the total population size at time zero \( N(0) = S(0) + I(0) + R(0) \), and to hold the population steady require that \( N'(t) = S'(t) + I'(t) + R'(t) = 0 \), so that \( N = N(t) \).

Compartmental models are schematically described by a diagram often called a “flowchart”. Each compartment in a flowchart is represented by a box indexed by the name of the class. Arrows indicate the direction of movement of individuals between the classes. The movement arrows are typically labelled by the transition rates. The corresponding flowchart for the SIR model we have described is shown below.

![Flowchart of the Kermack and McKendrick SIR epidemic model](image)

There have been numerous developments to this type of modelling, with different class structures, stratifying the population by non-pathogen specific factors such as age or gender.\(^{131,132}\) Our modelling will stem from this general method, but be purpose built to reflect our population and be specific to the pathology of both HIV and HCV.
2.8.3 Network and stochastic models

Alongside compartmental models, there are two other commonly used mathematical frameworks within epidemiology. One of these is network models, with notable examples including work by Anderson and May\textsuperscript{186} and Klovdahl\textsuperscript{143} on HIV transmission dynamics. Within these models, people are represented as nodes with transmission pathways linking between them, known as edges. By using this approach, every person in the population can be treated as an individual with their own set of relationships and disease status. Over time, the disease spreads between nodes connected by edges.\textsuperscript{186} Additionally, nodes can be assigned characteristics, which represent heterogeneity within the population such as age or gender. These characteristics can be used to affect the probability that an edge will form between nodes, or change the probability weighting of transmission along the edge, affecting the probability that disease may be transmitted between the two individuals.\textsuperscript{137}

The advantages of using network models are that they provide an intuitive way of describing a population and their interactions, as well as being able to include a high level of detail in representing the heterogeneity in the population.\textsuperscript{62} Network models also allow for more detailed non-random mixing between individuals, unlike the “mass-action” aspect of compartmental modelling (where we assume the entire population are connected and mix proportionately, although compartmental models may include some degree of preferential mixing between compartments).\textsuperscript{62}

The disadvantages of this network models are that the level of complexity often required can make mathematical analysis difficult and numerical simulations are often very computationally intensive.\textsuperscript{62} Furthermore, these models require a large and accurate data set to inform the structure, especially in regards to the interactions between the individuals within the model’s population.\textsuperscript{62}

The second alternative to compartmental models make use of Markov chains. This type of model has been used in epidemiology since 1928 and was proposed by Reed and Frost.\textsuperscript{1} In the Reed–Frost model, we define the numbers of susceptible individuals at time $t$ as $S_t$, and infected individuals as $I_t$. Individuals who are infected have a probability of infecting susceptible individuals for each specified unit of time. In that time, infected individuals are assumed to be able to infect any member of the population who is susceptible, much akin to the mass-action principal of compartmental modelling. This probability is independent, with probability denoted $p$. At the next time step $t+1$, $S_{t+1}$ has a binomial distribution with index $S_t$ and mean, $S_t(1-p)I_t$ and $I_{t+1} = S_t - S_{t+1}$. The drawback of this formulation is that the number of potentially infectious contacts increases as the population size increases. In practice though, the Reed and Frost model is usually only applied to small populations, such as a household of individuals, where this drawback does not detract from the accuracy of the model.\textsuperscript{1}
There are variations however to this structure which overcome this drawback, for example, if each individual is assumed to make \( k \) fixed contacts. These are chosen randomly from the other individuals in the population. Infection can then be transmitted if one or more people in contact is infectious, and where \( k \) can take the form of a random variable.\(^{22}\) It is also possible to assign characteristics to each individual in the model, which can raise or lower the chance of a contact forming between two individuals, or once a contact is established, to modify the probability \( p \) of infection between those individuals.

The advantages of this type of model are that the stochastic nature allows this model to be used for small population sizes, which is something compartmental models are not equipped to process. Also due to the relatively simple structure as compared to network models, chain binomial models are more computationally affordable.

### 2.8.4 Uncertainty and model calibration

Often there is a configuration to which models must be initialised to reflect real world data. In this thesis for example, having a model which requires an initial stable state where HIV or HCV prevalence is at a set percentage of the population. To achieve this, we require model calibration.\(^{51}\)

Within mathematical models, there is always uncertainty in both the data to which a model is being calibrated to, and in the parameters the model draws upon. The entire collection of ranges in which parameters can belong is known as the model’s parameter space.\(^{35}\)

In brief, model calibration commonly consists of either (1) randomly sampling the values of model parameters (such as the transmission factor of HIV) from the parameter space and selecting only combinations of parameter values which agree with your desired initial conditions. Or (2) tuning the select parameter (or parameters) in order to ensure that your model runs are within a set tolerance to your observed data. It is also possible to use a combination of both approaches.\(^{51}\)

Uncertainty in model parameters can be particularly influential in dynamic models, such that the outcome of model results may differ considerably between different sets of parameter values.\(^{224}\) Thus, individual model projections generally have considerable variability and it is therefore important to perform multiple model runs and uncertainty analyses, which serve two main purposes.\(^{35}\) The first is to assess the confidence and variability in the model projections. The second is to ascertain which parameters contribute most to this uncertainty, highlighting potential dimensions of the epidemic which are more important or influential, and to potentially identify a need for further research into critical parameter values which are currently derived by inadequate data.\(^{35}\)
2.8.5 Cost-effectiveness analysis

To gauge the financial viability of an intervention, we can use mathematical modelling to undertake a cost-effectiveness analysis. The overall aim of which is to determine if a proposed intervention will yield adequate health benefits compared to its cost.\(^{205}\)

Within this thesis the costs considered will comprise of: the average expense per year for the care of individuals at each stage of disease progression; the cost of screening; the cost of processing laboratory tests; and the extra incurred time of medical staff applied at their rate of pay. However the forms an intervention can take are numerous and each require careful considerations of costings and impact.\(^{205}\)

The benefit of an intervention for our model can be measured in a number of ways, however a commonly used measure, and indeed the one we use within this work, is based upon the number of years of healthy living gained from the intervention. This is measured using quality adjusted life-years (QALYs), which are defined in the following way: "One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance."\(^{205}\)

The UK NHS considers an intervention to be cost-effective if for each individual QALY gained, the intervention is cost-saving or induces costs less than £20,000 compared to the current standard of care.\(^{284}\) The cost per QALY gained by the intervention scenario is usually estimated as the incremental cost-effectiveness ratio (ICER).\(^{284}\) There are however a number of complexities which need to be taken into account. For example a widely held assumption is that both costs and benefits incurred closer to the present have a higher intrinsic value than costs and benefits which occur further in to the future.\(^{205}\) Therefore, each year subsequent to the present year, the total costs and benefits are both assumed to be worth less than their value in the previous year, in the UK this value is 3% per year. This represents a discount rate of 3%, which is the current value recommended to be applied to UK cost-effectiveness analyses.\(^{284}\) Another factor to consider is the duration over which we observe the costs and benefits of the intervention, which is referred to as the time horizon, in order to calculate the ICER.\(^{205}\) The choice of time horizon is very important, as it can have a large impact on results.
As an example, let us take an intervention with very high initial costs and minimal costs thereafter, but where the benefits are not largely until a medium to long term period after the initial input costs. In this case we might expect a very high ICER over a time horizon of 10 years due to the upfront costs and unmatured impacts, leading to an intervention which does not look cost-effective. But over a time horizon of 30 or 50 years, this intervention may prove to be cost-effective or even cost-saving as the impacts grow without further costs being incurred. Projecting too far into the future however is not reasonable, as the state of healthcare, treatment options and other key factors is likely to have changed beyond the scope of the initial model. Therefore time horizons must be chosen to strike a balance between including as much of the impact and costs of the intervention as possible, with a judgement about the period of validity of the intervention in the current healthcare system. 209

2.8.6 Modelling of the HIV and HCV epidemic in MSM

The work in this thesis primarily builds on the first UK focused modelling of the HCV and HIV co-epidemic in MSM, which examined the the impact of DAAs on reversing the high HCV prevalence found in HIV diagnosed MSM, 179 finding DAA scale-up to be an effective intervention, especially when paired with behavioural interventions. This thesis also draws from modelling based on data from the Netherlands which also supported the evidence indicating the significant impact of HCV incidence reduction from scaling up the use of DAAs within HIV diagnosed MSM, 25 plus modelling focused on HIV diagnosed MSM from the Swiss cohort, which found that although HCV treatment alone was not adequate to curb the increasing incidence of the Swiss HCV epidemic, additional behavioural intervention could. 256

What differentiates this work is the inclusion of the entire MSM population. This novel approach allows for a broader idea of the full HCV infection dynamics and the ability to more fully capture and model the complex behaviours of MSM discussed in section 2.5. We build on the contribution of this work to existing modelling more fully in (1) section 3.4.3, which further discusses the role of modelling in establishing the drivers and key factors of the HCV epidemic in MSM, (2) section 4.4.3 which discusses modelling that considers the impact of DAAs on the HCV elimination targets, plus the effect of PrEP on HIV and STI co-infections and finally (3) section 5.4.3 which discusses key modelling studies focused on the cost-effectiveness of scaling up the use of DAAs and increasing screening in MSM to work towards the HCV elimination targets.
Chapter 3  Drivers of the HCV epidemic in MSM

3.1 Introduction

As discussed in detail in chapter 2, a skewed HCV epidemic continues unfolding amongst predominantly HIV positive MSM in the UK, Europe, the US and Australia.31 Indeed, the incidence of HCV among HIV positive MSM is generally 5-20 times higher than HIV negative MSM.31,344 In the UK, HCV seroprevalence among HIV negative MSM was estimated to be 1.2% (0.6-2.1%) in 2009,232 but was 9.9% amongst HIV positive MSM in 2012.179 Although amongst higher risk sub-groups of HIV-negative MSM HCV prevalence is known to be much higher, for example in one recent study, MSM on PrEP were found to have similar incidence to HIV-positive MSM.242 This chapter examines the key factors proposed in the current literature to determine the drivers behind the outbreak and pattern of this epidemic within MSM.

Both behavioural and biological factors have been proposed to account for the large discrepancy in HCV burden between HIV positive and HIV negative MSM.63,310 Biological factors include reduced chances of spontaneously clearing the HCV virus111,199 and higher HCV viral loads potentially leading to greater infectivity in HIV positive MSM.17,289 Behavioural factors include sexual partner selection based on HIV status and heterogeneity in sexual risk.63,79 Heterogeneities in risk and precautionary behaviours incorporate differences in numbers of sexual partners and use of condoms, different preferences for ano-brachial insertion (fisting) and injecting of drugs.63,145,166,170 Additionally, partner selection and risk behaviours may interact, such as reduced condom use occurring between couples that assume they are HIV seroconcordant.79 These heterogeneities in sexual risk and mixing could lead to groups with higher-risk, and thus greater sexually transmitted infection (STI) and HIV prevalence.

I developed a dynamic joint HIV/HCV transmission model among MSM to gain insight into the contribution of behavioural and biological factors and to discover primarily why HCV is concentrated among HIV positive MSM. We assessed how variations in these biological and behavioural factors’ may affect the HCV distribution, and evaluated the resulting implications for HCV TasP in HIV diagnosed MSM.179
3.2 Methods

3.2.1 Modelling

Model structure

For a given compartment of our model, we represent the full disease and risk status of an individual by $X_{ij}$ where $X$ denotes HIV status, $i$ denotes HCV status, and $j$ the risk group.

The possible stages of HIV infection ($X$) are: $S$ for susceptible, $A$ for acute HIV infection, $C$ for chronic undiagnosed HIV infection and $D$ for diagnosed HIV infection. We denote the stage of HCV infection (subscript $i$) where: $S$ is susceptible, $I$ is chronic HCV that has not yet received treatment, and $F$ is chronic HCV, where HCV treatment was attempted but failed. We also split the population into low and high risk groups (subscript $j$), $L$ for low risk and $H$ for high risk. So for example $A_{SL}$ denotes low risk group individuals who are acutely infected with HIV and susceptible to HCV.

All MSM enter the model at a rate $\theta$, and exit the model due to ageing, at an equal rate $\mu$, with our modelling assuming entry and exit at 15 and 65 years of age respectively. Additional mortality is included due to: mono-infection of HCV $\mu_{HCV}$; undiagnosed HIV infection where individuals are not on HAART $\mu_{HIV}^{Undiag}$; and diagnosed HIV infection with a proportion of MSM on HAART $\mu_{HIV}^{Diag}$. We also include mortality due to HCV and HIV co-infection with death rates of those with undiagnosed HIV status denoted by $\mu_{CO}^{Undiag}$ and diagnosed HIV status as $\mu_{CO}^{Diag}$.

$\sigma_j$ denotes the force of infection for HIV, which is dependent on risk group $j$. Once HIV infected, $\alpha$ is the rate individuals transition from the acute phase of HIV to chronic infection, and $d_{HIV}$ the subsequent rate at which chronically infected MSM with HIV are diagnosed.

$\lambda_{jk}$ is the force of infection for HCV, which is defined in greater detail later in this section. The HCV force of infection is dependent on risk group $j$ and HIV-status $k$. Where $k = 0$, this denotes those which are still susceptible to HIV, $k = 1$ denotes those that have an undiagnosed HIV infection and $k = 2$ denotes those with a diagnosed HIV infection. We also make use of $u$ to denote both HIV infected but undiagnosed MSM or HIV susceptible MSM (where $k = 0$ or 1) and the symbol $d$ to denote HIV diagnosed MSM (where $k = 2$).
$r_k$ is the rate of successful HCV treatment which governs the rate at which treatment naive HCV infected individuals return to the susceptible category. Conversely $f_k$ represents the rate of HCV treatment failure which governs the rate at which treatment naive HCV infected individuals move to the treatment failure compartment. Individuals who fail treatment are not retreated, and so stay in the treatment failure compartment until exiting the model. These two rates are also dependent on the HIV diagnosis status of the individuals in the compartment $k$. A comprehensive summary of the model parameters is detailed in table 3.1.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_k$</td>
<td>The rate of successful treatment of individuals with diagnosed HCV.</td>
</tr>
<tr>
<td>$f_k$</td>
<td>The rate of treatment failure for individuals with diagnosed HCV.</td>
</tr>
<tr>
<td>$\theta_j$</td>
<td>The number of new individuals entering the population per year.</td>
</tr>
<tr>
<td>$\lambda_{jk}$</td>
<td>The rate at which individuals are infected with HCV.</td>
</tr>
<tr>
<td>$\sigma_j$</td>
<td>The rate at which individuals are infected with HIV.</td>
</tr>
<tr>
<td>$\mu$</td>
<td>The rate at which people leave the model due to aging out of the model.</td>
</tr>
<tr>
<td>$\mu_{HCV}$</td>
<td>The additional death rate due to HCV mono-infection.</td>
</tr>
<tr>
<td>$\mu_{HIV}^{Diag}$</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV diagnosed</td>
</tr>
<tr>
<td>$\mu_{HIV}^{Undiag}$</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV undiagnosed</td>
</tr>
<tr>
<td>$\mu_{CO}^{Diag}$</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV diagnosed</td>
</tr>
<tr>
<td>$\mu_{CO}^{Undiag}$</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV undiagnosed</td>
</tr>
</tbody>
</table>

Table 3.1 - Parameters included in the model equations with descriptions.

During the model runs, we assume that individuals do not move from their respective risk groups. This assumption is based on data from the EMIS and the UK gay men’s survey that suggests MSM have a similar rate of unprotected sex, injecting drug use, and fisting from their 20s to their 50s, plus data from MSM HCV incidence studies that suggests there is no clear relationship between age and HCV acquisition risk. The transitions involved in the model for HIV and HCV are however described diagrammatically in figure 3.1.
Figure 3.1 - Flow diagram for the joint HIV and HCV model.

Model equations

Complementary to diagram 3.1, the differential equations which govern the model (where \( j = L \) or \( H \)) are as follows:

\[
\begin{align*}
\frac{dS_j}{dt} &= \theta_j + r_0S_{ij} - \sigma_jS_j - \lambda_{j0}S_{ij} - \mu S_j \\
\frac{dS_{ij}}{dt} &= \lambda_{j0}S_j - r_0S_{ij} - \sigma_jS_{ij} - f_0S_{ij} - \mu_{HCV}S_{ij} \\
\frac{dS_{Fj}}{dt} &= f_0S_{ij} - \sigma_jS_{Fj} - \mu_{HCV}S_{Fj} \\
\frac{dA_j}{dt} &= r_1A_{ij} + \sigma_jS_{A} - \lambda_{jA}S_{ij} - aA_{ij} - \mu A_{ij} - \mu_{\text{HIV}}A_{ij} \\
\frac{dA_{Fj}}{dt} &= f_1A_{ij} + \sigma_jS_{A} - aA_{ij} - \mu_{\text{HIV}}A_{ij} \\
\frac{dC_j}{dt} &= r_1C_{ij} + aA_{ij} - \lambda_{jC}S_{ij} - dC_{ij} - \mu_{\text{HIV}}C_{ij} \\
\frac{dC_{Fj}}{dt} &= aA_{Fj} + f_1C_{ij} - dC_{Fj} - \mu_{\text{HIV}}C_{Fj} \\
\frac{dD_j}{dt} &= r_2D_{ij} + d_{\text{HIV}}C_{ij} - \lambda_{jD}S_{ij} - dS_{ij} - \mu_{\text{HIV}}D_{ij} \\
\frac{dD_{Fj}}{dt} &= r_2D_{ij} + d_{\text{HIV}}C_{ij} - f_2D_{ij} - \mu_{\text{HIV}}D_{ij} \\
\end{align*}
\]
Deriving the mixing matrix

To derive the forces of infection for HIV and HCV we firstly derive the mixing between the subgroups of MSM represented by our compartments. In our model, MSM mix preferentially by both risk status and their assumed HIV status and so our task is to account for how the HIV and risk status of both the primary individual and their sexual partners interact. Because of the overall complexity in doing this, we build the mixing equations over a number of stages for clarity. For ease of reference, we show all the parameters found within our mixing equations in table 3.2.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscripts</td>
<td></td>
</tr>
<tr>
<td>$j$</td>
<td>Denotes the risk group. This can take values $L$ for low risk and $H$ for high risk.</td>
</tr>
<tr>
<td>$k$</td>
<td>Denotes HIV status. This can take the values $0$ for HIV negative, $1$ for HIV positive but undiagnosed and $2$ for HIV diagnosed. Sometimes we use $u$ to denote either $k = 0$ or $1$ and $d$ to denote $k = 2$.</td>
</tr>
<tr>
<td>Sub-populations</td>
<td></td>
</tr>
<tr>
<td>$N_{jk}$</td>
<td>Without subscript, $N$ represents the entire population of the model. Presence of subscripts slice the total population by the indicated subscript(s). For example, $N_j$ refers to every member of the population who is in risk category $j$ and $N_{jk}$ refers to every member of the population who is in risk category $j$ and of HIV status $k$.</td>
</tr>
<tr>
<td>$u$</td>
<td>MSM who are either HIV negative or HIV infected but undiagnosed.</td>
</tr>
<tr>
<td>$d$</td>
<td>MSM who are HIV diagnosed.</td>
</tr>
<tr>
<td>Parameters</td>
<td></td>
</tr>
<tr>
<td>$M_{\text{Risk}}$</td>
<td>Denotes the mixing equations for MSM of type $j$ with type $j'$.</td>
</tr>
<tr>
<td>$M_{\text{HIV}}^{ij/k/k'}$</td>
<td>Denotes the mixing equations for MSM of type $jk$ with type $j'k'$ in the presence of no HIV serosorting errors.</td>
</tr>
<tr>
<td>$M_{\text{Error}}^{ij/k/k'}$</td>
<td>Denotes the mixing equations for MSM of type $jk$ with type $j'k'$ in the presence of HIV serosorting errors.</td>
</tr>
<tr>
<td>$b$</td>
<td>The proportion of MSM who mix like with like by risk status $j$.</td>
</tr>
<tr>
<td>$p_j$</td>
<td>The average number of partners for MSM in risk group $j$.</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>The proportion of MSM who mix like with like by HIV status (serosort).</td>
</tr>
<tr>
<td>$e$</td>
<td>Chance of a serosorting judgement being incorrect. With random mixing occurring when the judgement is incorrect.</td>
</tr>
<tr>
<td>$c_0$ &amp; $c_1$</td>
<td>$c_1$ is the expected protection provided by the chance of condom use between a serosorting HIV diagnosed MSM and a partner they also assume is HIV positive. $c_0$ is the expected protection provided by the chance of condom use between all other sexual partnerships.</td>
</tr>
</tbody>
</table>

Table 3.2 - Parameters included in the mixing equations with descriptions.
Firstly, we define the probability of mixing between two individuals based only on their risk group, denoted $M_{jj'}^{Risk}$ (one individual from risk group $j$ with their partner from risk group $j'$). $b$ represents the proportion of individuals who mix exclusively with partners of the same risk group, with other partnerships assumed to form randomly with all the available population. This random mixing is weighted by the average number of partners in each risk group. $N_j$ is used to represent the entire population in risk group $j$, $p_j$ is the average number of partners which individuals in risk group $j$ form over a year, and $\delta_{jj'}$ is the kronecker delta function that is equal to 1 when $j = j'$ and equal to 0 otherwise.

\[
M_{jj'}^{Risk} = \delta_{jj'} b + (1-b) \left[ \frac{p_{j'} N_{j'}}{\sum_{n} N_{jn}} \right]
\]

Next, we build on this, taking into account mixing by HIV status and formulate the family of equations within $M_{jkjk'}^{HIV}$. These represent the probability that an MSM in risk group $j$, and HIV-status group $k$, forms a sexual partner with an MSM in risk group $j'$, and HIV-status group $k'$. Notably, this depends on both the perceived HIV diagnosis status of the primary individual and their partner.

\[
M_{juju}^{HIV} = \delta_{jj'} b \left[ \xi + (1 - \xi) \frac{N_{ju}}{\sum_{n} N_{jn}} \right] + (1-b) \left[ \xi \frac{p_{j'} N_{ju}}{\sum_{n} p_n N_{nu}} + (1-\xi) \frac{p_j N_{ju}}{\sum_{n} p_n N_{no}} \right]
\]

\[
M_{jdjd}^{HIV} = \delta_{jj'} b \left[ \xi + (1-\xi) \frac{N_{jd}}{\sum_{n} N_{jn}} \right] + (1-b) \left[ \xi \frac{p_{j'} N_{jd}}{\sum_{n} p_n N_{nd}} + (1-\xi) \frac{p_j N_{jd}}{\sum_{n} p_n N_{no}} \right]
\]

\[
M_{jujd}^{HIV} = \delta_{jj'} b (1 - \xi) \frac{N_{ju}}{\sum_{n} N_{jn}} + (1-b) (1-\xi) \frac{p_{j'} N_{ju}}{\sum_{n} p_n N_{no}}
\]

\[
M_{jdju}^{HIV} = \delta_{jj'} b (1 - \xi) \frac{N_{jd}}{\sum_{n} N_{jn}} + (1-b) (1-\xi) \frac{p_j N_{jd}}{\sum_{n} p_n N_{no}}
\]

This set of equations $M_{jkjk'}^{HIV}$, then are adapted to include judgement errors when individuals assume their partners’ HIV status. This is important, as EMIS shows that condom use is much lower if an HIV diagnosed MSM thinks their sexual partner is also HIV positive. So, where $e$ is the chance an erroneous judgement about HIV status resulting in random mixing:

\[
e = \delta_{jj'} b (1 - \xi) \frac{N_{ju}}{\sum_{n} N_{jn}} + (1-b) (1-\xi) \frac{p_{j'} N_{ju}}{\sum_{n} p_n N_{no}}
\]
\[ M_{j u ru}^{\text{Error}} = \delta_{j j} b \left[ \zeta (1 - e) + (1 - \zeta (1 - e)) \frac{N_{ju}}{\sum_{n} n_{jn}} \right] + (1 - b) \left[ \zeta (1 - e) \frac{p_{j N_{ju}}}{\sum_{n} p_{n} N_{nu}} + (1 - \zeta (1 - e)) \frac{p_{j N_{ju}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \]
\[ M_{jd jr}^{\text{Error}} = \delta_{j j} b \left[ \zeta (1 - e) + (1 - \zeta (1 - e)) \frac{N_{jd}}{\sum_{n} n_{jn}} \right] + (1 - b) \left[ \zeta (1 - e) \frac{p_{j N_{jd}}}{\sum_{n} n_{jn}} + (1 - \zeta (1 - e)) \frac{p_{j N_{jd}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \]
\[ M_{ju jr}^{\text{Error}} = \delta_{j j} b \left[ \zeta (1 - e) \frac{N_{ju}}{\sum_{n} n_{jn}} + (1 - b) \left[ (1 - \zeta (1 - e)) \frac{p_{j N_{jd}}}{\sum_{n} n_{jn}} + (1 - \zeta (1 - e)) \frac{p_{j N_{ju}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \right] \]

This penultimate set of equations is then adapted to give the final mixing equations \( M_{kj kr}^{\text{Error}} \), which also include the level of protection given by condom use, which as previously mentioned is lower if an HIV diagnosed MSM thinks they are having sex with another HIV positive MSM. The parameters \( c_0 \) and \( c_1 \) represent the reductions in transmission probabilities due to condom based protection from infection based on the consistency of condom use for that pairing type (see section below for how \( c_0 \) and \( c_1 \) are fully defined), with \( c_1 \) being for “HIV diagnosed MSM with an assumed HIV diagnosed partner” pairings and \( c_0 \) for all other pairings. In the model, we have to remember that when a HIV diagnosed MSM thinks they have chosen a sexual partner that is HIV diagnosed, they will use condoms with lower consistency and so have protection \( c_1 \), irrespective of whether they were right or not in their assumption.

\[ M_{ju ju} = \delta_{j j} b c_0 \left[ \zeta (1 - e) + (1 - \zeta (1 - e)) \frac{N_{ju}}{\sum_{n} n_{jn}} \right] + (1 - b) c_0 \left[ \zeta (1 - e) \frac{p_{j N_{ju}}}{\sum_{n} n_{jn}} + (1 - \zeta (1 - e)) \frac{p_{j N_{ju}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \]
\[ M_{jd jr} = \delta_{j j} b \left[ \zeta (1 - e) c_1 + (1 - \zeta) c_0 + \zeta c_1 \right] \frac{N_{jd}}{\sum_{n} n_{jn}} + (1 - b) c_0 \left[ (1 - \zeta (1 - e)) \frac{p_{j N_{jd}}}{\sum_{n} n_{jn}} + (1 - \zeta (1 - e)) \frac{p_{j N_{jd}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \]
\[ M_{ju ju} = \delta_{j j} b \left[ (1 - \zeta (1 - e)) \frac{N_{ju}}{\sum_{n} n_{jn}} + (1 - b) c_0 \left[ (1 - \zeta (1 - e)) \frac{p_{j N_{ju}}}{\sum_{n} n_{jn}} + (1 - \zeta (1 - e)) \frac{p_{j N_{ju}}}{\sum_{n} n_{o} p_{n} N_{no}} \right] \right] \]
Condom usage terms

The model parameters $c_0$ or $c_1$ formally represent the probability that condoms will not protect an individual from HIV or HCV infection i.e. what proportion of transmissions still will occur based on the consistency of condom. $c_1$ denotes this value for pairings between HIV diagnosed MSM with an assumed HIV positive partner and $c_0$ denoting this value for the other pairings.

I calculate these values by combining the parameter value for the protection a condom offers when used, denoted as $P$ and the rate of condom use within the pairings. Between HIV diagnosed MSM with an assumed HIV diagnosed partner this is rate is $D$, whereas all other partnerships are assumed to use condoms with a different, but otherwise roughly equal consistency, denoted $U$. The parameters $c_0$ and $c_1$ are therefore defined as:

$$c_0 = 1 - UP$$
$$c_1 = 1 - DP$$

Forces of infection for HIV and HCV

The forces of infection $\lambda_{jk}$ for HCV and $\sigma_j$ for HIV are dependent on the risk group $j$ and HIV infection and diagnosis status $k$. Additionally, to define the HIV and HCV force of infection, we require the introduction of a number of extra parameters:

- $\Omega$ is the factor of increased HIV infectiousness of those in the acute phase of HIV versus the asymptomatic chronic phase.
- $\Delta$ is the reduced infectiousness of HIV due to those on ART.
- $\Lambda$ is the factor of increased HCV infectivity of those with HIV co-infection.
- $\beta^{\text{hiv}}$ is the base transmission factor for HIV.
- $\beta^{\text{hcv}}$ is the base transmission factor for HCV.
- $R$ is the factor of additional HCV and HIV transmission risk, due to the high risk group’s participation in more frequent fisting and injecting behaviours alongside sexual encounters.
- $x_k$ is the chance an individual will spontaneously clear the virus with subscript $k = n$ or $p$ to denote their HIV status as negative ($k = 0$) or positive ($k = 1$ or $2$) respectively.
Given these parameters, the force of infection for HIV $\sigma_j$ and HCV $\lambda_{jk}$ are:

\[
\sigma_L = \beta_{hiv} p_L \left[ M_{Lulu} \left( \frac{\sum_{m=l} A_m + C_m}{\sum_{m} A_m + C_m} \right) + M_{Luhu} \left( \frac{\sum_{m l} A_m + C_m}{\sum_{m} A_m + C_m} \right) + \Delta M_{Lulu} + \Delta M_{Luhu} \right]
\]

\[
\sigma_H = \beta_{hiv} R_{PH} \left[ M_{Hulu} \left( \frac{\sum_{m=H} A_m + C_m}{\sum_{m} A_m + C_m} \right) + M_{Huhu} \left( \frac{\sum_{m h} A_m + C_m}{\sum_{m} A_m + C_m} \right) + \Delta M_{Hulu} + \Delta M_{Huhu} \right]
\]

\[
\lambda_{L0} = \beta_{hcv} p_L (1 - x_0) \left[ M_{Lulu} \left( \frac{\sum_{m=l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Luhu} \left( \frac{\sum_{m l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Lulu} + \Delta M_{Luhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

\[
\lambda_{L1} = \beta_{hcv} p_L (1 - x_1) \left[ M_{Lulu} \left( \frac{\sum_{m=l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Luhu} \left( \frac{\sum_{m l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Lulu} + \Delta M_{Luhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

\[
\lambda_{L2} = \beta_{hcv} p_L (1 - x_2) \left[ M_{Lulu} \left( \frac{\sum_{m=l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Luhu} \left( \frac{\sum_{m l} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Lulu} + \Delta M_{Luhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

\[
\lambda_{H0} = \beta_{hcv} R_{PH} (1 - x_0) \left[ M_{Hulu} \left( \frac{\sum_{m=H} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Huhu} \left( \frac{\sum_{m h} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Hulu} + \Delta M_{Huhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

\[
\lambda_{H1} = \beta_{hcv} R_{PH} (1 - x_1) \left[ M_{Hulu} \left( \frac{\sum_{m=H} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Huhu} \left( \frac{\sum_{m h} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Hulu} + \Delta M_{Huhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

\[
\lambda_{H2} = \beta_{hcv} R_{PH} (1 - x_2) \left[ M_{Hulu} \left( \frac{\sum_{m=H} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + M_{Huhu} \left( \frac{\sum_{m h} (S_m + \Lambda A_m + \Lambda C_m)}{\sum_{m} (S_m + A_m + C_m)} \right) + \Delta M_{Hulu} + \Delta M_{Huhu} \left( \frac{D_{IH} + D_{FH}}{D_{SH} + D_{IH} + D_{FH}} \right) \right]
\]

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Treatment Equations for HCV

Treatment for HCV is not included in this model unless we are running the DAA scale up scenario, for which we use the following equations:

\[
\begin{align*}
    r_0 &= \psi_u y_n \\
    r_1 &= \psi_u y_p \\
    r_2 &= \psi_d y_p \\
    f_0 &= \psi_u(1 - y_n) \\
    f_1 &= \psi_p(1 - y_n) \\
    f_2 &= \psi_d(1 - y_p)
\end{align*}
\]

\(r_k\) denotes the rate of successful treatments for HCV and \(f_k\) is the rate of unsuccessful treatments for HCV; where \(\psi_k\) is the rate of HCV treatment which varies by HIV diagnosis status and \(y_k\) is the efficacy of the treatment (which we allow to vary by HIV infection status, \(k = n\) for HIV negative and \(k = p\) for HIV positive).

3.2.2 Parameter derivation

Sexual risk behaviours were parameterized using data from the UK component of the European MSM Internet Survey (EMIS-UK);\(^\text{168}\) EMIS was a pan-European internet survey on knowledge, attitudes, needs and behaviour regarding HIV and STI transmission among MSM.\(^\text{168}\) Individuals could complete the survey online during Summer 2010. Over 180,000 men took part from 38 countries, including 18,000 in the UK.\(^\text{322}\) Below we cite the relevant questions from the survey used in constructing our derivations and then present our method and justifications for how these responses were used to generate the modelling parameters.

Mixing of MSM by HIV Status

“Q69. What do you think your current HIV status is (whether or not you've ever tested for HIV)?
1=Definitely negative (I don't have HIV) 2=Probably negative 3=Not sure / we don't know 4=Probably positive 5=Definitely positive (I do have HIV)”

I used responses to this question to gauge the perceived HIV status of the respondent. We only took answer 5 (10.4% report this) to be a valid indicator of the individual to be HIV diagnosed. All other
responses are classed as “HIV negative or HIV positive but undiagnosed” (89.6%). The percentage of 
HIV positive respondents is notably larger than the 5%\textsuperscript{23} estimate of HIV prevalence in the UK for MSM 
in 2010, but we would expect this due to an inherent bias of EMIS to have attracted more HIV 
diagnosed MSM than found in the general MSM population.\textsuperscript{229} 

“Q185. What did you know or think about his HIV status before having sex? 1=I knew or thought he 
was HIV negative 2=I knew or thought he was HIV positive 3=I don’t remember 4=I didn’t have any 
thoughts about his HIV status” 

This question allows us to identify the respondent’s perception of the HIV status of their last sexual 
partner. Stratifying by the respondent’s own HIV-diagnosis status, we estimated the proportion of 
respondent’s that thought their last partner was HIV positive or HIV negative. For those that said they 
“did not think about it” we assumed that a proportion of these partners were HIV positive based on 
the 2010 UK prevalence of HIV infection. For now assuming their judgements are correct, this allowed 
us to estimate the likely proportion of sexual partners for respondents that were HIV positive and the 
proportion that were not. For example in our data 36.2% of HIV diagnosed MSM thought their last 
partner was HIV positive; 16.9% thought they were HIV negative; and 46.9% hadn’t thought about it 
when selecting a partner. Assuming their judgements were correct and with a 5% HIV prevalence in 
the UK, we estimate that (36.2% + 0.05 \times 46.9%) = 38.5% of HIV diagnosed MSM’s sexual 
partnerships were with HIV positive partners. Conversely, because 16.9% thought their partner was 
HIV negative we estimate that (16.9% + (1 \minus{} 0.05) \times 46.9%) = 61.5% of HIV positive MSM’s 
sexual partnerships were with HIV negative partners. From EMIS, we used these point estimates to 
construct a single parameter for the degree of like-with like mixing of MSM by HIV diagnosis status. 

For the purpose of this analysis, we refer to MSM who are HIV infected but undiagnosed or HIV 
negative as simply “non-diagnosed”. Firstly, we assume that \(Y = 0.05\) is the proportion of MSM with 
HIV; \(e\) is the chance of errors in HIV judgements; and \(\zeta\) is the probability that an individual will 
preferentially seek a partner of the same HIV diagnosis status. 

If we define \(mix_{kk'}^{HIV}\) as the probability that an individual of HIV diagnosis state \(k = u \text{ or } d\) has a 
sexual partner of HIV diagnosis state \(k' = u \text{ or } d\), then we can estimate \(mix_{kk'}^{HIV}\) as:
\[ \begin{align*}
    mix_{uu}^{HIV} &= \xi (1 - e) + (1 - \xi (1 - e))(1 - Y) \\
    mix_{ud}^{HIV} &= (1 - \xi)Y + \zeta eY \\
    mix_{du}^{HIV} &= (1 - \xi)(1 - Y) + \zeta e(1 - Y) \\
    mix_{dd}^{HIV} &= \xi (1 - e) + (1 - \xi (1 - e))Y
\end{align*} \]

EMIS data indicates that this mix function should have the following values:

- \( mix_{uu}^{HIV} = 94.3\% \)
- \( mix_{ud}^{HIV} = 5.7\% \)
- \( mix_{du}^{HIV} = 61.5\% \)
- \( mix_{dd}^{HIV} = 38.5\% \)

Of these values, our main aim is to capture the best fit for \( mix_{dd}^{HIV} \). Under fitting of \( \xi \) and assuming \( e = 0 \) and \( Y = 0.05 \) as in the UK, then we parametrize \( \xi = 0.352 \), which then results in mixing probabilities of:

- \( mix_{uu}^{HIV} = 96.8\% \)
- \( mix_{ud}^{HIV} = 3.2\% \)
- \( mix_{du}^{HIV} = 61.5\% \)
- \( mix_{dd}^{HIV} = 38.5\% \)

**Chance of error when evaluating HIV status of a sexual partner**

The data from Q186 was used to get an estimation of the likelihood of error when evaluating the HIV status of a sexual partner, following from question Q185, which asked what people thought about the HIV status of their last casual partner.

“Q186. [if Q185=1 or 2] Why did you think this? Please read the list below and tick the answer that best applies. 1=He told me some time ago / we had known for some time 2=He told me (online or in person) before or during sex 3=I knew it from his profile on the Internet 4=He made it clear without actually telling me 5=Someone else told me 6=I were at an event where everyone was HIV positive 7=I were at an event where everyone was HIV negative 8=I guessed 9=Other reason”
If guessing a partner was HIV negative in Q185: we assumed that answers 2 and 3 were likely to be correct assumptions; it was uncertain whether answers 1, 4, 5, 7 and 9 would yield errors in judgement; and that answer 6 and 8 were highly likely to be unable to determine HIV-status correctly.

If guessing a partner was HIV positive in Q185: we assumed that answers 1, 2, 3 and 6 were likely to be correct assumptions; it was uncertain whether answers 4, 7 and 9 could yield errors in judgement; and that answers 5 and 8 were highly likely to be unable to determine the HIV status of partners accurately.

Based on this, the proportion of assumptions likely to be correct were 54.3% and 68.7% when a partner was assumed HIV negative or HIV positive respectively. The proportion of assumptions which were correct or uncertain amounted to 84.9% and 87.9% when a partner was assumed HIV negative or HIV positive MSM, respectively. This allows us calculate the error range as between 15.1-45.7% (midpoint 30.6%) when an MSM thought their partner was HIV negative, and 12.1-31.3% (midpoint 19.2%) when an MSM thought their partner was HIV positive. These midpoints were averaged to 25%.

I also note that in this instance guessing a partner’s actual HIV status is akin to guessing if they are diagnosed or not, as if the partner in question was unaware of their HIV infection, then they could not communicate if they were HIV positive to their partners.

**Condom usage by perceived HIV Status**

“Q187. Did you have anal intercourse (fuck) on that occasion? 1=No 2=Yes, he fucked me 3=Yes, we fucked him 4=Yes, we fucked each other “

“Q188. [if Q187=2 or 4] Did he use a condom when he was active in anal intercourse (when he fucked you)? 1=No 2=Yes 3=I don’t remember/I don’t know”

“Q190. [if Q187=3 or 4] Did you use a condom when you were "active" in anal intercourse? 1=No 2=Yes 3=I don’t remember/I don’t know”

If an individual responded to Q187 with answer 4, then we required an answer of “yes” to both Q188 and Q190 to count as full condom use. Otherwise, we only required the response “yes” to Q188 if they answered with response 2 for Q187, or the response “yes” to Q190 if they answered with response 3 to Q187. Interestingly, from this we found that when HIV diagnosed MSM have sex with a partner they
assume to be HIV positive there was a 13% chance of condom usage, whereas all other pairings had similar levels of condom usage of approximately 68%.

**Defining the high/low risk sexual behaviour group**

“Q157. [if Q155=2] How many steady male partners have you had anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 or more”

“Q165. [if Q163=2] How many non-steady partners did you have anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 12=11-20 13=21-30 14=31=40 15=41-50 16=More than 50”

For both the question on steady and non-steady partners, we made use of the midpoint for each categorical response and added the two resulting values for each MSM together to determine the average number of partners for that individual. For the last category of each question (more than 10 steady partners and more than 50 casual partners) we used the shape of the long-tailed partner distributions to estimate the average number of partners for those who answered in this final range (11.85 and 64.5 for respectively). This process indicated an average number of partners for all MSM of 7.4.

I used the distribution of total partners to determine a cut-off for defining the high and low risk group at 15 partners in the last year, based on the shape of the histogram in figure 3.2, with the cut-off occurring before the second localised peak in total partner numbers. Using this cut-off 82.6% of MSM fall into the low risk group and 17.4% in the high-risk group. With this split, the average number of partners in the last year was 2.9 in the low risk group and 29.1 in the high-risk group.

![Figure 3.2 - Histogram of the distribution of total sexual partners in the last year](image)
Calculation of relative risk (risk ratio) of HIV and HCV transmission due to injecting drugs and fisting between low and high risk group

I firstly find the prevalence of these activities from EMIS.

“Q221. Have you ever injected any drug other than anabolic steroids or medicines? 1=No, never 2=Yes, within the last 12 months 3=Yes, more than 12 months ago”

Percentage of low risk MSM reporting injecting drug use in last 12 months - 1.0% (0.8-1.1%)
Percentage of high risk MSM reporting injecting drug use in last 12 months - 3.6% (3.0-4.2%)

“Q174. When did you last put your hand into a man’s rectum (do the fist-fucking)?”

Percentage of low risk MSM reporting fisting (receptive) in last 12 months - 8.6% (8.0-9.0%)
Percentage of high risk MSM reporting fisting (receptive) in last 12 months - 21.1% (19.7-22.7%)

“Q175. When did you last have a man’s hand in your rectum (get fist-fucked)?”

Percentage of low risk MSM reporting fisting (insertive) in last 12 months - 14.0% (13.2-14.6%)
Percentage of high risk MSM reporting fisting (insertive) in last 12 months - 38.7% (37.0-40.6%)

Odds ratios from previously published studies have considered the degree to which HIV and HCV acquisition risk is elevated amongst MSM reporting these risk behaviours

Added risk of HIV acquisition from injecting drugs in last 12 months— OR 2.23 (1.49-3.33)\textsuperscript{145}
Added risk of HCV transmission from injecting drugs in the last 12 months— OR 2.05 (0.72-5.82)\textsuperscript{170}
Added risk of HIV acquisition from fisting (receptive) in last 12 months— OR 3.10 (1.46, 6.60)\textsuperscript{166}
Added risk of HIV acquisition from fisting (insertive) in last 12 months— OR 1.58 (0.85, 2.95)\textsuperscript{166}
Added risk of HCV acquisition from fisting (receptive) in last 12 months— OR 4.75 (2.14-10.57)\textsuperscript{63}
Added risk of HCV acquisition from fisting (insertive) in last 12 months— OR 5.53 (2.59-11.81)\textsuperscript{63}

Combining these multiplicatively gives us an estimate of the average amount these behaviours as a whole may be elevating HIV and HCV acquisition in the high risk group compared to the low risk group. The following calculation is used to estimate the combined increased acquisition risk for HIV and HCV in the low and high risk groups:
Elevated acquisition risk in low risk group=$\sum$(Prevalence of Activity in Low group x Activity OR)
Elevated acquisition risk in low risk group=$\sum$(Prevalence of Activity in High group x Activity OR)

The summations are over the different risk behaviours – injecting drug use, insertive and receptive fisting. To estimate the increased relative risk in high risk MSM due to these behaviours, the elevated acquisition risk in high risk MSM is divided by the elevated acquisition risk in low risk MSM. To estimate the likely uncertainty range around the relative risk for HIV and HCV, we randomly sample (n=100,000) from the uncertainties ranges using a uniform distribution for the ORs and proportions reporting each risk behaviour, and for each set of sampled values re-estimate the relative risk. This gives the following ranges for HIV and HCV:

\[ R_{HIV} = 2.69 \ (2.33-3.04) \]
\[ R_{HCV} = 2.71 \ (2.36-3.06) \]

Given the similar values for each infection, we assume a point value of \( R = 2.7 \) for increased risk and vary both equally in the sensitivity and uncertainty analyses.

**Like-with-like mixing by risk group**

Little data exists on the degree to which like with like mixing occurs amongst MSM in the UK based on the number of sexual partners an individual has within a year. However we attempted to make use of data from EMIS from Q182 which asks about where an individual met their last sexual partner. This was done to see if MSM belonging to either risk group mainly meet partners in venues more often frequented by other of the same risk.

“Q182. Where did you first meet him? 1=A gay community centre, gay organisation or gay social group 2=A gay café or gay bar 3=A gay disco or nightclub 4=A backroom of a bar, gay sex club, a public gay sex party 5=A gay sex party in a private home 6=A gay sauna 7=A porn cinema 8=A cruising location (street, roadside service area, park, beach, baths, lavatory) 9=A website for gay or bisexual men 10=Elsewhere”
For our calculation we firstly define:

\( p_j \) as the number of partners per year in the high or low risk group.

\( N_j \) as the proportion of the population in the high or low risk group.

\( V_j^x \) as the proportion of individuals from the high or low risk group, who met their last partner in venue \( x \) from the answer selections above.

I exclude venues 9 as it is impossible to tell how MSM will mix based on their online information from our data set, and whether it will be preferentially or not. For example hook-up apps may cause high risk individuals to mix preferentially and websites for MSM seeking relationships may also promote mixing between MSM with less partners. We also exclude 10 as we don’t have specific information about the venue type. Venues 1-8 however we can assume that once present, will ensure even mixing for all individuals there.

If we define that \( \text{mix}^{\text{risk}}_{jj'} \) as the probability that an individual of risk group \( j \) will mix with an individual of risk group \( j' \), then \( \text{mix}^{\text{risk}}_{jj'} \) can be estimated as follows:

\[
\text{mix}^{\text{risk}}_{jj'} = \sum_{x=1:8} V_j^x \left( \frac{V_j^x p_j N_j}{V_L^x p_L N_L + V_H^x p_H N_H} \right)
\]

Using this equation we therefore predict with our EMIS data that:

\[
\begin{align*}
\text{mix}^{\text{risk}}_{HH} &= 0.7012 \\
\text{mix}^{\text{risk}}_{HL} &= 0.2988 \\
\text{mix}^{\text{risk}}_{LH} &= 0.6643 \\
\text{mix}^{\text{risk}}_{LL} &= 0.3357
\end{align*}
\]

Based on the overall frequency of partnerships provided by MSM from the low and high risk group, we expect that:

\[
\begin{align*}
\text{mix}^{\text{risk}}_{HH} &= 0.6898 \\
\text{mix}^{\text{risk}}_{HL} &= 0.3102 \\
\text{mix}^{\text{risk}}_{LH} &= 0.6898 \\
\text{mix}^{\text{risk}}_{LL} &= 0.3102
\end{align*}
\]
So, to calculate the proportion of MSM who preferentially mix by risk status \((b\), as defined earlier) we use the equations:

\[
\begin{align*}
    mix_{HH}^{\text{risk}} &= b + (1 - b)0.6898 \\
    mix_{HL}^{\text{risk}} &= (1 - b)0.3102 \\
    mix_{LH}^{\text{risk}} &= (1 - b)0.6898 \\
    mix_{LL}^{\text{risk}} &= b + (1 - b)0.3102
\end{align*}
\]

The closest fit we have to the data is when \(b = 0.03675\) - so an estimated 3.7% of MSM preferential mix by risk status.

However, due to the fact that 56% of individuals said they met their last partner on the internet (people often state their sexual preferences and risk behaviour attracting similar partners)\(^{66}\). Preferential mixing by risk status is likely to be greater than the 3.7% we estimated from physical venues. To this end and we assumed a conservative but larger risk-mixing parameter based on 20% of MSM preferentially mix by risk status. However to balance this assumption, we explored its potential role through uncertainty and sensitivity analysis.

**Biological parameters**

The remaining parameters of our model refer to the biological aspects or medical progression of HCV and HIV both in cases of mono and co-infection. This includes: death rates; disease progression rates; diagnosis rates; frequency of screening; efficacy of treatment; and adjustments to these rates and parameters based on the complications of HIV/HCV co-infection. We have previously introduced all of these parameters through-out chapter 2, however a full list of all these parameters along with all other model parameters can be seen in table 3.3 with comments on the derivation and details of usage where appropriate.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow and Outflow for the model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of initiation of sexual activity</td>
<td>15</td>
<td>EMIS</td>
<td>EMIS data indicates that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Exit age for the model due to sexual cessation</td>
<td>65</td>
<td>EMIS</td>
<td>EMIS data indicates that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Standard exit rate</td>
<td>0.02</td>
<td>EMIS</td>
<td>1/(period of sexual activity) = 1/50 = 0.02</td>
</tr>
<tr>
<td>Inflow of population to the model</td>
<td>0.02</td>
<td>EMIS</td>
<td>A steady population was assumed in absence of HIV mortality and so we equated the inflow rate to the exit rate.</td>
</tr>
<tr>
<td>Excess death rate due to chronic HCV mono-infection</td>
<td>0.0014</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Excess death rate due to mono-infection with HIV untreated</td>
<td>0.089</td>
<td>57</td>
<td>Untreated HIV in MSM results in 11.2 (10.4-12.2) years until death. Death rate is the reciprocal.</td>
</tr>
<tr>
<td>Decreased mortality hazard ratio for HIV mono-infection due to HIV treatment</td>
<td>0.29</td>
<td>57,184</td>
<td>If infected with HIV but on treatment expected to live to 73, so 38 years compared to 11.2 without HAART. 11.2/38</td>
</tr>
<tr>
<td>Excess death rate due to HIV for HIV-HCV co-infection with no HIV treatment</td>
<td>0.089</td>
<td>57</td>
<td>Meta-analysis of studies of co-infection death rates, 10 pre-HAART, 27 post HAART suggested that pre-HAART death rate largely only affected by HIV progression. So then we defer to the death rate for when HIV in untreated.</td>
</tr>
<tr>
<td>Excess death rate due to HIV for HIV-HCV co-infection with no HIV treatment</td>
<td>0.0035</td>
<td>7,286</td>
<td>2.5 times higher than the excess death rate in HCV mono-infected individuals = 2.5*0.0014</td>
</tr>
<tr>
<td>Excess death rate due to HIV for HIV-HCV co-infection with ART treatment</td>
<td>0.00238</td>
<td>7,286</td>
<td>1.7 times higher than the excess death rate in HCV mono-infected individuals 1.7*0.0014</td>
</tr>
<tr>
<td>HCV related parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HCV</td>
<td>Fit to Model</td>
<td>-</td>
<td>Meta-analysis of new direct acting antiviral treatments in various combinations. Point estimate used in this case for easy comparison of interventions over different scenarios.</td>
</tr>
<tr>
<td>Efficacy of HCV treatment</td>
<td>90%</td>
<td>343</td>
<td></td>
</tr>
<tr>
<td>Spontaneous clearance probability for HCV in HIV negative MSM</td>
<td>0.25</td>
<td>193</td>
<td>A meta-analysis of studies. However looking at specifically males 36/181 cleared the virus.</td>
</tr>
<tr>
<td>Odds ratio for spontaneous clearance probability for HCV in HIV positive MSM compared to HIV negative MSM</td>
<td>0.68</td>
<td>11111269</td>
<td>Clearance rates of HIV positive MSM versus HIV negative MSM, Found to be 0.15 over two different studies, in PWID11111 and MSM. 209</td>
</tr>
<tr>
<td>HIV related parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HIV</td>
<td>Fit to Model</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Increased HIV infectiousness during acute HIV phase</td>
<td>26</td>
<td>121</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, stage of virus estimated for passing on infection, all couples start negative.</td>
</tr>
<tr>
<td>Duration of acute HIV infection</td>
<td>2.9</td>
<td>121</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, infectiousness monitored over the duration of infection.</td>
</tr>
<tr>
<td>OR for transmission of HIV infection on HAART compared to untreated HIV</td>
<td>0.1</td>
<td>55,252</td>
<td>A meta-analysis of varying ART regimes looking at the transmission of HIV virus on treatment.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Proportion of diagnosed MSM on HAART treatment</td>
<td>0.832</td>
<td>UK report of all HIV diagnosed cases, what proportion were receiving treatment that year (2011).</td>
<td></td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>3.2</td>
<td>Modelling approach to back calculate the diagnosis rates for HIV, range for 2010.</td>
<td></td>
</tr>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>2.35</td>
<td>Various estimates from elevated amounts of HCV viral load in those with HIV, plus vertical transmission probability. Lower-end estimate was taken to be cautious, as we acknowledge that higher viral loads might not directly translate to higher infectivity.</td>
<td></td>
</tr>
<tr>
<td><strong>Behavioural parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by HIV diagnosis status</td>
<td>0.352</td>
<td>From EMIS data we see that it is more likely for those of the same HIV status to form partnerships. The parameter is the proportion of partnerships chosen between people of the same HIV status assuming no errors in judging each other’s HIV status. The remainder of partnerships are assumed to be chosen randomly.</td>
<td></td>
</tr>
<tr>
<td>Condom usage between two diagnosed MSM</td>
<td>13.0%</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV status of last partner showed a lower condom usage between partners when the asked participant was HIV diagnosed and assumed their partner was HIV positive.</td>
<td></td>
</tr>
<tr>
<td>Condom usage between other MSM pairings</td>
<td>68.0%</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV status of last partner.</td>
<td></td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>0.7</td>
<td>Analysed data combined from US participants in the EXPLORE trial (1999-2001) public use data set and in the VAX trial (1998-1999) data set. 95% CI shown from source.</td>
<td></td>
</tr>
<tr>
<td>Chance of error when evaluating HIV status of a sexual partner</td>
<td>24.9%</td>
<td>From EMIS participants, the proportion of individuals who make assumptions about partner’s HIV status for reasons which are unlikely to be effective at determining their partner’s HIV status.</td>
<td></td>
</tr>
<tr>
<td>Proportion of individuals in the Low risk group</td>
<td>82.6%</td>
<td>I used EMIS to split the population into low and high risk based on the number of sexual partners for anal intercourse &gt;15 in the last year.</td>
<td></td>
</tr>
<tr>
<td>Proportion of individuals in the High risk group</td>
<td>17.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of partners for anal intercourse. (When heterogeneity is turned on, low and high risk group in brackets)</td>
<td>7.4 [2.9, 29.1]</td>
<td>From EMIS data, within the low and high groups we formed we averaged the number of sexual partners in each group shown.</td>
<td></td>
</tr>
<tr>
<td>Increased overall risk ratio of HIV and HCV transmission due to injecting drugs and fisting between low and high risk group</td>
<td>2.7</td>
<td>Using EMIS data to assess the prevalence of fisting and IDU in our population in the last year combined with estimates for the increased risk these pose to HIV and HCV acquisition, we compared the two risk groups to see the difference in risk they had associated with these factors. CI is the lowest and highest chance calculated from EMIS data and OR of risky behaviours from literature.</td>
<td></td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by risk behaviour category</td>
<td>0.2</td>
<td>Using EMIS data we assessed where individuals in each risk group meet their partners, to see if it was more likely for individuals in the same risk group to mix more often.</td>
<td></td>
</tr>
</tbody>
</table>

*Time unit is years unless otherwise specified.*

Table 3.3 Model parameters with ranges and details of estimation included.
3.2.3 Model calibration and scenarios

For each different behavioural and biological risk factor scenario (detailed below), the model was calibrated to the stable 2010 prevalence of 5% HIV among MSM and a chronic HCV prevalence of 10% amongst HIV infected MSM. The model was run with a non-least squares fitting algorithm which took point values of all other parameters relevant to the scenario shown in table 3.4, except the transmission parameters for HCV and HIV which were used to fit the simulation. This approach gives a simplified characterisation of the HIV and HCV epidemics among MSM in the UK. We did not fit the HCV prevalence amongst HIV-uninfected MSM. However, we explored several scenarios involving the inclusion of various biological and behavioural factors to see how they affected the HCV prevalence amongst HIV-uninfected MSM while for each scenario assuming a 10% HCV prevalence amongst HIV infected MSM:

1. **Baseline**: No effect of HIV infection on HCV progression, transmissibility or spontaneous clearance; no heterogeneity in sexual risk behaviour or HIV preferential mixing among MSM.

2. **Biological factors only**: Infection with HIV reduces HCV spontaneous clearance probability, increases HCV-related mortality, and increases HCV infectivity.

3. **Mixing by HIV status with biological factors**: MSM select partners preferentially based on HIV status with errors in judgement, with an additional sub-scenario assuming less condom usage among partnerships where HIV diagnosed individuals think their partner is also HIV positive (irrespective of whether right or not). Biological factors included as above.

4. **Heterogeneity in sexual risk behaviour with biological factors**: Heterogeneity in sexual risk behaviour based on number of casual partners. Two additional sub-scenarios further assume that a) MSM select partners preferentially based on risk group, or b) MSM select partners preferentially based on risk and assume further elevated transmission risk associated with high risk MSM based on their higher prevalence of injecting drugs and fisting. Biological factors included as above.

5. **All factors**: Mixing by HIV status and heterogeneity in sexual risk included as described above with all associated effects from previous scenarios. Biological factors included as above.
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description (*/** indicates values shown for different sub-scenarios in figure 1 and 5 and +/-100% values used in figure 3 and 6)</th>
<th>HCV mono-infection excess annual death rate</th>
<th>Co-infection excess annual death rate without HAART</th>
<th>Co-infection excess annual death rate on HAART</th>
<th>RR for HCV infectivity if HIV+ compared to if HIV-</th>
<th>High/low risk partner ratio</th>
<th>High/low risk fisting/IDU risk ratio</th>
<th>Proportion MSM mixing by HIV Status</th>
<th>Error in HIV-status judgement of sex partners</th>
<th>High/low risk condom use ratio</th>
<th>Proportion MSM mixing by risk status</th>
<th>RR of spontaneous clearance if HIV+ compared to HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No effects present</td>
<td>0</td>
<td>0.089 (HIV related death rate)</td>
<td>0.0258 (HIV related death rate)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Biological factors</td>
<td>HCV death rates and HCV spontaneous clearance and infectivity are dependent on HIV status</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>Mixing by HIV status</td>
<td>Biological factors with MSM preferentially selecting partners by HIV status, and sub-scenario with less condom use in assumed HIV+ pairings* plus error in judgements of HIV status</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>Heterogeneity in sexual risk behaviour</td>
<td>Biological factors with greater sexual partners amongst high risk MSM. Sub-scenarios consider effects of MSM selecting partners based on risk behaviour and include risk from fisting or IDU**</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>All factors</td>
<td>All the effects from the other scenarios</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35</td>
<td>10.0</td>
<td>10.0</td>
<td>2.7</td>
<td>35.2%</td>
<td>24.9%</td>
<td>0.2 [0, 0.4]</td>
<td>0.68 [1, 0.36]</td>
</tr>
</tbody>
</table>

Table 3.4 - Parameterization of the scenarios with point values shown for each model. Sub-scenarios within the main scenarios take the parameter values corresponding to the values given by * and ** in the table where relevant.
3.2.4 Model analyses and sensitivity analyses

Impact on the HCV ratio

To explore the impact of these scenarios on the relative HCV burden among HIV positive MSM, we define the “HCV ratio” as the chronic prevalence of HCV in HIV positive MSM divided by the chronic prevalence of HCV in HIV negative MSM. We firstly use point values for each parameter as in table 3.4 and assess whether each scenario produces a HCV ratio commonly observed in the UK and other settings (HCV ratio >5). Then, to test the model’s sensitivity to parameter variation, for scenario 5 (All factors included), we undertook a univariate sensitivity analysis where we varied each parameter individually across +/-100% of their point value, and assessed the effect on the HCV ratio. These wide parameter uncertainty ranges were used to account for unknown biases and uncertainties in the data, with the same range being assumed for each parameter to see how each affected the results over the same relative range. We then performed bivariate sensitivity analyses on key parameters identified at the univariate level, quantifying their importance for three different levels of error in judgement of HIV status of sexual partners (-100%, 0% and +100% of point value).

Impact on HCV treatment-as-prevention initiatives

I also explored the impact of HCV treatment-as-prevention for the different scenarios. For each, we assessed the 10-year decrease in chronic HCV prevalence amongst HIV positive MSM and all MSM achieved for an illustrative HCV treatment intervention that annually treated 10% of HIV diagnosed HCV co-infected MSM, assuming a 90% SVR with HCV DAAs. By also sampling 5000 parameter sets including all those varied within our univariate sensitivity analysis undertaken on scenario 5, we considered the effect of these variations on the HCV ratio and the impact of the illustrative HCV treatment-as-prevention strategy. Lastly, for scenario 5 (All factors), we individually varied key parameters across +/-100% of the point value to assess their influence on the reduction in chronic HCV prevalence achieved with treatment.
3.3 Results

3.3.1 HCV Ratio Analysis

Model projections of the HCV ratio for the different scenarios in table 3.4 are shown in figure 3.3. If no biological or behavioural factors are included (Scenario 1), the predicted HCV ratio is low but greater than one (1.39) due to MSM entering the model being susceptible to both diseases, so creating an increased proportion of HIV negative MSM without HCV. Including biological factors only (Scenario 2) marginally elevates the HCV ratio (1.41) because the greater HCV transmissibility in HIV-HCV co-infected MSM increases HCV transmission in both HIV negative and positive MSM almost equally. Similarly, including preferential mixing by HIV status (Scenario 3) cannot reproduce the high HCV ratio observed in the UK (HCV ratio of 5-20), with modelling projecting an HCV ratio of 1.7, which increases to 2.2 with inclusion of lower condom use in partnerships where HIV diagnosed individuals assume their partner is HIV positive.

![Diagram showing modelled HCV ratio for different scenarios](image)

Figure 3.3 - Modelled HCV Ratio for over multiple scenarios (ratio of HCV chronic prevalence among HIV positive compared to HIV negative MSM) incorporating different biological and/or behavioural factors as detailed in table 3.4. *These scenarios also include the biological factors. IDU denotes injecting drug use.

In contrast, higher and more commonly observed HCV ratios (>5) are achieved through including heterogeneity in sexual risk behaviour (scenario 4). For instance, stratifying MSM in to low and high risk groups based on the number of casual partners, with greater injecting drug use and fisting among high risk individuals, and preferential mixing between these groups produces a HCV ratio of 9.7.
Lastly, combining all behavioural and biological factors (scenario 5) substantially amplifies the HCV ratio to 19.7, with different factors acting synergistically to transmit HCV amongst HIV positive MSM but not HIV negative MSM.

3.3.2 Univariate and bivariate sensitivity analyses on the HCV ratio

Univariate variations of parameters in scenario 5 around their point values (+/-100% - table 3.4) identified four key parameters that substantially effect the HCV ratio (figure 3.4): (1) proportion of individuals preferentially mixing by HIV status (HCV ratio varies from 9.7-43.9); (2) error in HIV status judgements (HCV ratio varies 16.2-24.4); (3) ratio difference in numbers of partners between low and high risk MSM groups (HCV ratio varies 3.4-28.6); and (4) ratio difference in frequency of ‘risky’ behaviours between low and high risk MSM groups (HCV ratio varies 8.3-33.5). Parameters that did not affect the HCV ratio as significantly are shown in figure 3.5.

Figure 3.4 - Effect of univariate changes in individual parameters on the HCV ratio for the “All effects” scenario 5. All other parameters are set to their point values in table 3.4. Only those parameters that markedly affect the HCV ratio are shown. Numbers shown on x-axis are -100% of the point value, the point value and +100% of point value.
The bivariate sensitivity analysis explored the relationship between the four most influential parameters from the univariate analysis (figure 3.6). The two risk heterogeneity parameters were varied simultaneously, forming one combined measure. The HCV ratio is highly sensitive to levels of heterogeneity in sexual risk behaviour and preferential mixing by HIV status which also amplify each other. Indeed, the figures illustrate that HCV ratios of 5-20 are possible with high levels of risk heterogeneity alone, or moderate levels of both preferential mixing by HIV status and risk heterogeneity with any level of error in HIV status judgements. Greater error in HIV status judgements dampens the HCV ratio.
Figure 3.6 - Contour maps showing how the HCV ratio is affected by both the level of HIV preferential mixing and sexual risk heterogeneity for three levels of error in judging the HIV status of a sexual partner: (A) zero error (e=0%), (B) medium error (e=25%), (C) and high error (e=50%). All other parameters are set to their point values in table 3.4. Sexual risk heterogeneity is the simultaneous variance of the ratio in the average number of partners between the low and high risk groups and the additional relative risk for HCV transmission in high risk MSM due to risky sexual behaviours, from -100% to +100% of their estimated point values, which vary respectively from 1 at -100% to 20.0 at +100% and 1 at -100% to 5.4 at +100%.

3.3.3 Impact of HCV treatment-as-prevention

Annually treating 10% of HIV diagnosed HCV co-infected MSM for HCV over 10 years reduces HCV chronic prevalence among HIV positive MSM by a relative 40.3-50.3% across the different scenarios (Figure 3.7). However, impact among the entire MSM population varies markedly, from a relative reduction in chronic HCV among MSM of 3.5% for scenario 1 to 29.3% for scenario 5 (Figure 3.7). Figure 3.8 illustrates this effect further with the HCV ratio having a relatively small influence on the HCV treatment-as-prevention impact among HIV positive MSM (Figure 3.8), but a large influence amongst all MSM (Figure 3.8). At higher HCV ratios, more of the epidemic is concentrated among HIV positive MSM, so focussing treatment efforts on this population effectively combats the epidemic among all MSM overall. Univariate variations in parameters that have a large effect on the HCV ratio also substantially affect the impact of HCV treatment amongst HIV positive MSM on the overall HCV epidemic (figures 3.9 and 3.10).
Figure 3.7 - Impact of HCV treatment on the relative reduction in HCV chronic prevalence(%) among (A) HIV positive MSM and (B) all MSM, achieved by treating 10% of HIV diagnosed MSM with HCV per year for 10 years. Projections assume the point value of parameters for each scenario in table 3.4 and assume 90% HCV treatment efficacy. *These scenarios also include the biological factors.
Figure 3.8 - Effect of variations in the HCV ratio on the impact of HCV treatment-as-prevention (% relative reduction in chronic HCV prevalence at 10 years when treating at a rate of 10% of HIV diagnosed HCV co-infected MSM annually, y-axis) among (A) HIV positive MSM, and (B) all MSM. We assume 90% HCV treatment efficacy, and uniformly sampled other parameters randomly between +/-100% of their point values.
Figure 3.9 - Effect of univariate changes in individual parameters on the impact of HCV treatment on reducing HCV chronic prevalence in HIV positive MSM within the “All effects” scenario. All other parameters are set to their point values unless varied. Numbers shown on x axis are -100% of the point value, the point value and +100% of point value.
Figure 3.10 - Effect of univariate changes in individual parameters on the impact of HCV treatment on reducing HCV chronic prevalence in all MSM within the “All effects” scenario. All other parameters are set to their point values unless varied. Numbers shown on x axis are -100% of the point value, the point value and +100% of point value.
3.4 Discussion

3.4.1 Overview

We find biological factors alone (lower spontaneous clearance rate and higher HCV infectivity and mortality amongst HIV infected MSM) are unable to explain why the HCV epidemic is concentrated among HIV positive MSM. Instead, we suggest that behavioural factors (heterogeneity in sexual risk behaviour alone or combined with preferential mixing by HIV status) are highly likely to account for the higher HCV burdens among HIV positive MSM. Thus, HCV infection and HIV co-infection should be seen as a marker of high sexual risk behaviours, which are preferentially undertaken within partnerships with other HIV positive MSM. This is likely to have been aided by the scale-up of effective HIV treatment improving the survival of higher-risk MSM, paired with possible increases in risk behaviour due to “treatment optimism”.

Importantly, these results positively highlight the large impact we could have treating HIV-positive MSM with DAAs, reflecting the 50% reduction in incidence observed in a Dutch cohort between 2014 and 2016 after DAAs become available in 2015. But also that changes in sexual behaviour or mixing patterns could reshape the HCV epidemic. For example, decreases in preferential mixing by HIV status could occur due to reductions in perceived risk resulting from widespread ART or PrEP use reducing HIV infectivity and susceptibility, which could increase HCV transmission amongst HIV negative MSM. Alternatively, fewer high risk MSM acquiring HIV (due to PrEP) may also raise the likelihood of HCV transmission among HIV negative MSM, although this may be offset by increased HCV monitoring of MSM being prescribed PrEP.

Furthermore, HCV treatment-as-prevention initiatives among HIV diagnosed MSM will have greatest impact on overall levels of HCV transmission in settings where HCV is concentrated among HIV positive MSM, as less of the epidemic is driven by HIV negative MSM. Conversely, settings which have, or develop, a greater burden of HCV among HIV negative MSM would may need to consider HCV treatment to the HIV negative MSM.
3.4.2 Strengths and limitations

Our analysis has a number of limitations. Firstly, we utilized a simplified model of HCV and HIV transmission and ART that was calibrated approximately to the UK without recreating historical epidemic trends, which suggest a slowly increasing HIV and HCV epidemic.\(^{23,179}\) This was because our intention was to explore qualitatively how behavioural and biological factors contribute to HCV epidemic patterns, not make detailed predictions about the epidemics’ trajectory. Importantly, this simplification should not affect the degree to which HCV propagates preferentially amongst HIV positive MSM. A further simplification includes not explicitly modelling the role of fisting or indeed chem-sex. We instead use injection of drugs as an estimate of the risk for this behaviour, and associate both injecting drug use and fisting practices with an increased transmission risk as found in the literature.\(^{63,145,166,170}\) We however acknowledge that this does not include aspects of chem-sex including alternative routes of substance ingestion such as snorting or smoking, which should be examined in future work to improve the accuracy of the model. Furthermore, how these behaviours contribute to the epidemics modelled is somewhat uncertain. For example, the exact biological mechanisms for HCV transmission are unclear and these behaviours are often found to occur in tandem with other routes of HIV and HCV transmission such as sexual intercourse and other risky behaviours. But our model was highly sensitive to the impact of these effects as can be seen in figure 3.9 and 3.10. More detailed treatment of these factors would improve the model accuracy but would first require a detailed examination of HIV and HCV transmission mechanisms. Although injecting drug use is a risk factor for HIV/HCV acquisition amongst MSM, it is unclear the degree to which this is due to injecting drug use itself or co-occurring high risk sexual behaviours. Also, datasets such as EMIS only ask basic questions around the topic of injecting drug use over the last year, thus preventing any explicit modelling of its role in HCV transmission amongst MSM.

Secondly, there exists uncertainty in our parameters and variation across settings, most notably amongst those related to self-reported behavioural data. We performed extensive sensitivity and scenario analyses to explore the effect of varying different behavioural factors. As such, our analyses form a platform from which to explore how variations in parameter assumptions effect observed epidemic patterns and TasP impact. For example, the results are highly sensitive to how many MSM mix preferentially by HIV status, and moderately sensitive to mixing by risk status as seen in figures 3.9 and 3.10, and these may vary by setting or study. Lower mixing by HIV status means HCV is more evenly distributed through all MSM regardless of HIV status and therefore makes treating only HIV positive MSM or HCV have less of an impact on the overall prevalence. However, care should be taken
in generalising our results to low and middle-income settings where limited data suggests lower HCV-co-infection prevalence amongst MSM,\textsuperscript{225} and where differences in sexual behaviour and the underlying HIV and HCV epidemic are likely to heavily effect the HCV epidemic that occurs.

Thirdly, although parameterizing our model to EMIS-UK data produced realistic projections for the HCV ratio (~20), caution should be applied in acknowledging the realism of our model. For instance, the model did not incorporate all sources of HCV infection, such as amongst migrants with historic HCV infection. Conversely, compared to a national probability survey on sexual behaviours, the EMIS-UK dataset was biased towards higher-risk MSM due to their web-based convenience sampling approach\textsuperscript{229}, as well as MSM with higher education levels\textsuperscript{229}. These MSM may have a greater interest in HIV prevention and so increased propensity to mix preferentially by HIV status and use condoms with perceived serodiscordant partners.

Finally, our estimate for increased HCV infectiousness amongst HIV positive MSM is uncertain, although data from vertical transmission studies\textsuperscript{17} suggests our assumption is reasonable. We assume that higher HCV viral load in blood samples amongst HIV positive MSM translates to increased infectivity,\textsuperscript{289} but this may not be the case. However, this should not be a concern because this parameter had little effect on the resulting model projections.

### 3.4.3 Comparison with other modelling studies

To our knowledge, this is the first modelling analysis of the joint epidemics of HIV and HCV among MSM, although many previous analyses have modelled the transmission of HIV and HCV amongst people who inject drugs.\textsuperscript{14,151,315-317} Many previous MSM based analyses have modelled just HIV\textsuperscript{239} and some have also modelled other sexually transmitted co-infections.\textsuperscript{81,108,109,120,239} However, existing HIV and STI co-infection models generally considered different questions, focusing primarily on the degree to which STIs contribute to HIV transmission, and so the possible impact of STI treatment on this. Importantly, existing work has modelled the HCV epidemic amongst HIV diagnosed MSM, and evaluated the impact of scaling-up HCV treatment in this group,\textsuperscript{179,256} with our new analysis supports findings of these previous two studies by indicating that scaling-up HCV treatment among HIV positive MSM could have substantial prevention benefits among this group.\textsuperscript{179} Additionally, it extends previous work by dynamically modelling the transmission of HCV to and from the HIV negative population, assessing how different behavioural and biological factors could result in the observed epidemic patterns, and evaluating the implications for HCV TasP, largely indicating reduced efficacy of HIV diagnosed focused TasP where the HCV is lower.
Chapter 4 Reaching the HCV elimination targets

4.1 Introduction

In chapter 3, we explored the contributors to the global HCV epidemic in MSM, with our modelling suggesting that the polarised pattern of HCV skewed towards HIV infected MSM is due to heterogeneity in risk behaviours and HIV seroadaptive behaviours. In this chapter we compliment the modelling in chapter 3 with the addition of PrEP and a more thorough examination of HCV screening and treatment.

HIV PrEP is a pre-emptive anti-retroviral medication, which has high efficacy for preventing HIV acquisition with many countries currently expanding its availability currently among MSM. However, as occurred with the expansion of ART, there are concerns that PrEP use could result in increased sexual risk taking, and in doing so reduce PrEP’s HIV prevention benefits and increase the transmission rates of other STIs, including HCV. Although current evidence for changes in risk behaviour following the introduction of PrEP are mixed, it is possible that biases in reporting may mask changes in risk behaviour and/or behavioural changes may only occur once PrEP is more established. In general, clinical trials found no increase in the incidence of STIs among MSM PrEP users, although this could differ with full PrEP roll-out. Evidence to support this comes from a recent meta-analysis, discovering that outside clinical trials, PrEP users have an 11-15 times higher incidence of STIs than non-PrEP users. Although this result is not necessarily indicative of risk compensation as there is higher baseline risk among PrEP users, other recent studies seem to give a consistent picture that the incidence of STIs is increasing following initiation of PrEP.

The WHO recently developed a Global Health Strategy to eliminate HCV, aiming to reduce HCV incidence by 90% by 2030. In 2018, the National Health Service (NHS) England announced their commitment to achieving this same goal by 2025. Naturally, current elimination initiatives are attempting to achieve this goal among MSM, but are mainly targeting HIV diagnosed MSM.
This includes previous modelling studies which have considered what is required to eliminate HCV among HIV diagnosed MSM\textsuperscript{175,176}, but none have fully accounted for the HCV transmission dynamics among HIV negative MSM. In this chapter, we use modelling to determine what HCV testing and treatment strategies are needed to reduce the overall incidence of HCV among MSM by 90\% by 2025 or 2030 in the UK, as advocated by NHS-England and WHO. We assess how PrEP and any associated changes in condom use, may affect the impact of these interventions, and evaluate the added benefit of screening and treating MSM on PrEP.

4.2 Methods

4.2.1 Modelling

Model structure

I modify the basic structure of the model detailed in section 3.2.1, adding in two extra stages of disease associated with HCV in order to model the progression through screening and treatment more accurately, plus adding two stages associated with HIV to include the addition of PrEP use.

Formally, the possible stages of HIV infection are therefore set as $S$ for susceptible and not taking PrEP, $SP$ for susceptible and taking PrEP, $A$ for acute HIV infection and not taking PrEP, $AP$ for acute HIV infection and taking PrEP, $C$ for chronic undiagnosed HIV infection and $D$ for diagnosed HIV infection.

I denote the stages of HCV infection (subscript $i$) with $S$ for susceptible, $A$ for acute infection, $C$ for chronic infection and $D$ for diagnosed chronic infection.

I also split the population into low and high risk groups (subscript $j$), $L$ for low risk and $H$ for high risk. So for example $A_{SL}$ denotes low risk group individuals who are acutely infected with HIV, not currently on PrEP and susceptible to HCV. Therefore, each individual at any given time has; a risk group; is in one of four possible HCV states; and one of six possible HIV states. This creates a total of $4 \times 6 \times 2 = 48$ compartments. Individuals are assumed not to change risk group over their lifetime.

For HIV and HCV, the different possible transitions between disease states are shown in figure 4.1. The rates of transitions however may vary depending on factors we will address subsequently.
Individuals enter the model susceptible to HIV and HCV and as non-PrEP users, with a proportion being low risk, and the remainder high risk. As with chapter 3, HIV and HCV transmission occurs at rates related to an individuals’ sexual risk and prevalence of HIV and HCV among their sexual partners and MSM mix preferentially, more commonly choosing partners of the same sexual risk and HIV-status. Depending on the scenario being modelled, HIV negative individuals may initiate using PrEP which confers partial protection to acquiring HIV.\textsuperscript{171,188,196} we also allow for PrEP drop-out and re-initiation.\textsuperscript{171,188} PrEP users are screened quarterly for HIV and upon a positive diagnosis stop using PrEP. This frequent HIV-testing leads to our assumption that PrEP users are diagnosed before reaching the chronic stage of HIV infection.\textsuperscript{204} Conversely, non-PrEP users who acquire acute HIV infection, firstly transition to undiagnosed infection, and are then diagnosed at current UK rates of HIV-testing (with on average 2.3 years between infection and diagnosis).\textsuperscript{210} Acute HIV is assumed to have elevated HIV transmission risk (26-fold),\textsuperscript{121} while 83.2\%\textsuperscript{23} of HIV diagnosed MSM are assumed to be on ART, which reduces HIV transmission risk by 90\%\textsuperscript{55,252} and increases survival 4.4-fold.\textsuperscript{57,184}

Individuals that are newly HCV infected firstly develop acute HCV infection, following which they either develop chronic HCV or spontaneously clear their infection and return to being susceptible. The baseline model assumes HIV negative MSM are diagnosed for HCV based upon symptomatic presentation of chronic HCV, assumed to be between 5-15 years. Conversely, undiagnosed HIV positive MSM only receive testing for HCV following HIV diagnosis, with 88\% of HIV diagnosed MSM being screened annually in the UK for our baseline model.\textsuperscript{179} In the baseline scenario, we assume an average time from diagnosis to completing HCV treatment of 2.2 years, consistent with data from the UK for pre-DAA treatments.\textsuperscript{179} we then consider the impact of improved screening scenarios, which assume different frequencies of HCV screening, and faster linkage-to-treatment following diagnosis (6 months to treatment completion); more consistent with current treatment rates.\textsuperscript{26} This assumes a 3-month waiting time and an HCV treatment duration of 12 weeks, with high cure rates (sustained viral response of 90\%) regardless of HIV-status.\textsuperscript{179} Unlike in chapter 3, MSM failing treatment are retreated at the same rate as initial HCV treatment.
Figure 4.1 - Model schematic for the HIV and HCV model components.

Model equations

To include the additions to the model from section 3.2.1, we denote the average time to spontaneous recovery of HCV $a^{HCV}$ and the chance of spontaneous recovery, $x_k$, which depends on the HIV status $k$ of the individual. Equivalently, people move from the acute phase of HIV at rate $a^{HIV}$ to undiagnosed chronic HIV infection if not on PrEP, but move directly to a diagnosed state of HIV if on PrEP due to consistent three monthly HIV screening.

I also now explicitly denote the rate of HCV diagnosis $d^{HCV}_{kl}$ which depends on the HIV and PrEP status ($l = 0$ for those not using PrEP and $l = 1$ for those using PrEP) of the individual, but can occur at both chronic and acute stages of HCV. However, those with acute or undiagnosed HIV infection are assumed to not be screened for HCV as this would occur in tandem with an HIV test, so it does not make sense for these individuals to be only diagnosed for HCV alone. Similarly, the rate of HIV diagnosis $d^{HIV}_l$ depends on whether the individual is currently on PrEP or not.
$r_{kl}$ is the rate at which MSM are successfully treated for HCV once diagnosed, which returns HCV diagnosed MSM to the HCV susceptible category. At baseline we assume this rate is equal in all MSM. However, over our intervention scenarios we vary this parameter by the HIV infection/diagnosis status and PrEP status of MSM, to reflect different HCV treatment strategies employed.

For MSM not currently on PrEP, but still susceptible to HIV, we denote the rate of PrEP uptake as $\pi_j$. For MSM who are on PrEP, we similarly have a cessation rate of PrEP use, which we denote by $\eta_j$. Both of these parameters depend on the risk group of the MSM. This is because the coverage of PrEP use for each risk group must reach different equilibrium values after the scale-up of PrEP. All parameters used in our modelling equations are listed in Table 4.1 or ease of referral.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscripts</td>
<td>Denotes the risk group. This can take values $L$ for low risk and $H$ for high risk.</td>
</tr>
<tr>
<td>$j$</td>
<td>Denotes HIV status. This can take the values 0 for HIV negative, 1 for HIV positive but undiagnosed and 2 for HIV diagnosed. Sometimes we use $u$ to denote either $k = 0$ or 1 and $d$ to denote $k = 2$.</td>
</tr>
<tr>
<td>$k$</td>
<td>Denotes current PrEP usage. This can take values 0 for not using PrEP and 1 for using PrEP.</td>
</tr>
<tr>
<td>$l$</td>
<td>Denotes the risk group. This can take values $L$ for low risk and $H$ for high risk.</td>
</tr>
<tr>
<td>Parameters</td>
<td></td>
</tr>
<tr>
<td>$a^{HCV}$</td>
<td>The rate at which HCV infections transitions from acute to chronic.</td>
</tr>
<tr>
<td>$a^{HIV}$</td>
<td>The rate at which HIV infections transitions from acute to chronic.</td>
</tr>
<tr>
<td>$d^{HCV}_{kl}$</td>
<td>The rate at which individuals with HCV are diagnosed.</td>
</tr>
<tr>
<td>$d^{HIV}_l$</td>
<td>The rate at which individuals with HIV are diagnosed.</td>
</tr>
<tr>
<td>$r_{kl}$</td>
<td>The rate of successful treatment of individuals with diagnosed HCV, returning them to being susceptible to HCV.</td>
</tr>
<tr>
<td>$x_k$</td>
<td>The proportion of individuals who spontaneously clear HCV infection.</td>
</tr>
<tr>
<td>$\pi_j$</td>
<td>The rate at which individuals currently on PrEP stop using PrEP.</td>
</tr>
<tr>
<td>$\eta_j$</td>
<td>The rate at which HIV susceptible people start using PrEP.</td>
</tr>
<tr>
<td>$\theta_j$</td>
<td>The number of new individuals entering the population per year.</td>
</tr>
<tr>
<td>$\lambda_{jkl}$</td>
<td>The rate at which individuals are infected with HCV.</td>
</tr>
<tr>
<td>$\sigma_{jl}$</td>
<td>The rate at which individuals are infected with HIV.</td>
</tr>
<tr>
<td>$\mu$</td>
<td>The rate at which people leave the model due to aging out of the model.</td>
</tr>
<tr>
<td>$\mu^{HCV}$</td>
<td>The additional death rate due to HCV mono-infection</td>
</tr>
<tr>
<td>$\mu^{HIV}_{Diag}$</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV diagnosed</td>
</tr>
<tr>
<td>$\mu^{HIV}_{Undiag}$</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV undiagnosed</td>
</tr>
<tr>
<td>$\mu^{HIV}_{Diag}$</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV diagnosed</td>
</tr>
<tr>
<td>$\mu^{HIV}_{Undiag}$</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV undiagnosed</td>
</tr>
</tbody>
</table>

Table 4.1 - Parameters included in the differential modelling equations with descriptions.
The overall model equations are as follows, where risk $j = L$ for low risk, $j = H$ for high risk and stages of HCV denoted by index $i$ within a compartment $X_{ij}$ are ($s$ = uninfected, $a$ = HCV acute, $c$ = HCV chronic, $d$ = HCV diagnosed):

**$S$ - Susceptible to HIV and not on PrEP**

\[
\frac{dS_i}{dt} = \theta_j + \rho_{0i}S_{ij} + a^{HCV}x_0S_{Aj} + \eta_jS_{ij} - \pi_jS_i - \sigma_jS_i - \lambda_{j00}S_i - \mu_S S_i
\]

\[
\frac{dS_{Aj}}{dt} = \lambda_{j00}S_{ij} + \eta_jS_{ij} - \pi_jS_{Aj} - \sigma_jS_{Aj} - a^{HCV}x_0S_{Aj} - a^{HCV}(1 - x_0)S_{Aj} - d^{HCV}_{00}S_{Aj} - \mu_A S_{Aj} - \mu_{HCV}S_{Aj}
\]

\[
\frac{dS_{cj}}{dt} = a^{HCV}(1 - x_0)S_{Aj} + \eta_jS_{cj} - \pi_jS_{cj} - d^{HCV}_{00}S_{cj} - \sigma_jS_{cj} - \mu_S S_{cj} - \mu_{HCV}S_{cj}
\]

\[
\frac{dS_{Dj}}{dt} = d^{HCV}_{00}S_{Aj} + d^{HCV}_{00}S_{cj} - \pi_jS_{Dj} - \rho_{0i}S_{Dj} - \sigma_jS_{Dj} - \mu_S S_{Dj} - \mu_{HCV}S_{Dj}
\]

**$SP$ - Susceptible to HIV and on PrEP**

\[
\frac{dSP_{ij}}{dt} = \rho_{0i}SP_{Dj} + a^{HCV}x_0SP_{Aj} + \pi_jSP_{ij} - \eta_jSP_{ij} - \sigma_jSP_{ij} - \lambda_{j01}SP_{ij} - \mu_S SP_{ij}
\]

\[
\frac{dSP_{Aj}}{dt} = \lambda_{j01}SP_{ij} + \pi_jSP_{ij} - \eta_jSP_{Aj} - \sigma_jSP_{Aj} - a^{HCV}x_0SP_{Aj} - a^{HCV}(1 - x_0)SP_{Aj} - d^{HCV}_{01}SP_{Aj} - \mu_S SP_{Aj} - \mu_{HCV}SP_{Aj}
\]

\[
\frac{dSP_{cj}}{dt} = a^{HCV}(1 - x_0)SP_{Aj} + \pi_jSP_{cj} - \eta_jSP_{cj} - d^{HCV}_{01}SP_{cj} - \sigma_jSP_{cj} - \mu_S SP_{cj} - \mu_{HCV}SP_{cj}
\]

\[
\frac{dSP_{Dj}}{dt} = d^{HCV}_{01}SP_{Aj} + d^{HCV}_{01}SP_{cj} + \pi_jSP_{Dj} - \eta_jSP_{Dj} - \rho_{0i}SP_{Dj} - \sigma_jSP_{Dj} - \mu_S SP_{Dj} - \mu_{HCV}SP_{Dj}
\]

**$A$ - Acute HIV infection and not on PrEP**

\[
\frac{dA_{ij}}{dt} = \rho_{10}A_{Dj} + \sigma_jA_{ij} + a^{HIV}x_0A_{Aj} - \lambda_{j10}A_{ij} - a^{HIV}A_{ij} + \eta_jA_{ij} - \mu_A A_{ij} - \mu_{HIV}A_{ij}
\]

\[
\frac{dA_{Aj}}{dt} = \sigma_jA_{ij} + \lambda_{j10}A_{ij} - a^{HIV}A_{ij} - a^{HIV}x_1A_{Aj} - a^{HIV}(1 - x_1)A_{Aj} + \eta_jA_{Aj} - \mu_A A_{Aj} - \mu_{CO} A_{Aj}
\]

\[
\frac{dA_{cj}}{dt} = a^{HIV}(1 - x_1)A_{Aj} + \sigma_jA_{cj} - a^{HIV}A_{cj} + \eta_jA_{cj} - \mu_A A_{cj} - \mu_{CO} A_{cj}
\]

\[
\frac{dA_{Dj}}{dt} = \sigma_jA_{Dj} - \rho_{10}A_{Dj} + \eta_jA_{Dj} - \mu_A A_{Dj} - \mu_{CO} A_{Dj}
\]
\( A^P \) - Acute HIV infection and on PrEP

\[
\frac{dA^P_{Sj}}{dt} = r_{11}A^P_{Dj} + \sigma_{1j}S^P_{Sj} + a^{HCV}_{1}A^P_{A_{j}} - \lambda_{j11}A^P_{Sj} - d^{HIV}_{1}A^P_{Sj} - \eta_{j}A^P_{Sj} - \mu A^P_{Sj} - \mu^{Undiaq}_{CO} A^P_{Sj}
\]

\[
\frac{dA^P_{Aj}}{dt} = \sigma_{j1}S^P_{Aj} + \lambda_{j11}A^P_{Sj} - d^{HIV}_{1}A^P_{Aj} - a^{HCV}_{1}A^P_{A_{j}} - a^{HCV}(1 - x_{1})A^P_{A_{j}} - d^{HCV}_{11}A^P_{A_{j}} - \eta_{j}A^P_{Aj} - \mu A^P_{Aj} - \mu^{Undiaq}_{CO} A^P_{Aj}
\]

\[
\frac{dA^P_{Cj}}{dt} = a^{HCV}(1 - x_{1})S^P_{Aj} + \sigma_{j1}S^P_{Cj} - d^{HIV}_{1}A^P_{Cj} - d^{HCV}_{11}A^P_{Cj} - \eta_{j}A^P_{Cj} - \mu A^P_{Cj} - \mu^{Undiaq}_{CO} A^P_{Cj}
\]

\[
\frac{dA^P_{Dj}}{dt} = a^{HCV}_{11}A^P_{Aj} + d^{HCV}_{11}A^P_{Cj} + \sigma_{j1}S^P_{Dj} - d^{HIV}_{1}A^P_{Dj} - r_{11}A^P_{Dj} - \eta_{j}A^P_{Dj} - \mu A^P_{Dj} - \mu^{Undiaq}_{CO} A^P_{Dj}
\]

C - Chronic HIV infection that is undiagnosed

\[
\frac{dC_{Sj}}{dt} = a^{HIV}_{1}A_{Sj} + r_{10}C_{Dj} + a^{HCV}_{1}A_{Cj} - \lambda_{j10}C_{Sj} - a^{HIV}_{1}C_{Sj} - \mu C_{Sj} - \mu^{Undiaq}_{CO} C_{Sj}
\]

\[
\frac{dC_{Aj}}{dt} = \lambda_{j10}C_{Sj} + a^{HIV}_{1}A_{Aj} - a^{HCV}_{1}A_{Cj} - a^{HCV}(1 - x_{1})A_{Cj} - a^{HIV}_{1}C_{Aj} - \mu C_{Aj} - \mu^{Undiaq}_{CO} C_{Aj}
\]

\[
\frac{dC_{Cj}}{dt} = a^{HCV}(1 - x_{1})C_{Aj} + a^{HIV}_{1}A_{Cj} - d^{HIV}_{1}C_{Cj} - \mu C_{Cj} - \mu^{Undiaq}_{CO} C_{Cj}
\]

\[
\frac{dC_{Dj}}{dt} = a^{HIV}_{1}A_{Cj} - d^{HIV}_{1}C_{Dj} - r_{10}C_{Dj} - \mu C_{Dj} - \mu^{Undiaq}_{CO} C_{Dj}
\]

D - Diagnosed chronic HIV infection

\[
\frac{dD_{Sj}}{dt} = r_{20}D_{Dj} + d^{HIV}_{0}C_{Sj} + d^{HIV}_{1}A^P_{Sj} + a^{HCV}_{1}D_{A_{j}} - \lambda_{j20}D_{Sj} - \mu D_{Sj} - \mu^{Diag}_{HIV} D_{Sj}
\]

\[
\frac{dD_{Aj}}{dt} = \lambda_{j20}D_{Sj} + d^{HIV}_{0}C_{Aj} + d^{HIV}_{1}A^P_{Aj} - a^{HCV}_{1}D_{A_{j}} - a^{HCV}(1 - x_{1})D_{A_{j}} - d^{HCV}_{12}D_{Aj} - \mu D_{Aj} - \mu^{Diag}_{CO} D_{Aj}
\]

\[
\frac{dD_{Cj}}{dt} = a^{HCV}(1 - x_{1})D_{Aj} + d^{HIV}_{0}C_{Cj} + d^{HIV}_{1}A^P_{Cj} - d^{HIV}_{12}D_{Cj} - \mu D_{Cj} - \mu^{Diag}_{CO} D_{Cj}
\]

\[
\frac{dD_{Dj}}{dt} = d^{HIV}_{0}C_{Dj} + d^{HIV}_{1}A^P_{Dj} + d^{HIV}_{12}D_{Aj} - r_{20}D_{Dj} - \mu D_{Dj} - \mu^{Diag}_{CO} D_{Dj}
\]
Deriving the mixing matrix

I show the parameters found within our mixing equations for ease of referral in table 4.2.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subscripts</strong></td>
<td></td>
</tr>
<tr>
<td>(j)</td>
<td>Denotes the risk group. This can take values (L) for low risk and (H) for high risk.</td>
</tr>
<tr>
<td>(k)</td>
<td>Denotes HIV status. This can take the values (0) for HIV negative, (1) for HIV positive but undiagnosed and (2) for HIV diagnosed. Sometimes we use (u) to denote either (k = 0) or (1) and (d) to denote (k = 2).</td>
</tr>
<tr>
<td>(l)</td>
<td>Denotes current PrEP usage. This can take values (0) for not using PrEP and (1) for using PrEP.</td>
</tr>
<tr>
<td><strong>Sub-populations</strong></td>
<td></td>
</tr>
<tr>
<td>(N_jk)</td>
<td>(N) Represents the entire population. Presence of subscripts slice the total population by the subscript. For example, (N_j) refers to every member of the population who is in risk category (j).</td>
</tr>
<tr>
<td>(u_0)</td>
<td>Refers to non-PrEP users who are either HIV negative/HIV undiagnosed.</td>
</tr>
<tr>
<td>(u_1)</td>
<td>Refers to PrEP users who are either HIV negative/HIV undiagnosed.</td>
</tr>
<tr>
<td>(d_0)</td>
<td>Refers to HIV diagnosed individuals.</td>
</tr>
<tr>
<td><strong>Parameters</strong></td>
<td></td>
</tr>
<tr>
<td>(M_{j'j}^{Risk})</td>
<td>Denotes the mixing equations for MSM of type (j) with type (j').</td>
</tr>
<tr>
<td>(M_{j'j</td>
<td>k'\ell</td>
</tr>
<tr>
<td>(M_{j'j</td>
<td>k'\ell</td>
</tr>
<tr>
<td>(M_{j</td>
<td>k'\ell</td>
</tr>
<tr>
<td>(b)</td>
<td>The proportion of MSM who mix like with like by risk status (j).</td>
</tr>
<tr>
<td>(p_j)</td>
<td>The average number of partners for MSM in risk group (j).</td>
</tr>
<tr>
<td>(\zeta)</td>
<td>The proportion of MSM who mix like with like by HIV status (serosorting) (k).</td>
</tr>
<tr>
<td>(e)</td>
<td>Chance of a serosorting judgement being incorrect. This leads to random mixing when the judgement is incorrect.</td>
</tr>
<tr>
<td>(c_0) &amp; (c_1)</td>
<td>(c_1) is the protection provided by condom use between a serosorting HIV diagnosed MSM and a partner they also assume is HIV positive. (c_0) is the protection provided by condom use between all other sexual partnerships.</td>
</tr>
<tr>
<td>(y)</td>
<td>This factor represents a modifier for the chance that a sexual encounter involving at least one MSM on PrEP will have a lower chance to use a condom and hence less condom protection provided ((y \leq 1)). However, condom use between any two partners is equal to (c_1) at minimum.</td>
</tr>
</tbody>
</table>

Table 4.2 - Parameters included in the mixing equations with descriptions.

In this chapter, MSM continue to preferentially mix, driven by risk and HIV status, however we have the added complication of including MSM who are using PrEP. To this end, we revisit the process of constructing our mixing equations with this addition in mind, building the mixing equations over the same steps but adapting for PrEP use.
I denote the probability of mixing between two individuals that is only based on their risk group by 
$M_{jj'}^{Risk}$ (one individual from risk group $j$ with their partner from risk group $j'$). $b$ is the proportion of individuals who mix exclusively with partners of the same risk group, with other partnerships assumed to form randomly with all the available population. The random portion of this mixing is weighted by the proportion of all sexual partnerships provided by each risk group. $N_j$ is used to represent the entire population in risk group $j$, $p_j$ is the average number of partners which individuals in risk group $j$ form over a year, and $\delta_{jj'}$ is the kronecker delta function that is equal to 1 when $j = j'$ and equal to 0 otherwise.

$$M_{jj'}^{Risk} = \delta_{jj'}b + (1-b) \sum_{aln} \frac{p_{jj'} N_{jj'} N_n}{p_n N_n}$$

The equations $M_{jkljk'l'}^{HIV}$ represent the probabilities that an MSM in risk group $j$, HIV status group $k$ and PrEP status $l$, forms a sexual partnership with an MSM in risk group $j'$, HIV status group $k'$ and PrEP status $l'$. This probability varies depending on the HIV diagnosis status of the primary individual and their partner.

I denote $N_{jkl}$ as the number of individuals in risk group $j$, HIV status group $k$ with PrEP status $l$. $\zeta$ is the proportion of MSM where they specifically mix to form a partnership with someone of the same HIV status. We weight the chance that each partnership is with a specific subgroup by the number of MSM in that subgroup and their average number of partners. The remaining proportion of MSM ($1 - \zeta$) that do not mix by HIV status are assumed to mix randomly with individuals in all subgroups, again weighted by the number of individuals in each of those MSM subgroups and the average number of partnerships formed by each of those subgroups.

I assume in this model that PrEP users preferentially mix with MSM who they assume to be uninfected with HIV, i.e. undiagnosed HIV positive MSM or HIV susceptible MSM on or off PrEP, and vice versa. They do not preferentially mix with HIV diagnosed MSM. This equates to PrEP users having the same mixing preferences as other HIV negative/undiagnosed MSM.

Firstly, we consider the effect of a proportion $\zeta$ of MSM who prefer to mix only with MSM of the same HIV status (either negative or positive). MSM who are HIV positive but not diagnosed are assumed to prefer mixing with other undiagnosed/susceptible MSM.
This function $M_{j|k|l|k|l}(t)$ then has to be adapted because there is generally judgement errors when individuals choose partners by their assumed HIV status. We adapt $M_{j|k|l|k|l}(t)$ to include a chance of error in choosing a partner of the same HIV status, denoted by $e$. Where there is an error in judgement, the primary individual who intended to mix with a specific type of MSM, will instead mix randomly.

\[
M_{j|u_0, u_0'}(t) = \delta_{j|j'}b \left[ \frac{\zeta - e}{N_{j|0} + N_{j|1}} + \frac{(1 - \zeta) + e}{N_{j|0} + N_{j|1} + N_{j|0}} \right] + (1 - b) \left[ \frac{p_{j|u_0} N_{j|u_0}}{\sum_{alln} p_n (N_{nu0} + N_{nu1})} + \frac{(1 - \zeta) + e}{N_{j|0} + N_{j|1} + N_{j|0}} \right]
\]

This is then finally adapted to give a final function $M_{j|k|l|k|l}(t)$, that also includes the level of protection given by condom use; which varies by pairings of MSM. The parameters $c_0$ and $c_1$ are used to denote these pairing with $c_0$ being the level of condom use between MSM when they are not mixing by HIV status or when undiagnosed MSM are mixing by HIV status, and $c_1$ being the level of condom use between diagnosed MSM when they are mixing by HIV status. In the model, we also have to remember that when an MSM preferentially mixes, they will use condoms with a probability based on the assumption of their partner’s HIV and/or PrEP status, even where this judgement is incorrect. However, our data from EMIS suggested that condom use only differed when diagnosed MSM were mixing by HIV status, and so we only have two levels of condom use defined in the model.

\[
M_{j|u_0, u_0'}(t) = \delta_{j|j'}b \left[ \frac{\zeta - e c_0}{N_{j|0} + N_{j|1}} + \frac{(1 - \zeta) + e c_0}{N_{j|0} + N_{j|1} + N_{j|0}} \right] + (1 - b) \left[ \frac{p_{j|u_0} N_{j|u_0}}{\sum_{alln} p_n (N_{nu0} + N_{nu1})} + \frac{(1 - \zeta) + e c_0}{N_{j|0} + N_{j|1} + N_{j|0}} \right]
\]
To illustrate the use of \( c_1 \) we also show the cases of \( M_{j_0,j'u_0} \) and \( M_{j_0,j'd_0} \)

\[
M_{j_0,j'u_0} = \delta_{j,j'} b \left[ \frac{c_1}{N_{j'u_0}} \sum_{q} \frac{p_{j_0,N_{j'u_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
+ (1 - b) \left[ \frac{c_1}{N_{j'u_0}} \sum_{n} \frac{p_{j_0,N_{j'u_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
M_{j_0,j'd_0} = \delta_{j,j'} b \left[ \frac{c_1}{N_{j'd_0}} \sum_{q} \frac{p_{j_0,N_{j'd_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
+ (1 - b) \left[ \frac{c_1}{N_{j'd_0}} \sum_{n} \frac{p_{j_0,N_{j'd_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right]
\]

To also model the potential risk compensation in the form of a reduction in condom use by PrEP users, we include the modifier \( y \), to allow a reduction in condom use between PrEP users and their partners.

The functionality of \( y \) is described subsequently in the section on condom use and is only applied in cases where one or more partners are using PrEP. With this in mind, other terms in mixing scenario 1 follow similarly and thus the full mixing equations are:

\[
M_{j_0,j'u_0} = \delta_{j,j'} b \left[ \frac{(1 - \zeta)c_0}{\sum_{q} N_{j'u_0}} + \frac{(1 - \zeta)c_0}{N_{j'u_0}} \sum_{n} \frac{p_{j_0,N_{j'u_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
+ (1 - b) \left[ \frac{(1 - \zeta)c_0}{\sum_{q} N_{j'u_0}} + \frac{(1 - \zeta)c_0}{N_{j'u_0}} \sum_{n} \frac{p_{j_0,N_{j'u_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
M_{j_0,j'u_1} = \delta_{j,j'} b \left[ \frac{(1 - \zeta)c_0}{\sum_{q} N_{j'u_0}} + \frac{(1 - \zeta)c_0}{N_{j'u_0}} \sum_{n} \frac{p_{j_0,N_{j'u_1}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
+ (1 - b) \left[ \frac{(1 - \zeta)c_0}{\sum_{q} N_{j'u_0}} + \frac{(1 - \zeta)c_0}{N_{j'u_0}} \sum_{n} \frac{p_{j_0,N_{j'u_1}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
M_{j_0,j'd_0} = \delta_{j,j'} b \left[ \frac{(1 - \zeta)c_0}{N_{j'd_0}} \sum_{q} \frac{p_{j_0,N_{j'd_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right] \\
+ (1 - b) \left[ \frac{(1 - \zeta)c_0}{N_{j'd_0}} \sum_{q} \frac{p_{j_0,N_{j'd_0}}}{\sum_{n} p_{n} (N_{nu_0} + N_{nu_1} + N_{nd_0})} \right]
\]
\[M_{ju1,j'u_0} = \delta_{jj'} b \left[ (\zeta - \zeta e) c_0 y \frac{N_{ju0}}{\sum_{all \ n} N_{juq}} + ((1 - \zeta) + \zeta e) c_0 y \frac{N_{ju0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (\zeta - \zeta e) c_0 y \frac{p_{jj'} N_{j'u_0}}{\sum_{all \ n,q} p_{n} N_{nuq}} + ((1 - \zeta) + \zeta e) c_0 y \frac{p_{jj'} N_{j'u_0}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]

\[M_{ju1,j'u_1} = \delta_{jj'} b \left[ (\zeta - \zeta e) c_0 y \frac{N_{ju1}}{\sum_{all \ n} N_{juq}} + ((1 - \zeta) + \zeta e) c_0 y \frac{N_{ju1}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (\zeta - \zeta e) c_0 y \frac{p_{jj'} N_{j'u_1}}{\sum_{all \ n,q} p_{n} N_{nuq}} + ((1 - \zeta) + \zeta e) c_0 y \frac{p_{jj'} N_{j'u_1}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]

\[M_{ju1,j'd_0} = \delta_{jj'} b \left[ ((1 - \zeta) c_0 y + \zeta e c_1) \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ ((1 - \zeta) c_0 y + \zeta e c_1) \frac{p_{jj'} N_{j'd_0}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]

\[M_{jd_0,j'u_0} = \delta_{jj'} b \left[ ((1 - \zeta) c_0 + \zeta e c_1) \frac{N_{ju0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ ((1 - \zeta) c_0 + \zeta e c_1) \frac{p_{jj'} N_{j'u_0}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]

\[M_{jd_0,j'u_1} = \delta_{jj'} b \left[ ((1 - \zeta) c_0 y + \zeta e c_1) \frac{N_{ju1}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ ((1 - \zeta) c_0 y + \zeta e c_1) \frac{p_{jj'} N_{j'u_1}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]

\[M_{jd_0,j'd_0} = \delta_{jj'} b \left[ (\zeta - \zeta e) c_1 + ((1 - \zeta) c_0 + \zeta e c_1) \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (\zeta - \zeta e) c_1 \frac{p_{jj'} N_{j'd_0}}{\sum_{all \ n} p_{n} N_{nd0}} + ((1 - \zeta) c_0 + \zeta e c_1) \frac{p_{jj'} N_{j'd_0}}{\sum_{all \ n} p_{n} (N_{nu0} + N_{nu1} + N_{nd0})} \right] \]
Condom usage terms

As used in the formulation for $M_{jklj'k'l'}$ above the model parameters $c_0$ and $c_1$ denote the chance an infection will be able to transmit through the protection offered by condom use. This is calculated from the consistency in which a pairing uses a condom and the efficacy of condoms: where $c_1$ is for “HIV diagnosed MSM with an assumed HIV positive partner” $c_0$ for “HIV negative or HIV positive but undiagnosed MSM with any partner or a pairing of a HIV positive MSM with an assumed HIV negative partner”. The efficacy of a condom when used is denoted as $P$ (equal for both HCV and HIV).

I start in the absence of PrEP related risk compensation, by assuming HIV diagnosed MSM with an assumed HIV diagnosed partner are assumed to use condoms with consistency $D$, whereas all other partnerships are assumed to use condoms with equal consistency $U$. The parameters $c_0$ and $c_1$ are therefore defined as:

$$c_0 = 1 - UP$$
$$c_1 = 1 - DP$$

The addition to the above setup is that any pairing involving a person on PrEP with a partner who is not diagnosed for HIV, will have condom usage term $c_0y$. The $y$ factor ($y \geq 1$), is the modifier for the condom term $c_0$. It represents the notion that less condoms may be used by people on PrEP and their partners, as a risk compensation behaviour. The smallest value of $y$ we will allow will result in $c_0y = c_1$ where PrEP users are using condoms at the same consistency as a HIV diagnosed MSM with an assumed HIV positive partner. Alternatively, if $y = 1$, this results in individuals on PrEP using condoms with the same consistency as people who are HIV negative or undiagnosed HIV positive who are not on PrEP.

Forces of infection for HIV and HCV

The forces of infection $\lambda_{jkl}$ for HCV and $\sigma_{jl}$ for HIV also become dependent on PrEP status as well as the sexual risk group and HIV infection/diagnosis status. To recap, the additional biological or risk based influences are denoted:

$\Omega$ is the increased HIV infectiousness of those in the acute phase of HIV,
$\Delta$ is the reduced HIV infectiousness of HIV due to those on HAART,
$\Lambda$ is the increased HCV infectivity of those with HIV,
\( \beta^{HV} \) is the transmission factor for HIV in the chronic phase of infection with no ART treatment. 

\( \beta^{HCV} \) is the transmission factor for HCV.

\( R \) is the additional multiplicative risk factor associated with the high risk group due to more frequent fisting and IDU behaviours.

\( p_L \) and \( p_H \) are the rates of sexual partners for low and high risk MSM.

\( \omega \) is the efficacy of PrEP. Thus the proportion of infections that will not be mitigated by taking PrEP is denoted by \((1 - \omega)\).

For low or high risk \((j = L \text{ or } H)\), HCV infection stage \(n\), the HIV force of infection \( \sigma_{jL} \) is:

\[
\sigma_{L0} = \beta^{HV} p_L \left[ \sum_{all \, j} M_{L,u0j0} \left( \frac{\sum_{all \, n} (\Omega A_{nj} + C_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \, j} M_{L,u0j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) \right] + \sum_{all \, j} M_{L,u0j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right)
\]

\[
\sigma_{L1} = \beta^{HV} (1 - \omega) p_L \left[ \sum_{all \, j} M_{L,u1j0} \left( \frac{\sum_{all \, n} (\Omega A_{nj} + C_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \, j} M_{L,u1j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) \right] + \sum_{all \, j} M_{L,u1j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right)
\]

\[
\sigma_{H0} = \beta^{HV} R p_H \left[ \sum_{all \, j} M_{H,u0j0} \left( \frac{\sum_{all \, n} (\Omega A_{nj} + C_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \, j} M_{H,u0j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) \right] + \sum_{all \, j} M_{H,u0j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right)
\]

\[
\sigma_{H1} = \beta^{HV} (1 - \omega) R p_H \left[ \sum_{all \, j} M_{H,u1j0} \left( \frac{\sum_{all \, n} (\Omega A_{nj} + C_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \, j} M_{H,u1j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right) \right] + \sum_{all \, j} M_{H,u1j1} \left( \frac{\sum_{all \, n} (\Omega A_{nj})}{\sum_{all \, n} (S_{nj} + A_{nj} + C_{nj})} \right)
\]
\[
\lambda_{L0l} = \beta^{HCV} p_L \sum_{all \, j} M_{Lul,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Lul,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Lul,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

\[
\lambda_{L1l} = \beta^{HCV} p_L \sum_{all \, j} M_{Lul,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Lul,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Lul,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

\[
\lambda_{L20} = \beta^{HCV} p_L \sum_{all \, j} M_{Ld0,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,I,Fn=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Ld0,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Ld0,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

\[
\lambda_{H0l} = \beta^{HCV} R_{p_H} \sum_{all \, j} M_{Hu,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hu,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hu,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

\[
\lambda_{H1l} = \beta^{HCV} R_{p_H} \sum_{all \, j} M_{Hu,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hu,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hu,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

\[
\lambda_{H20} = \beta^{HCV} R_{p_H} \sum_{all \, j} M_{Hd0,ju0} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hd0,ju1} \left( \frac{\sum_{n=A,C,D}(S_{nj} + \Lambda A_{nj} + \Lambda C_{nj})}{\sum_{n=S,A,C,D}(S_{nj} + A_{nj} + C_{nj})} \right) \\
+ \sum_{all \, j} M_{Hd0,jd0} \left( \frac{\sum_{n=A,C,D} \Lambda D_{nj}}{\sum_{n=S,A,C,D}(D_{nj})} \right)
\]

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Treatment Equations for HCV

These factors combine to form $r_{kl}$, the rate of successful treatments for HCV.

$$r_{kl} = \frac{\psi}{(z_{delay} + z_{treat})}$$

Where $\psi$ is the efficacy of HCV treatment. $z_{treat}$ denotes the duration of a course of HCV treatment. Further to this, MSM have a delay between diagnosis and starting treatment. We denote the waiting time as $z_{delay}$, which can vary depending on the PrEP status and HIV infection/diagnosis status of MSM $z_{kl}$. Under treatment failure, MSM are retreated for HCV until cured.

4.2.2 Parameter derivation
Proportion of HIV undiagnosed/negative MSM eligible for PrEP

I used the guidelines for PrEP eligibility in England. We then compared this to the data from EMIS as closely as possible. The PrEP eligibility criteria for the UK are as follows:

"1. MSM, trans women or trans men who are currently HIV negative and who are clinically assessed to be at high risk of HIV acquisition through fulfilling the following criteria:

- Have a documented confirmed HIV negative test during an earlier episode of care in the preceding year (i.e. 42-365 days ago);

- Report condomless intercourse in the previous 3 months and this is documented in the clinical notes;

- Affirm their likelihood of repeated condomless intercourse in the next 3 months and this is documented in the clinical notes.

OR

2. The HIV negative partner (confirmed by a current documented negative HIV test) of a diagnosed person with HIV who is not known to be virally suppressed and with whom condomless intercourse is anticipated and so is clinically assessed and considered to be at high risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors treatment as part of an active risk reduction intervention including health education, safer sex promotion, and exploration of treatment as prevention for the HIV positive partner;
3. HIV negative heterosexual men and women clinically assessed and known to have had condomless sex with a person with HIV (who is not known to be virally suppressed) within the past 3 months and for whom it is anticipated that this will occur again, either with the same person or another person with similar status, and so is clinically assessed and considered to be at high risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors as part of an active risk reduction intervention including health education and safer sex promotion.

AND

Where the treating clinician recommends and monitors PrEP as part of an active risk reduction intervention including health education and safer sex

Where the patient is and remains actively involved in the risk reduction intervention and is able to affirm their appropriate adherence to PrEP;

AND

The use and outcomes of the intervention is recorded via the agreed prior approval and monitoring systems. “

“Exclusions

- Individuals in monogamous relationships with a partner who is known to be diagnosed with HIV and whose viral load is undetectable.
- Individuals without a current confirmed negative HIV test result (to minimise the risk of patients with undiagnosed HIV starting PrEP and developing drug resistant virus)
- Individuals who do not or no longer meet the criteria for high risk of HIV acquisition
- Individuals whose only risk of HIV acquisition is due to injecting drug use (as the current HIV incidence in this group in the UK is too low for PrEP to be cost effective)
- People known to be diagnosed with HIV
- Individuals under 16 years of age
- Treatment outside of Level 3 GUM services”

The way in which we processed this was to only look at the criteria applicable to MSM and approximate the proportion of MSM eligible as closely as possible with our data.

For criteria 1a (HIV test in the last 12 months), we considered any MSM who had indicated an HIV test which had resulted in a HIV negative status (EMIS Q71) which was taken in the last year (EMIS Q104). This criteria was met by 41.3% of HIV negative/undiagnosed MSM.
For criteria 1b (unprotected anal sex in previous 90 days) we did not have the data to know if an individual did not use a condom in the last 3 months. We did however know if the individual had not used a condom during a sexual encounter in the past 4 weeks or 6 months (EMIS Q150, Q152, Q153 and Q154). We also excluded any MSM who indicated that this condomless sex was only with steady partners (EMIS Q166). At 4 weeks and 6 months, this criterion was met by 16.6% and 26.6% of HIV negative/undiagnosed MSM respectively.

Criteria 1c (high likelihood of unprotected sex in the next 90 days) was beyond the scope of the data, so we assumed that if criteria 1b was met, so was criteria 1c.

For criteria 2 (HIV negative person who is in a sexual relationship with a HIV diagnosed man who is not virally supressed and condomless anal intercourse is anticipated), we included anyone who had indicated one or more current steady partners (EMIS Q40 and Q41) who they knew to be serodiscordant to themselves (EMIS Q47). We had no data on the state of their partner’s viral suppression however, so the criteria of being virally unsuppressed was assumed to be met in all cases of serodiscordance. This criteria was met by 2.2% of HIV negative/undiagnosed MSM. Criteria 3 was not relevant to our population demographic.

I also excluded any MSM under 16 and people known to be diagnosed with HIV by filtering the data. Other exclusion criteria were outside the scope of our data or were included within the synthesis of the previous criteria naturally.

The results for this analysis meant that overall (after application of all criteria) for the case of (i) forgoing condom use at some point in the past 4 weeks, 13.2% (6.1% low risk and 16.6% high risk) of HIV negative/undiagnosed MSM were eligible for PrEP and (ii) for the case of forgoing condom use at some point in the past 6 months, 18.1% (9.6% low risk and 23.0% high risk) of HIV negative/undiagnosed MSM were eligible for PrEP. In actuality, our estimate for the number of MSM eligible for PrEP will be somewhere in the middle of these values. This is as the criteria specify that eligible MSM will have forgone condom use at some point in the last 90 days; which lies between 4 weeks and 6 months.
These estimates may over-estimate the real eligibility of PrEP among MSM in England as we could not ascertain the proportion of MSM who are likely to forgo condom use in the next 90 days and we had no data on the viral load of HIV positive MSM in steady but serodiscordant partnerships. We also note that as EMIS is likely to attract a higher risk population of respondents, this will also mean we may be over-estimating overall PrEP eligibility.

Given too that not all MSM eligible for PrEP would take it up (assumed in the region of 5-10%), then we use a cautious lower bound of PrEP uptake of 12.5% (near to our lower estimated value - based on MSM having forgone condom use in the last 4 weeks) and an upper bound of 25.0% (which we examine in our sensitivity analysis) to cover the uncertainty in our estimates. This could even extend to scenarios which include greater uptake of PrEP in the UK than expected by and limited to the NHS England criteria.

**PrEP Uptake and drop-off and modified HIV testing Rate**

The rate at which people stop using PrEP once started is estimated from the iPrEX trial where out of the 2441 individuals who started PrEP, 381 stopped taking treatment over a median of 1.2 years equating to 13.9% of individuals dropping out of PrEP annually (by utilizing exponential decay to assert that $2066 = 2441e^{-\lambda \cdot 1.2}$ so that $\lambda = -\frac{1}{1.2} \log_e \left( \frac{2066}{2441} \right) = 0.139$). We fit the rate of PrEP uptake to match the number of individuals we want on PrEP at a given point in the future, using the drop-out rate in this calculation.

The efficacy of PrEP is highly linked to the adherence and consistency of use within those prescribed it.\textsuperscript{106,188,196} Although adherence was quite low within initial trials, more recent open label trials have shown a much higher level of adherence.\textsuperscript{188,318} we use 86% as the given efficacy as found in the PROUD study from the UK,\textsuperscript{188} which is the same as was estimated in the French IPERGAY study.\textsuperscript{196}

**HCV testing and treatment rates**

Testing and treatment rates for HCV vary, with HIV diagnosed MSM advised to be tested at least yearly, followed after diagnosis by an estimated 2.2 year delay before treatment for the pre-DAA era\textsuperscript{179} and 12.0% of HIV diagnosed MSM declining annual HCV screening.\textsuperscript{179} In HIV negative MSM or HIV positive but undiagnosed MSM, the duration of time between initial HCV infection and
treatment is largely unknown, and so we assume a long time period. We therefore cautiously assume this is on average 10 years (assuming a wide parameter range from 5-15 years) from initial infection and that time to treatment is similar to HIV diagnosed MSM at 2.2 years, but with no rejection of treatment due to experiencing symptoms. In all cases of treatment uptake, diagnosis is followed by treatment with direct acting antivirals which we assume to have a treatment duration of 12 weeks.146

With the introduction of PrEP, PrEP users may be screened more often for HCV, but exactly how often in the UK remains undecided at present. We explore the possibilities of yearly, six monthly and three monthly screening in different scenarios. We also consider the impact of a shorter time duration to treatment in some or all groups, with treatment courses completed in six months from diagnosis of HCV infection in these simulations. A full list of all parameters can be found in table 4.3 with sensitivity ranges, comments on the derivation and details of usage where appropriate.
### Inflow and Outflow for the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of initiation of sexual activity</td>
<td>15</td>
<td>EMIS</td>
<td>EMIS data backs up that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Exit age for the model due to sexual cessation</td>
<td>65</td>
<td>EMIS</td>
<td>EMIS data backs up that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Standard exit rate</td>
<td>0.02</td>
<td>EMIS</td>
<td>A steady population was assumed in absence of HIV mortality and so we equated the inflow rate to the exit rate.</td>
</tr>
<tr>
<td>Inflow of population to the model</td>
<td>0.02</td>
<td>EMIS</td>
<td></td>
</tr>
</tbody>
</table>

### HCV related parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission factor for HCV</td>
<td>Fit to Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of HCV treatment</td>
<td>90%</td>
<td>134</td>
<td>A meta-analysis of new direct acting antiviral Sofosbuvir treatment in various combinations. Point estimate used in this case for easy comparison of interventions over different scenarios.</td>
</tr>
<tr>
<td>Spontaneous clearance probability for HCV in HIV negative MSM</td>
<td>0.25 (0.22-0.29)</td>
<td>193</td>
<td>A meta-analysis of studies. However looking at specifically males 36/181 cleared the virus, giving the range we show as 95% CI.</td>
</tr>
<tr>
<td>Odds ratio for spontaneous clearance probability for HCV in HIV positive MSM compared to HIV negative MSM</td>
<td>0.68 (0.46-1)</td>
<td>111</td>
<td>Clearance rates of HIV positive MSM versus HIV negative MSM.</td>
</tr>
<tr>
<td>Duration of acute HCV infection</td>
<td>6 months</td>
<td>136</td>
<td>Given by clinical guidelines on when HCV is considered to transition to a chronic infection.</td>
</tr>
<tr>
<td>Proportion of HIV positive MSM willing to be HCV tested/treated*</td>
<td>88%</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Delay from HCV diagnosis on average to completed treatment.*</td>
<td>2.2 years</td>
<td>179</td>
<td>Taken from HIV diagnosed MSM and assumed for the rest of MSM also</td>
</tr>
<tr>
<td>Duration of HCV treatment*</td>
<td>12 weeks</td>
<td>146</td>
<td>Most common length of treatment courses with DAAs is 12 or 24 weeks, so we assume the average of these two durations.</td>
</tr>
<tr>
<td>Average time to HCV diagnosis of HCV in HIV diagnosed MSM*</td>
<td>1.13 years</td>
<td>37</td>
<td>In accordance with the guidelines on frequency of HCV testing in MSM known to have HIV infection, HCV is tested for yearly. However as only 88% are willing to be tested each year, the average time to diagnosis is 1/0.88 years.</td>
</tr>
<tr>
<td>Average time to HCV diagnosis in HIV negative or HIV positive but undiagnosed MSM*</td>
<td>10 (5-15) years</td>
<td>37</td>
<td>Often MSM do not receive diagnosis of HCV until there are symptoms unless individuals are at high risk from sources of infection. From this information we made an assumption of 10 years until a diagnosis is likely to be made.</td>
</tr>
<tr>
<td>Average time to diagnosis of HCV in MSM using PrEP*</td>
<td>Varied in Model</td>
<td></td>
<td>I look at the impact of different scenarios between the ranges of 10 years as in HIV negative or undiagnosed MSM and up to 3 months if they were tested at every PrEP visit.</td>
</tr>
</tbody>
</table>

### HIV related parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission factor for HIV</td>
<td>Fit to Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased HIV infectiousness during acute HIV phase</td>
<td>26 (10-67)</td>
<td>121</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, stage of virus estimated for passing on infection, all couples start negative.</td>
</tr>
<tr>
<td>Duration of acute HIV infection</td>
<td>2.9 (1.23-6) months</td>
<td>121</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, infectiousness monitored over the duration of infection.</td>
</tr>
</tbody>
</table>
### Table 4.3 - Model parameters with ranges and details of estimation included (time unit of years unless otherwise stated).

*Parameter is new or adapted for this version of the model as compared to the model presented in Chapter 3.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR for transmission of HIV infection on HAART compared to untreated HIV</td>
<td>0.1 (0.01-0.27)</td>
<td>55,252</td>
<td>A meta-analysis of varying ART regimes looking at the transmission of HIV virus on treatment.</td>
</tr>
<tr>
<td>Proportion of diagnosed MSM on HAART treatment</td>
<td>0.832 (0.829-0.834)</td>
<td>199</td>
<td>UK report of all HIV diagnosed cases, what proportion were receiving treatment that year (2011).</td>
</tr>
<tr>
<td>Diagnosis rate of HIV*</td>
<td>2.3 (1.2-3.5)</td>
<td>290</td>
<td>Using estimates from a modelling study which calculated 2016 HIV diagnosis rates in the UK.</td>
</tr>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>2.35 (1-3.7)</td>
<td>227,239</td>
<td>Estimated range from elevated amounts of HCV viral load in those with HIV. Estimates range between 2.88 times, 3.02 and 3.7 times more viral load than in HIV negative MSM. What is more, vertical transmission is 2.82 times more likely in women with HIV infection, Thus our chosen range depicts that higher viral load might not translate to higher infectivity at all, and goes up to our highest estimate to cover uncertainty.</td>
</tr>
<tr>
<td><strong>Behavioural parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by HIV diagnosis status</td>
<td>0.352 (0.282 -0.422)</td>
<td>EMIS</td>
<td>From EMIS data we see that it is more likely for those of the same HIV status to form partnerships. The parameter is the proportion of partnerships chosen between people of the same HIV status assuming no errors in judging each other’s HIV status. The remainder of partnerships are assumed to be chosen randomly.</td>
</tr>
<tr>
<td>Condom usage between two diagnosed MSM</td>
<td>13.0% (10.4-15.6%)</td>
<td>EMIS</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV status of last partner showed a lower condom usage between partners when the asked participant was HIV diagnosed and assumed their partner was HIV positive. We estimate a range +/-20% either side.</td>
</tr>
<tr>
<td>Condom usage between other MSM pairings</td>
<td>68% (52-78%)</td>
<td>EMIS</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV status of last partner. We estimate a range +/-20% either side.</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>0.7 (0.6-0.8)</td>
<td>270</td>
<td>Analysed data combined from US participants in the EXPLORE trial (1999-2001) public use data set and in the VAX trial (1998-1999) data set. 95% CI shown from source.</td>
</tr>
<tr>
<td>Chance of error when evaluating HIV status of a sexual partner</td>
<td>24.9% (12.1% -45.7%)</td>
<td>EMIS</td>
<td>From EMIS participants, the proportion of individuals who make assumptions about partner’s HIV status for reasons which are unlikely to be effective at determining their partner’s HIV status.</td>
</tr>
<tr>
<td>Proportion of individuals in the Low risk group</td>
<td>82.6% (79.1%-86.1%)</td>
<td>EMIS</td>
<td>I used EMIS to split the population into low and high risk based on the number of sexual partners for anal intercourse &gt;15 or &lt;15 in the last year.</td>
</tr>
<tr>
<td>Proportion of individuals in the High risk group</td>
<td>17.4% (20.9-13.9%)</td>
<td>EMIS</td>
<td>1-Number in the high risk group</td>
</tr>
<tr>
<td>Number of yearly partners with which there was anal intercourse by risk group.</td>
<td>2.9 in low risk and 29.1 in high risk, yearly.</td>
<td>EMIS</td>
<td>From EMIS data, within the low and high groups we formed the averaged number of anal sex partners in each group shown.</td>
</tr>
<tr>
<td>Increased overall risk ratio of HIV and HCV transmission due to injecting drugs and fisting between low and high risk group</td>
<td>2.7 (2.35-3.05)</td>
<td>63,145,154,170</td>
<td>Using EMIS data to assess the prevalence of fisting and IDU in our population in the last year combined with estimates for the increased risk these pose to HIV and HCV acquisition, we compared the two risk groups to see the difference in risk they had associated with these factors. CI is the lowest and highest chance calculated from EMIS data and OR of risky behaviours from literature.</td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by risk behaviour category</td>
<td>0.2 (0.1-0.3)</td>
<td>EMIS</td>
<td>Using EMIS data we assessed where individuals in each risk group meet their partners, to see if it was more likely for individuals in the same risk group to mix more often. A range of higher values were assumed due to uncertainty.</td>
</tr>
<tr>
<td><strong>PrEP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of MSM taking up PrEP by 2020*</td>
<td>12.5% lower estimate and 25.0% upper estimate</td>
<td>EMIS</td>
<td>Calculated from EMIS data applied to the eligibility criteria from NHS England. We use two values to encompass uncertainty.</td>
</tr>
<tr>
<td>Odds that a high risk MSM is using PrEP compared to a low risk MSM *</td>
<td>1.73-3.83</td>
<td>EMIS</td>
<td>Calculated from EMIS data applied to the eligibility criteria from NHS England.</td>
</tr>
<tr>
<td>Rate of PrEP uptake per year*</td>
<td>Fitted</td>
<td></td>
<td>Fitted to the number desired to be taking PrEP after specified time period</td>
</tr>
<tr>
<td>Rate of PrEP cessation per year*</td>
<td>0.14 (0.10-0.15)</td>
<td>106</td>
<td>From the IPEx trial drop-out rate</td>
</tr>
<tr>
<td>Efficacy of PrEP in reducing HIV incidence*</td>
<td>86%</td>
<td>188,196</td>
<td>The average from two large PrEP trials, the PROUD study and the IPERGAY trial</td>
</tr>
<tr>
<td>Rate of HIV testing for PrEP users*</td>
<td>For those not on PrEP, equal to the rate of HIV diagnosis 2.3 (1.2-3.5 years), and for those on PrEP quarterly</td>
<td>100,138,126</td>
<td>The necessary procedure to be prescribed the next 3 months of PrEP is to be tested quarterly.</td>
</tr>
<tr>
<td>Rate of HCV testing for PrEP users*</td>
<td>Varied in model</td>
<td></td>
<td>I examine the impact of testing for HCV over different time periods in PrEP users, from quarterly to yearly.</td>
</tr>
</tbody>
</table>
4.2.3 Model calibration and scenarios

Our baseline consists of existing levels of HCV screening and treatment and without PrEP, the model was calibrated to give a stable HIV and HCV epidemic, in line with UK-CHIC data\textsuperscript{179} and recent modelling from the UK.\textsuperscript{179} The calibration was done using a non-least squares fitting algorithm, using parameter sets sampled from their uncertainty ranges in Table 4.3. HCV and HIV transmission rates were fit such that the model resulted in an overall HIV prevalence of 5.9\%\textsuperscript{23,236} and chronic HCV prevalence of 10\% among HIV infected MSM.\textsuperscript{179} Model fits were only accepted if the resulting HCV prevalence among HIV negative MSM was within the 95\% CIs of UK data, which suggests a 1.2\% (95\% CI 0.6-2.1\%)\textsuperscript{232} HCV prevalence in this group. We ran our fitting algorithm until 500 accepted model fits were obtained, which were then used in our analysis to produce median estimates for all model projections, with uncertainty being captured by the 2.5\% to 97.5\% percentile range of these projections, denoted as the 95\% central range (95\% CR).

The calibrated model was used to estimate the impact of initiating a PrEP programme. PrEP was assumed to scale-up over two-years from 2018, with the coverage of PrEP reaching 12.5\% of HIV negative MSM by 2020 while assuming a 13.9\% annual stoppage rate for those on PrEP.\textsuperscript{171,188} These coverage estimates were based on NHS-eligibility criteria as described in section 4.2.2. The relative coverage of PrEP among low and high risk MSM reflects this eligibility criteria. The efficacy of PrEP for reducing the risk of HIV acquisition was assumed to be 86\%.\textsuperscript{171,188,196}

PrEP driven risk compensation was also modelled. However, because of inconclusive data on how sexual behaviours may change,\textsuperscript{171,188,196,295} we only considered reductions in condom use among MSM using PrEP to illustrate the effect that PrEP could have on the HCV epidemic in the UK, and the implications for scaling up HCV treatment. In our modelling, we either assume no risk compensation (Scenario S0) or that all PrEP users halve their consistency of condom use from 68\% to 34\% with all partners (Scenario S1). This assumption is varied in our sensitivity analyses.
4.2.4 Model analyses and sensitivity analyses

The main aim of the analysis is to determine what level of HCV screening and treatment is needed for different MSM sub-populations to eliminate HCV in all MSM, while incorporating the possible effects of PrEP scale-up. We firstly consider the possible effect that PrEP alone would have on the number of new HIV and HCV infections, as well as HCV prevalence and incidence in 2030 compared to 2018 levels. I then evaluated the impact of different HCV screening and treatment scenarios to see what is needed to achieve the NHS-England and WHO elimination targets. We firstly evaluated the impact of more frequent screening for either HIV diagnosed MSM or PrEP users, with PrEP users otherwise having the same low level of HCV screening as HIV negative MSM. The impact on HCV incidence among MSM using PrEP was estimated, with the relative change being compared to what the incidence was in those MSM in 2018. Similarly, the impact on HCV incidence in other groups was estimated. For these scenarios, we also assumed improved linkage-to-treatment for those MSM sub-groups with enhanced screening, with MSM completing treatment within 6 months of diagnosis. Lastly, we considered whether improved screening and linkage-to-treatment for HIV negative MSM not using PrEP was needed to reach the elimination targets. For MSM using PrEP and HIV diagnosed MSM, 3, 6 or 12-monthly screening were considered, while the screening frequency for HIV negative MSM not using PrEP was fitted to give an overall 90% reduction in HCV incidence by 2025 or 2030.

To ascertain which parameters are most important for determining variability in the impact projections across the 500 baseline model fits, a linear regression analysis of covariance (ANCOVA) was performed on the projected impact on overall HCV incidence (2018-2030) of undertaking 6 monthly screening among HIV diagnosed MSM and HIV negative MSM using PrEP (no risk compensation). The proportion of the sum of squares contributed by each parameter was calculated to determine each parameters’ importance to the variability in our projections.

I also performed a series of scenario analyses where we varied, (1) the level of risk compensation, with condom use decreasing to 13% among PrEP users instead of 34% or staying at 68%, (2) a 95% vs 90% efficacy of DAAs for curing HCV infection, (3) 25% vs 12.5% coverage of PrEP, (4) 4 vs 6 months between HCV diagnosis and treatment, and (5) PrEP is distributed evenly between high and low risk MSM instead of preferentially towards high risk MSM.
4.3 Results

4.3.1 Impact of PrEP on HIV

A 12.5% coverage of PrEP among HIV negative MSM translates to 26.0% of high risk HIV negative MSM and 10.2% of low risk HIV negative MSM receiving PrEP. Over 2018-2030, this PrEP coverage results in 44.9% (95% CR 30.9-65.1%) of new HIV infections being prevented if sexual behaviours remain unchanged (scenario S0). This large reduction is partly due to the large number of high risk MSM on PrEP (27.7% of total MSM on PrEP being high risk), and that HIV infections are concentrated within the high risk MSM population, as can be seen from figure 4.2.

![12.5% Coverage of PrEP at 2030](image)

**Figure 4.2** - Distribution of high risk and low risk MSM in each MSM subgroup by 2030 given 12.5% coverage of PrEP from 2018 until 2030.

Indeed, despite the fact that the high risk population comprises only 17.4% of the total population, they harbour 80.5% of the total HIV infections in our 2018 baseline. Indeed, figure 4.3 shows how PrEP at 12.5% coverage when distributed in different ways between high and low risk MSM can affect the proportion of HIV infections averted. The figure shows that targeting PrEP amongst high risk MSM has a larger impact on reducing forward transmissions, both rapidly in the early years, and then building gradually to 2030. Further to this, numerical analysis shows that the base reproductive value $R_0^{HIV}$ is often is less than 1 when we assume our NHS criteria for PrEP distribution with 12.5% coverage, with HIV prevalence tending to zero in our simulations over time. This results in much greater decreases in HIV infections than we would usually expect, as HIV is on the threshold of moving to a state of extinction with our coverage of PrEP at 12.5%.
4.3.2 Impact of PrEP on HCV

12.5% coverage of PrEP causes a decrease in HCV transmission if sexual behaviours remain unchanged (S0) and baseline levels of HCV screening remain the same, with overall HCV prevalence deceasing by 4.4% (95% CR -2.0-9.1%) and incidence decreasing by 9.5% (95% CR -4.8-18.3%) by 2030 (figure 4.4 and table 4.4). This decrease is due to PrEP reducing the absolute number of HIV infected MSM. As HIV-positive MSM are assumed to be more infectious and thus have a higher probability to transmit HCV to their partners, falling HIV prevalence in the absence of behavioural changes translates to less HCV infections over time.

Conversely, the HCV prevalence and incidence among HIV negative MSM using PrEP are 1.9 and 2.3-fold higher, respectively, than other HIV negative MSM (figure 4.4) due to many PrEP users being higher risk (figure 4.2). With a halving in condom use among PrEP users, the overall number of new HCV infections over 2018-2030 increases by 20.6% (95% CR 10.3-41.9%) compared to a baseline of no PrEP (table 4.4).
Table 4.4 - Model projections of the impact of PrEP on HCV prevalence, incidence and the relative change in new HIV and HCV infections for 12.5% PrEP coverage with and without risk compensation. The risk compensation scenario assumes condom use among PrEP users reduces from 68% to 34%. *PrEP users in ‘No PrEP’ scenario are assumed to be representative of MSM who are eligible for PrEP in 201

<table>
<thead>
<tr>
<th>PrEP scenario</th>
<th>Relative change (%) in new infections from 2018 to 2030 compared to no PrEP scenario</th>
<th>HCV prevalence by 2030</th>
<th>HCV Incidence by 2030 (per 100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PrEP</td>
<td>0.0%</td>
<td>0.0%</td>
<td>2.3%</td>
</tr>
<tr>
<td><strong>12.5% coverage of PrEP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario S0 – no risk compensation</td>
<td>-44.9%</td>
<td>-4.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Scenario S1 – condom use in PrEP users falls from 68% to 34%</td>
<td>-40.7%</td>
<td>+20.6%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
Figure 4.4 - Projections of HCV (A) prevalence and (B) incidence among different subgroups of MSM by 2030 for the baseline 'no PrEP' scenario and due to the introduction of PrEP both with and without risk compensation. The projections assume 12.5% coverage of PrEP in HIV negative MSM and no additional HCV screening. The risk compensation scenario assumes condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with the error bars representing the 2.5 to 97.5 percentiles from our 500 model fits. *PrEP users at baseline are assumed to be representative of MSM who are eligible for PrEP in 2018.
Importantly, in all scenarios modelled, although HIV positive MSM have the highest prevalence of HCV, HIV negative MSM not using PrEP still harbour a large burden of HCV infection, with on average 60.7% of all HCV infections being in this sub-group at 12.5% coverage of PrEP as seen in figure 4.5.

![Image](image_url)

**Figure 4.5** - Pie charts showing the degree to which different MSM subgroups contribute to the overall burden of HCV among MSM in 2030 with or without the introduction of PrEP at 12.5% coverage and no risk compensation.

### 4.3.4 Impact of increasing HCV screening in PrEP users

In the previous section, no additional HCV screening of PrEP users was assumed. Assuming 12.5% coverage of PrEP and no risk compensation (S0), then screening PrEP users every 12, 6 or 3-months (and time to completing treatment reduced to 6-months) reduces the HCV prevalence among PrEP users by 73.0% (95% CR 69.2-76.2%), 82.2% (95% CR 79.4-84.6%) and 86.9% (95% CR 84.5-88.8%) by 2030, respectively, and incidence by 38.4% (95% CR 30.4%-44.6%), 43.7% (95% CR 35.0-51.0%) or 46.6% (95% CR 37.3-54.3%), all compared to 2018 levels (figure 4.6). This also reduces the HCV incidence among all MSM by 40.7% (95% CR 33.3-47.2%), 45.6% (95% CR 37.6-53.0%) or 48.3% (95% CR 39.7-56.3%) by 2030 (compared to 2018 levels) if PrEP users are screened every 12, 6 or 3-months, respectively (figure 4.7). This sizeable impact is due to HCV transmission being primarily driven by high risk MSM, which predominate among PrEP users, with the large impact of HCV treatment in PrEP users having a large subsequent impact on the incidence of HCV across other high risk MSM (especially HIV positive MSM) due to them preferentially mixing with each other. Risk compensation reduces the impact of screening PrEP users, with the overall decrease in incidence reducing to 25.5% (95% CR 15.4-34.6%), 33.9% (95% CR 25.6-42.5%) and 38.6% (95% CR 29.6-47.1%) for 12, 6 or 3-monthly screening, respectively (figure 4.7).
Figure 4.6 - Relative reduction in HCV (A) prevalence and (B) incidence by 2030 compared to 2018 levels among PrEP users when they are screened for HCV every 3, 6, or 12 months and complete HCV treatment within 6 months of diagnosis. Projections are given with and without risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. The projections with no additional screening are also shown for comparison. Point estimates are the median of our model projections with the error bars representing the 2.5 to 97.5 percentiles from our 500 model fits. *This is compared to the prevalence of HCV in MSM who are eligible for PrEP in 2018.
Figure 4.7 - Relative decrease in overall HCV incidence by 2030 due to different HCV screening and treatment scenarios among MSM on PrEP and/or HIV diagnosed MSM. MSM subgroups with enhanced screening also receive HCV treatment within 6 months of diagnosis. Projections are given (A) without and (B) with risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with the error bars representing the 2.5 to 97.5 percentiles from our 500 model fits.
4.3.5 Screening requirements for reaching WHO or NHS-England HCV elimination targets

Figure 3 shows that screening HIV diagnosed MSM and/or PrEP users more often (3, 6 or 12-monthly) and reducing the time to completing treatment (6 months) can dramatically reduce the overall incidence of HCV by 2030. For instance, without risk compensation if we improve screening to 3-monthly in only HIV diagnosed MSM then incidence will decrease by 58.0% (95% CR 29.8-74.7%) by 2030, whereas it will decrease by 83.5% (95% CR 74.1-90.4%) if we also undertake 3-monthly screening in PrEP users. With risk compensation, less impact is achieved from screening, although this is small (<5% reduction) when both PrEP users and HIV diagnosed MSM are screened and treated.

Although considerable impact can be achieved from screening HIV diagnosed MSM and PrEP users, it is only possible to achieve an average 90% decrease in overall incidence by 2030 or 2025 if we also enhance HCV screening and linkage to treatment among HIV negative MSM not using PrEP. Without risk compensation, screening HIV negative non-PrEP users every 4.0 years (95% CR 2.8-5.1 years) or 1.7 years (95% CR 1.3-2.1 years) will result in a 90% reduction in incidence by 2030 or 2025, respectively, if PrEP users and HIV diagnosed MSM are screened yearly (figure 4.8). These screening frequencies reduce if PrEP users and HIV diagnosed MSM are screened more frequently but increase with risk compensation (figure 4.8).
Figure 4.8 - Required duration between HCV screening tests among HIV negative MSM not on PrEP (assuming 12.5% PrEP coverage) in order to reach a 90% HCV incidence reduction by (A) 2030 or (B) 2025 compared to 2018 levels. HIV diagnosed MSM and/or MSM on PrEP are screened every 3, 6 or 12 months, with all MSM subgroups receiving HCV treatment within 6 months of diagnosis. Projections are given with and without risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with the error bars representing the 2.5 to 97.5 percentiles from our 500 model fits.
### Table 4.5

<table>
<thead>
<tr>
<th>Screening population and frequency</th>
<th>Scenario</th>
<th>2.5% Percentile</th>
<th>Median</th>
<th>97.5% Percentile</th>
<th>Average duration between HCV screening required in HIV negative population not using PrEP to reach 90% HCV incidence reduction by 2030.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>scenario</td>
<td>-4.8%</td>
<td>9.5%</td>
<td>18.3%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>-65.9%</td>
<td>-26.5%</td>
<td>-8.9%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (12 months)</td>
<td>S0</td>
<td>21.2%</td>
<td>49.4%</td>
<td>66.2%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>-25.6%</td>
<td>24.8%</td>
<td>51.8%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (6 months)</td>
<td>S0</td>
<td>26.9%</td>
<td>55.5%</td>
<td>72.7%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>-16.8%</td>
<td>33.6%</td>
<td>60.1%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (3 months)</td>
<td>S0</td>
<td>29.8%</td>
<td>58.0%</td>
<td>74.9%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>-12.4%</td>
<td>37.4%</td>
<td>63.6%</td>
<td>-</td>
</tr>
<tr>
<td>PrEP users (12 Months)</td>
<td>S0</td>
<td>33.3%</td>
<td>40.7%</td>
<td>47.2%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>15.4%</td>
<td>25.5%</td>
<td>34.6%</td>
<td>-</td>
</tr>
<tr>
<td>PrEP users (6 Months)</td>
<td>S0</td>
<td>37.6%</td>
<td>45.6%</td>
<td>53.0%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>25.6%</td>
<td>33.9%</td>
<td>42.5%</td>
<td>-</td>
</tr>
<tr>
<td>PrEP users (3 Months)</td>
<td>S0</td>
<td>39.7%</td>
<td>48.3%</td>
<td>56.3%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>29.6%</td>
<td>38.6%</td>
<td>47.1%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (12 Months)</td>
<td>S0</td>
<td>61.6%</td>
<td>73.8%</td>
<td>82.3%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>46.9%</td>
<td>66.0%</td>
<td>77.3%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (6 Months)</td>
<td>S0</td>
<td>70.5%</td>
<td>80.8%</td>
<td>88.3%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>61.3%</td>
<td>76.1%</td>
<td>85.8%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (3 Months)</td>
<td>S0</td>
<td>74.1%</td>
<td>83.5%</td>
<td>90.4%</td>
<td>-</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>68.3%</td>
<td>80.1%</td>
<td>88.7%</td>
<td>-</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (12 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>70.5%</td>
<td>79.3%</td>
<td>86.9%</td>
<td>2.8 4.0 5.1</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>59.7%</td>
<td>73.0%</td>
<td>82.9%</td>
<td>2.4 3.3 4.2</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (6 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>77.4%</td>
<td>85.2%</td>
<td>91.8%</td>
<td>3.4 5.2 7.1</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>71.5%</td>
<td>81.6%</td>
<td>89.7%</td>
<td>3.2 4.5 6.0</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (3 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>80.3%</td>
<td>87.4%</td>
<td>93.4%</td>
<td>4.2 6.1 8.4</td>
</tr>
<tr>
<td>S1</td>
<td></td>
<td>75.8%</td>
<td>84.8%</td>
<td>91.9%</td>
<td>3.6 5.4 7.1</td>
</tr>
</tbody>
</table>

Table 4.5 - 2.5% and 97.5% percentiles and mean values for each main scenario at 12.5% PrEP coverage over 500 randomised runs. Showing (1) the overall change in HCV incidence by 2030 and (2) the HCV screening frequency required in HIV negative non-PrEP users to reach 90% HCV incidence reduction by 2030.
4.3.6 Uncertainty analysis

Uncertainty in the time to HCV diagnosis for HIV negative MSM not on PrEP contributed 48.0% of the variation in the projected impact on HCV incidence (2018-2030) of undertaking 6 monthly screening among HIV diagnosed MSM and HIV negative MSM on PrEP (tables 4.6-4.9). Uncertainty in the increased infectiousness of HCV due to HIV co-infection, and the ratio of high risk MSM on PrEP to low risk MSM on PrEP also accounted for 36.2% and 7.3% of the variation, respectively.

Figure 4.9 shows the effect of additional sensitivity analyses, with higher coverage of PrEP among HIV negative MSM (25% instead of 12.5%) resulting in the biggest effect, with over 10% greater impact being achieved by screening MSM on PrEP and HIV diagnosed MSM. Indeed, at 25.0% PrEP coverage, just screening these two groups can now result in HCV elimination by 2030. Otherwise, impact was reduced by around 10% if either there was a higher level of risk compensation (to 13% condom use among PrEP users) or PrEP was equally used by low and high risk MSM. Other changes in the model assumptions had a small effect, including shorter time to HCV treatment completion after diagnosis (4 instead of 6 months) or increases in the SVR of DAA treatment (95% instead of 90%).
### Change in HCV incidence by 2030 (1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average time to HCV diagnosis in HIV negative (or HIV positive but undiagnosed MSM)</td>
<td>48.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>36.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of high risk MSM using PrEP compared to a low risk MSM</td>
<td>73.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>2.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4.6 - ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the change in HCV incidence observed by 2030 when screening HIV diagnosed MSM and PrEP users 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.

### Screening frequency in HIV negative MSM not on PrEP to reach 90% HCV incidence reduction by 2030 (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>40.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of high risk MSM using PrEP compared to a low risk MSM</td>
<td>11.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>7.8%</td>
<td>0.0017</td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>7.3%</td>
<td>0.0024</td>
</tr>
<tr>
<td>Increased infectiousness of HIV during the acute phase</td>
<td>7.1%</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

Table 4.7 - ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the frequency of screening needed in HIV negative MSM not using PrEP in order to reduce HCV incidence by 90% by 2030 given HIV diagnosed MSM and PrEP users are screened 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.

### Change in HCV incidence by 2025 (1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>41.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average time to HCV diagnosis in HIV negative or HIV positive but undiagnosed MSM</td>
<td>40.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of high risk MSM using PrEP compared to a low risk MSM</td>
<td>5.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>4.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>1.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4.8 - ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the change in HCV incidence observed by 2025 when screening HIV diagnosed MSM and PrEP users 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.

### Screening frequency required in HIV negative MSM not on PrEP to reach 90% HCV incidence reduction by 2025 (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>41.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of high risk MSM using PrEP compared to a low risk MSM</td>
<td>20.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>9.5%</td>
<td>0.0059</td>
</tr>
<tr>
<td>Increased death rate due to HCV mono-infection</td>
<td>6.4%</td>
<td>0.0225</td>
</tr>
<tr>
<td>Spontaneous clearance rate of HCV in HIV negative MSM</td>
<td>4.9%</td>
<td>0.0457</td>
</tr>
</tbody>
</table>

Table 4.9 - ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the frequency of screening needed in HIV negative MSM not using PrEP in order to reduce HCV incidence by 90% by 2025 given HIV diagnosed MSM and PrEP users are screened 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.
One-way sensitivity analysis on the (A) percentage reduction in HCV incidence by 2030, and (B) the frequency of screening needed in HIV negative non-PrEP users to reach an overall 90% reduction in HCV among MSM by 2030, given 6 monthly HCV screening in HIV positive MSM and PrEP users. Scenario 0 shown for reference. Point and error bars represent the median values along with the 2.5 to 97.5 percentiles of the model projections across the 500 baseline model fits. Note: the 25% PrEP coverage scenario is not shown in panel B because it does not any require screening in HIV negative MSM not on PrEP to reach an overall 90% reduction in HCV among MSM by 2030.
4.4 Discussion

4.4.1 Overview

Our results highlight that PrEP users as well as HIV diagnosed MSM are important and convenient groups for targeting HCV screening and treatment initiatives because of their higher risk and frequent health check-ups. While enhanced screening amongst HIV diagnosed MSM is also beneficial due to the number of HCV infections which are diagnosed late in this group. Indeed, with 12.5% coverage of PrEP among HIV negative MSM, yearly screening of MSM on PrEP with rapid linkage-to-treatment could reduce the overall HCV incidence among MSM by up to 40.7% (95% CR 33.3-47.2%), with this increasing to 73.8% (95% CR 61.6-82.3%) if HIV diagnosed MSM also receive equivalent screening and treatment. However, although considerable impact is possible from just reaching these groups, elimination is not possible without improving screening and linkage-to-treatment for all MSM. Indeed, with yearly screening for PrEP users and HIV diagnosed MSM, HIV negative non-PrEP users need to be screened every 4.0 years (95% CR 2.8-5.1 years) to achieve the WHO elimination target by 2030, or every 6.1 years (95% CR 4.2-8.4 years) if PrEP users and HIV diagnosed MSM are screened 3-monthly. Importantly, both these screening frequencies are less than the average frequency of HIV testing among MSM in the UK (2.3 years), suggesting that elimination could be achieved if HCV-testing is incorporated into routine HIV check-ups.

Our projections also highlight the importance of maintaining condom use among PrEP users. Reductions in condom use among PrEP users not only reduce the benefits of PrEP on HIV, but also increases HCV transmission, especially among PrEP users and HIV diagnosed MSM. Importantly, though, enhanced HCV screening in PrEP users can offset these additional HCV risks with similar impact being achieved from these screening activities irrespective of the level of risk compensation.

4.4.2 Strengths and limitations

The strength of our analysis is in modelling the full epidemic of HIV and HCV among MSM in the UK, while accounting for heterogeneities in sexual risk, patterns of mixing by HIV-status, and using detailed UK data. Despite these strengths, there are limitations.
Firstly, because the model is UK-specific, it may have limited generalisability to other settings. Although most high income countries have a similar predominance of HCV in HIV diagnosed MSM, some epidemics are increasing or decreasing,\textsuperscript{97} while it is relatively stable in the UK.\textsuperscript{179} Additionally, our projections should not be generalised to lower and middle-income country settings which have different patterns of HIV and HCV prevalence among MSM.\textsuperscript{225}

Secondly, to simplify our modelling we did not attempt to recreate the historical HCV epidemic among MSM in the UK;\textsuperscript{23,179} rather we assumed a stable HCV prevalence as suggested would occur in the UK if DAA treatments were introduced without any scale-up.\textsuperscript{179}

Lastly, uncertainty exists in the data used by the model which propagates to uncertainty in our model projections. Our uncertainty analyses show the model is most sensitive to uncertainty in the time to HCV diagnosis among HIV negative non-PrEP users and uncertainty in the increased infectiousness of HCV among HIV co-infected MSM. Better data on these parameters would improve our model projections. Importantly, we also cannot be certain of the exact scale-up of PrEP, nor the level of risk compensation that may occur among PrEP users. Indeed, our sensitivity analyses show that if 25.0% PrEP coverage is achieved (instead of 12.5%) then the WHO HCV elimination targets (90% reduction in HCV incidence by 2030) could then be reached without increasing HCV screening among HIV negative non-PrEP users. In contrast, assuming greater risk compensation has little effect on the impact of increasing screening among HIV diagnosed MSM and MSM on PrEP.

4.4.3 Comparison with other modelling studies

Several modelling studies have projected the impact of HCV treatment among HIV diagnosed MSM, but none have modelled the full HCV transmission dynamics and HCV treatment elimination requirements for all MSM.\textsuperscript{176,175,257,263} Our analysis builds on these previous studies by evaluating the level of HCV screening and treatment needed in all MSM sub-groups. Our analysis is novel in considering the effect of PrEP on HCV elimination targets, and the additional screening opportunities this provides. Our work compliments recent modelling from the US showing the beneficial impact that PrEP scale-up could have on STI transmission through more frequent STI screening at routine PrEP check-ups.\textsuperscript{133}
Chapter 5 - HCV screening cost-analysis in MSM

5.1 Introduction

For MSM, the discussion of HCV elimination targets \(^{202,321}\) and the ability to achieve them cost-effectively has as of yet only been thoroughly considered within HIV diagnosed MSM. \(^{158,175,176,226}\) In this chapter, we perform a cost-effectiveness analysis of the HCV elimination strategies we examined in chapter 4, which consider the entire UK MSM population. In this analysis, we aim to address two main research questions: (1) Which HCV screening strategies for MSM are most cost-effective in the UK? (2) Is it possible to reach the HCV elimination targets among all UK MSM in a cost-effective manner? In the UK, this translates to a willingness-to-pay threshold of £20,000 per QALY saved. \(^{284}\)

The strength of our proposed strategies from chapter 4 is that they can be incorporated into existing sexual health and testing visits for MSM, and so we can easily and cheaply increase the frequency of HCV screening. All MSM are advised to be screened regularly for HIV and other STIs, \(^{53}\) but this usually excludes screening for HCV. \(^{53,337}\) Currently, HIV diagnosed MSM in the UK should attend 6-monthly check-up appointments to monitor their HIV infection and sexual health, \(^{53}\) while NHS-prescribed PrEP users have mandatory 3-monthly check-ups. \(^{204}\) Other MSM are advised to come for HIV and STI testing every 6-12 months, \(^{237}\) although recent data suggests their average frequency of HIV testing is every 2.3 years. \(^{210}\)

In chapter 4, our modelling suggested that increased screening of all MSM is necessary to reach the HCV elimination targets in the UK. In this chapter, we evaluate whether incorporating HCV screening into existing HIV and STI testing visits could be an efficient strategy to scale up HCV testing and treatment, and which is the most cost-effective strategy for achieving HCV elimination. In these analyses, we allow for recent improvements in the uptake and shorter treatment time for HCV paired with expanded use of PrEP. Using this backdrop, we firstly assess which are the most cost-effective HCV screening strategies, and then evaluate the most cost-effective combined strategy for reaching the WHO and NHS elimination targets. \(^{202,331}\)
5.2 Methods

5.2.1 Modelling

Model structure

I build on the structure of the model used in chapter 4, including changes which allow us to undertake a cost-effectiveness analysis. This firstly required us to incorporate the different stages of liver fibrosis and disease, plus the presence of HCV antibodies into the model, and secondly to parameterise the health care costs and health utilities associated with each stage of liver fibrosis and disease, plus the costs of HCV screening and treatment.

I begin by adding nine strata associated with different stages of liver fibrosis and disease resulting from HCV infection. An absence of liver damage is represented by fibrosis Stage 0 (F0). During the course of HCV infection this progresses to F1, followed by F2 and F3. From this stage, individuals progress to compensated cirrhosis (or F4) followed by decompensated cirrhosis or hepatocellular carcinoma. From decompensated cirrhosis, progression occurs either to hepatocellular carcinoma or to the need for a liver transplant. Those with hepatocellular carcinoma may also go on to have a liver transplant. If the patient receives a liver transplant, they enter a stage of ‘post liver transplantation’.

Furthermore, co-infection with HIV speeds up liver disease progression, although this can be slowed by the use of ART. Following a SVR from treatment, no further disease progression occurs in the mild (F0-F1) or moderate states (F2-F3), while disease progression occurs, albeit slower, among those with compensated cirrhosis. For more progressed stages of liver damage, the disease progression continues at equal rates to that expected during HCV infection. This is described diagrammatically by figure 5.1.
Figure 5.1 - Compartamental flow model diagram of the stages of liver fibrosis due to hepatitis C infection.
Lastly, we also stratify the population by HCV antibody positivity (Ab+). We incorporate this by adding into the possible stages of HCV infection. If an individual spontaneously clears HCV or is successfully treated, they return to a susceptible state, but with the presence of HCV antibodies. Overall this means there are now four descriptive variables associated with each compartment in the model. (1) High or low risk, (2) HIV disease status (3) HCV disease status and (4) stage of liver damage. This results in $2 \times 6 \times 5 \times 9 = 540$ compartments described in the form $X_{ij}^{n}$. Where $n$ denotes the stage of liver progression, $X$ is the status of HIV infection, $i$ is the status of HCV infection and $j$ is the risk group of the individual.

There is conflicting evidence surrounding whether previous HCV clearance provides a reduction in vulnerability to subsequent infection.\(^{110}\) Although high rates of reinfection clearance have been observed amongst MSM,\(^{128}\) it is a likely confounding factor that these individuals are genetically predisposed to clear HCV more readily. It is therefore difficult to disentangle this effect and establish a firm conclusion on the presence of additional HCV resistance following a previous case of clearance. For this reason we assume that transmission probabilities are equal for both initial HCV infection and subsequent reinfections.

With the inclusion of liver disease progression in to the model, we also redefine our HCV related death rates. Rather than including average death rates for HCV with or without HIV co-infection as in chapter 3 and 4, we now include death rates for HCV by stage of liver damage. Death rates are higher at later stages of liver disease (decompensated cirrhosis, hepatocellular carcinoma or needing liver transplantation), but are reduced by a successful liver transplant. We retain the HIV related death rates as described previously in 4.2.1.

HIV co-infection leads to faster progression of liver disease and hence individuals move to end-stage liver disease more rapidly.\(^{286}\) These HCV related death rates are represented by: $\mu_6$ for decompensated cirrhosis, $\mu_7$ for hepatocellular carcinoma, $\mu_8$ for liver transplant and $\mu_9$ for post liver transplant. Transition rates for the between stages of liver fibrosis and disease and HCV-related mortality rates are given in table 5.1.
Model equations

The progression of HIV and HCV are governed by the modelling equations presented in chapter 4, with adaptations to the disease based death rates as described previously in this section. However, each of these HIV and HCV disease states compartments are further sub-categorised by the 9 stages of liver damage, so that:

\[ \sum_{n=1}^{9} X_{ij}^n = X_{ij} \]

Movement occurs between the 9 stages of liver damage, however at a change in stage of HIV or HCV infection, individuals retain their current level of liver damage. The differential equations between the stages of liver damage are of the form:

\[ \frac{dX_{ij}^n}{dt} = PX_{ij}^n \]

These terms are governed by the following matrices; where \( X = S, A \) or \( D \) to denote any stage of HIV infection, and \( \Gamma \) if \( X = S \) and \( \Gamma = 2.5 \) if \( X = A, C \) and \( \Gamma = 1.7 \) if \( X = D \). For individuals that are not currently infected with HCV (\( i = S \)):

\[
\begin{pmatrix}
PX_{ij}^1 \\
PX_{ij}^2 \\
PX_{ij}^3 \\
PX_{ij}^4 \\
PX_{ij}^5 \\
PX_{ij}^6 \\
PX_{ij}^7 \\
PX_{ij}^8 \\
PX_{ij}^9
\end{pmatrix}
= \Gamma
\begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
X_{ij}^1 \\
X_{ij}^2 \\
X_{ij}^3 \\
X_{ij}^4 \\
X_{ij}^5 \\
X_{ij}^6 \\
X_{ij}^7 \\
X_{ij}^8 \\
X_{ij}^9
\end{pmatrix}
\]

And for individuals currently infected with HCV, where \( i = A, C \) or \( D \) to denote current HCV infection states:

\[
\begin{pmatrix}
PX_{ij}^1 \\
PX_{ij}^2 \\
PX_{ij}^3 \\
PX_{ij}^4 \\
PX_{ij}^5 \\
PX_{ij}^6 \\
PX_{ij}^7 \\
PX_{ij}^8 \\
PX_{ij}^9
\end{pmatrix}
= \Gamma
\begin{pmatrix}
-\rho_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\rho_3 & -\rho_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \rho_2 & -\rho_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \rho_3 & -\rho_4 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \rho_5 & -\rho_6 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \rho_6 & -\rho_7 & -\rho_6 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \rho_7 & -\rho_7 & -\rho_6 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \rho_8 & -\rho_8 & -\rho_8 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_9 & -\mu_9
\end{pmatrix}
\begin{pmatrix}
X_{ij}^1 \\
X_{ij}^2 \\
X_{ij}^3 \\
X_{ij}^4 \\
X_{ij}^5 \\
X_{ij}^6 \\
X_{ij}^7 \\
X_{ij}^8 \\
X_{ij}^9
\end{pmatrix}
\]
For example the change in the number of individuals of risk group $j$ with diagnosed HCV and HIV infections with F2 stage liver fibrosis is denoted by the equation:

$$\frac{dD_{Dj}^3}{dt} = \Gamma_D \rho_{Dj}^2 D_{Dj}^2 - \Gamma_D \rho_{Dj}^3 D_{Dj}^3$$

<table>
<thead>
<tr>
<th>HCV Related Liver Disease Progression</th>
<th>Symbol</th>
<th>Yearly probability range, or factor of progression speed</th>
<th>Ref</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly progression rate from f0 to f1</td>
<td>$\rho_1$</td>
<td>0.0529-0.2095</td>
<td>177</td>
<td>sampled from normal distribution</td>
</tr>
<tr>
<td>Yearly progression rate from f1 to f2</td>
<td>$\rho_2$</td>
<td>0.0216-0.1013</td>
<td>177</td>
<td>sampled from normal distribution</td>
</tr>
<tr>
<td>Yearly progression rate from f2 to f3</td>
<td>$\rho_3$</td>
<td>0.0450-0.1145</td>
<td>177</td>
<td>sampled from normal distribution</td>
</tr>
<tr>
<td>Yearly progression rate from f3 to compensated cirrhosis</td>
<td>$\rho_4$</td>
<td>0.0513-0.1838</td>
<td>177</td>
<td>sampled from normal distribution</td>
</tr>
<tr>
<td>Yearly progression rate from compensated cirrhosis to decompensated cirrhosis</td>
<td>$\rho_5$</td>
<td>0.0166-0.0921</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Yearly progression rate from compensated cirrhosis or decompensated cirrhosis to hepatocellular carcinoma</td>
<td>$\rho_6$</td>
<td>0.0003-0.0684</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Yearly progression rate from decompensated cirrhosis or HCC to liver transplant</td>
<td>$\rho_7$</td>
<td>0.0062-0.0962</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Yearly progression rate from liver transplant to post liver transplant</td>
<td>$\rho_8$</td>
<td>1.0423-2.4412</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Decompensated cirrhosis related death rate per year</td>
<td>$\mu_6$</td>
<td>0.1063-0.1842</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Hepatocellular carcinoma related death rate per year</td>
<td>$\mu_7$</td>
<td>0.3904-0.7697</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Liver transplant related death rate per year</td>
<td>$\mu_8$</td>
<td>0.0911-0.4348</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Post liver transplant related death rate per year</td>
<td>$\mu_9$</td>
<td>0.0280-0.1016</td>
<td>265</td>
<td>Instantaneous rates calculated from sampled beta distributions of transition probabilities</td>
</tr>
<tr>
<td>Relative risk for progression rate from compensated to decompensated cirrhosis following SVR</td>
<td>$\epsilon_5$</td>
<td>0.07 (95%CI 0.03,0.2)</td>
<td>312</td>
<td>Sampled from transformed lognormal distribution</td>
</tr>
<tr>
<td>Relative risk for progression rate from compensated cirrhosis to HCC following SVR</td>
<td>$\epsilon_6$</td>
<td>0.23 (95%CI 0.16,0.35)</td>
<td>198</td>
<td>Sampled from transformed lognormal distribution</td>
</tr>
<tr>
<td>Factor increase in HCV related liver disease progression rate due to HIV co-infection (Not on ART HIV treatment)</td>
<td>$\Gamma_A &amp; \Gamma_C$</td>
<td>2.5 (95%CI 1.8-3.4)</td>
<td>286</td>
<td>2.5 times higher than in HCV mono-infected individuals. Lognormal distribution.</td>
</tr>
<tr>
<td>Factor increase in HCV related liver disease progression rate due to HIV co-infection (On ART HIV treatment)</td>
<td>$\Gamma_D$</td>
<td>1.7 (95%CI 1.1-2.8)</td>
<td>286</td>
<td>1.7 times higher than in HCV mono-infected individuals. Lognormal distribution.</td>
</tr>
</tbody>
</table>

Table 5.1 - Yearly death and transition probabilities associated with stages of liver damage.
5.2.2 Parameter derivation
Health utilities and cost estimations

To estimate the number of MSM in the UK population we firstly make use of a study which utilised a mathematical approach, combining the total number of MSM who participated in the EMIS survey with the level of internet access in the UK and levels of self-reported HIV-diagnoses. The result of this method gave an estimated value of 613,658 MSM living in the UK in 2011.\textsuperscript{172} This estimate is close to survey calculated MSM population estimates by Natsal, which found that approximately 2.5% of the males in the UK population, (which in 2011 translated to 774,200 individuals) were MSM.\textsuperscript{191} Using an intermediate estimate between these values and allowing for population growth in the UK between 2011 and 2018, we use an estimate of 700,000 MSM within our model.

The costs of HCV care for different stages of HCV-related disease were drawn from previously published estimates for the UK (Table 5.2),\textsuperscript{180,341} and adapted to modern costs by utilising another recent modelling study.\textsuperscript{279} We broadly split these costs into three categories which we inflate to 2018 prices using the hospital and community health services index.\textsuperscript{221} The first category comprises the ongoing health costs associated with all pre-liver transplant stages of HCV infection.\textsuperscript{22} The second category comprises the cost of a liver transplantation, which is based on: the procedural cost and the extra hospital based costs in the same year; and the subsequent annual cost of the patient for the years after a successful transplantation.\textsuperscript{180} The final category is the cost of a course of treatment for HCV, assumed to be a combination of Sofosbuvir and Ledipasvir, per treatment,\textsuperscript{180} which is assumed to be paid over the duration of treatment for 12 weeks.

I also consider the intervention costs of HCV screening. We assume that the inexpensive HCV antibody test is done first on all MSM who are screened,\textsuperscript{279,326} then a follow up test for viral RNA is undertaken if the antibody test is positive i.e. the individual is HCV infected or is susceptible but with existing HCV antibodies.\textsuperscript{279,326} We also assume that all the blood samples used for HCV testing come from existing blood samples taken during routine sexual health check-ups. This assumptions allows us to price the cost of the screening to be equal to the price of the HCV lab tests, plus an assumed 5 minute increased appointment duration for HCV counselling charged at the rate of a specialist nurse’s salary.\textsuperscript{279} Once a positive HCV RNA test result is identified, then the costs of the follow up steps required for initiating treatment are incurred.\textsuperscript{279}
For those with HIV/HCV co-infection, we have to consider the added impact that HIV also has on their quality of life.\textsuperscript{208,281} We approach this by multiplicatively combining the QALY of each individual based on both their stage of liver damage and stage of HIV infection. Our model does not explicitly consider the progression of HIV infection to AIDS, but we acknowledge that AIDS is associated with a significant decrease in health and hence QALYs.\textsuperscript{208,281} However UK data from 2016 indicated there were only 278 diagnoses of AIDS defining symptoms from a total estimate of 102,000 people living with HIV.\textsuperscript{39} Due to this, only a very small percentage of people with HIV in the UK will be suffering from AIDS, and so we model all stages of chronic HIV infection with one QALY value.
<table>
<thead>
<tr>
<th>Annual healthcare Costs for HCV</th>
<th>Value £</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected with HCV</td>
<td>0.00</td>
<td>Constant</td>
<td>341</td>
</tr>
<tr>
<td>F0 and F1 Mild HCV</td>
<td>187.59</td>
<td>Gamma(0.659,289)</td>
<td>341</td>
</tr>
<tr>
<td>F2 and F3 Moderate HCV</td>
<td>974.68</td>
<td>Gamma(0.485,2038)</td>
<td>341</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td>1,546.98</td>
<td>Gamma(0.211,7452)</td>
<td>341</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>12,397.57</td>
<td>Gamma(0.901,13974)</td>
<td>341</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>11,170.04</td>
<td>Gamma(0.926,12251)</td>
<td>341</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>40,273.00</td>
<td>PPI*Gamma(89.75,304.5)</td>
<td>180</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>2,041.00</td>
<td>PPI*Gamma(15.22,91.1)</td>
<td>180</td>
</tr>
<tr>
<td>Hospital costs year of transplant</td>
<td>13,937.00</td>
<td>PPI*Gamma(13.78,686.4)</td>
<td>180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment costs for HCV</th>
<th>Value £</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV DAAs and pre-treatment counselling</td>
<td>40,680.00</td>
<td>Constant</td>
<td>180 279</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening Costs for HCV</th>
<th>Value £</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-body test</td>
<td>10.22</td>
<td>Uniform +/- 20%</td>
<td>279</td>
</tr>
<tr>
<td>HCV RNA test</td>
<td>45.57</td>
<td>Uniform +/- 20%</td>
<td>279</td>
</tr>
<tr>
<td>Hourly rate of pay for specialist nurse</td>
<td>15.72</td>
<td>Uniform +/- 20%</td>
<td>279</td>
</tr>
<tr>
<td>New patient engagement</td>
<td>325.84</td>
<td>Uniform +/- 20%</td>
<td>279</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QALY Weights (HCV)</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>1</td>
<td>Constant</td>
<td>180</td>
</tr>
<tr>
<td>Mild HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Treatment (F0 and F1)</td>
<td>0.77</td>
<td>Beta (521.2375,155.6943)</td>
<td>180</td>
</tr>
<tr>
<td>SVR (F1 only)</td>
<td>0.82</td>
<td>Beta (65.8678,14.5488)</td>
<td>180</td>
</tr>
<tr>
<td>Moderate HCV (F2 and F3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Treatment</td>
<td>0.66</td>
<td>Beta (168.2461,86.6723)</td>
<td>180</td>
</tr>
<tr>
<td>SVR</td>
<td>0.72</td>
<td>Beta (58.0608,22.592)</td>
<td>180</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Treatment</td>
<td>0.55</td>
<td>Beta (47.1021,38.5381)</td>
<td>180</td>
</tr>
<tr>
<td>SVR</td>
<td>0.61</td>
<td>Beta (58.0608,37.1124)</td>
<td>180</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>0.45</td>
<td>Beta (123.75,151.25)</td>
<td>180</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>0.45</td>
<td>Beta (123.75,151.25)</td>
<td>180</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>0.45</td>
<td>Beta (123.75,151.25)</td>
<td>180</td>
</tr>
<tr>
<td>Post-transplant</td>
<td>0.67</td>
<td>Beta (59.2548,29.1852)</td>
<td>180</td>
</tr>
<tr>
<td>Liver-related death</td>
<td>0</td>
<td>Constant</td>
<td>180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QALY Weights (HIV)</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected with HIV</td>
<td>1</td>
<td>Constant</td>
<td>180</td>
</tr>
<tr>
<td>Acute HIV</td>
<td>0.94</td>
<td>Constant</td>
<td>281</td>
</tr>
<tr>
<td>Undiagnosed Chronic HIV infection</td>
<td>0.82</td>
<td>Constant</td>
<td>281</td>
</tr>
<tr>
<td>Diagnosed HIV infection (most are on ART)</td>
<td>0.94</td>
<td>Constant</td>
<td>281</td>
</tr>
</tbody>
</table>

Table 5.2 - Health related costs and QALY weights associated with different stages of disease progression. *PPI = Hospital and Community Health Services Pay and Price Index Inflation 2003/04 to 2018/2019 (1.69). QALY (quality adjusted life year).
5.2.3 Model calibration and analyses

Similarly to chapter 4, we calibrate to a status-quo scenario of a steady HIV and HCV epidemic,\textsuperscript{179} with existing levels of HCV screening and DAA treatment, and in the absence of PrEP. We use parameter sets sampled from their uncertainty ranges in section 4.2.2, with HCV and HIV transmission rates fit such that we generate an overall HIV prevalence of 5.9\%\textsuperscript{23,236} and chronic HCV prevalence of 10\% among HIV infected MSM.\textsuperscript{179} Model fits are only accepted if the resulting HCV prevalence among HIV negative MSM was within the 95\% confidence intervals of UK estimates suggesting a 1.2\% (95\% confidence interval 0.6-2.1\%)\textsuperscript{232} HCV prevalence in this group. We split our parameters into two distinct groups. The first group consists of necessary parameters to run the epidemic simulation (table 5.3), while the second set of parameters calculate the total cost and QALYs (table 5.2), which are used to estimate the mean ICER and assessed against the £20,000 per QALY willingness to pay threshold recommended by NICE.\textsuperscript{284}

Due to the computationally inexpensive nature of applying our second set of parameters, we ran our epidemic fitting algorithm until we had 100 accepted model fits, then subsequently ran 100 cost and QALY scenarios on each epidemic run, thus totalling 10,000 total sets of model runs. We present the median value of our main results along with the 95\% central range (95\% CR).

I firstly examine how faster linkage to HCV treatment with DAAs for all MSM and the initiation of widespread PrEP could impact on the number of HCV infections averted and QALYs gained compared to the status quo scenario. We do not model the costs of these changes, as they are currently an emerging consequence of developing medical care and are distinct from our proposed screening interventions. The impact of these two changes however serves as a backdrop for our screening intervention scenarios. Thus, this scenario including both PrEP and faster linkage to HCV treatment will serve as our baseline for the comparison of our proposed screening interventions.

I also mainly focus on results based on a short time horizon of 12 years, leading up to 2030, as after this critical point in time, HCV care may undergo radical changes due to the worldwide effort which may result in the elimination of HCV.\textsuperscript{1} we do however perform sensitivity analyses based on a longer time horizon of 32 years, ending in 2050, to examine the longer-term impacts on our proposed interventions.
In line with our previous modelling in chapter 4, our intervention scenarios focus on higher frequencies of screening in different sub-groups. We increase the screening in HIV diagnosed MSM to 6 months versus 12 months; we initiate screening in PrEP users every 12, 6 or 3 months versus systematic screening every 10-15 years; and we also consider screening HIV negative non-PrEP users at just above the estimated average frequency (or half this frequency) of current HIV and STI testing, instead of systematic screening every 10-15 years. We determine the incremental cost and impact of each strategy individually, compared to the baseline scenario, including strategies which achieve the WHO and NHS HCV elimination targets. These scenarios are described in table 5.4, which displays their characteristics.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Universal rapid treatment</th>
<th>Widespread PrEP initiation</th>
<th>HCV Screening frequency in PrEP users</th>
<th>HCV Screening frequency in HIV diagnosed MSM</th>
<th>HCV Screening frequency in HIV negative non PrEP users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status quo</td>
<td>No</td>
<td>No</td>
<td>10-15 years</td>
<td>1 year</td>
<td>10-15 years</td>
</tr>
<tr>
<td>Baseline</td>
<td>Yes</td>
<td>Yes</td>
<td>10-15 years</td>
<td>1 year</td>
<td>10-15 years</td>
</tr>
<tr>
<td>12 Monthly PrEP</td>
<td>Yes</td>
<td>Yes</td>
<td>1 year</td>
<td>1 year</td>
<td>10-15 years</td>
</tr>
<tr>
<td>6 Monthly PrEP</td>
<td>Yes</td>
<td>Yes</td>
<td>0.5 years</td>
<td>1 year</td>
<td>10-15 years</td>
</tr>
<tr>
<td>3 Monthly PrEP</td>
<td>Yes</td>
<td>Yes</td>
<td>0.25 years</td>
<td>1 year</td>
<td>10-15 years</td>
</tr>
<tr>
<td>6 Monthly HIV diagnosed</td>
<td>Yes</td>
<td>Yes</td>
<td>10-15 years</td>
<td>0.5 years</td>
<td>10-15 years</td>
</tr>
<tr>
<td>12 Monthly PrEP and 6 Monthly HIV diagnosed</td>
<td>Yes</td>
<td>Yes</td>
<td>1 year</td>
<td>0.5 years</td>
<td>10-15 years</td>
</tr>
<tr>
<td>6 Monthly PrEP and 6 Monthly HIV diagnosed</td>
<td>Yes</td>
<td>Yes</td>
<td>0.5 years</td>
<td>0.5 years</td>
<td>10-15 years</td>
</tr>
<tr>
<td>3 Monthly PrEP and 6 Monthly HIV diagnosed</td>
<td>Yes</td>
<td>Yes</td>
<td>0.25 years</td>
<td>0.5 years</td>
<td>10-15 years</td>
</tr>
<tr>
<td>5 Yearly screening in HIV negative non-PrEP users</td>
<td>Yes</td>
<td>Yes</td>
<td>10-15 years</td>
<td>1 year</td>
<td>5 years</td>
</tr>
<tr>
<td>2.5 Yearly screening in HIV negative non-PrEP users</td>
<td>Yes</td>
<td>Yes</td>
<td>10-15 years</td>
<td>1 year</td>
<td>2.5 years</td>
</tr>
<tr>
<td>3 Monthly PrEP, 5 yearly non-PrEP users and 6 Monthly HIV diagnosed. (2030 Elimination scenario)</td>
<td>Yes</td>
<td>Yes</td>
<td>0.25 years</td>
<td>0.5 years</td>
<td>5 years</td>
</tr>
<tr>
<td>3 Monthly PrEP, 2.5 yearly non-PrEP users and 6 Monthly HIV diagnosed. (2025 Elimination scenario)</td>
<td>Yes</td>
<td>Yes</td>
<td>0.25 years</td>
<td>0.5 years</td>
<td>2.5 years</td>
</tr>
</tbody>
</table>

Table 5.3 - A list of all the main scenarios and screening interventions run using our model.
5.2.4 Model analyses and sensitivity analyses

For all intervention scenarios, we compare the cost of the intervention and QALYs gained to create the efficiency frontier that links up the most cost-effectiveness interventions. Using this method, we explore the most efficient order of implementation or these interventions. Further to this, we examine the total costs, mean ICERS and cost per HCV infection averted for scenarios which reach the 2030 and 2025 HCV elimination targets.

I then carried out a univariate sensitivity analysis on the mean ICERS focused on the HCV elimination scenario to reach the WHO elimination target to test the importance of assumptions made in the main analysis. This includes: an increased time horizon of 32 years (instead of 12 years); 25% prevalence of PrEP (instead of 12.5% coverage); DAAs at 95% efficacy (instead of 90%); halving the cost of HCV treatment from £40,680 to £20,340; half the rate of condom use between PrEP users and their partners (from 68% to 34%); and a 50% reduction in HIV serosorting such that 17.6% of HIV diagnosed MSM’s partnerships are preferentially formed with other HIV diagnosed MSM (instead of 35.2%).

Finally, we performed an ANOVA analysis\textsuperscript{34} of the costs and health utilities implemented to ascertain how uncertainty in each of these parameters contributed to the overall variability in the mean ICERS, again focusing on the WHO HCV elimination target scenario.
5.3 Results

5.3.1 The cost-effectiveness of HCV screening interventions

Relative to our null scenario (no PrEP and average time from diagnosis to completing treatment is 2.2 years) we find that our baseline scenario (HCV treatment completed within 6 months of diagnosis and 12.5% of HIV negative MSM using PrEP) results in 10,881 (7,117-14,457 95% CR) HCV infections averted over 12 years from 2018 to 2030, with a mean of 50.5% of all HCV infections being prevented over this period relative to the status quo scenario. The baseline scenario also gains 19,580 (15,017-25,352 95% CR) QALYS in this period.

As can be seen in table 5.4, with 6-monthly HCV screening of HIV diagnosed MSM, compared to our baseline scenario we avert 1,417 (1,029-1,793 95% CR) HCV infections (13.2% of the total in the baseline scenario) and gain 640 (394-2,516 95% CR) QALYS while saving £44.5 million (£14.2-68.7 million 95% CR). This is due to a significant TasP effect, resulting in saving £54.4 million by spending an extra £9.9 million on screening and subsequent HCV care.

Compared to the baseline scenario, with increased screening frequency in PrEP users to 12, 6 or 3 months, 2,510 (1,450-4,195 95% CR), 2,977 (1,730-5,079 95% CR) and 3,229 (1,885-5,575 95% CR) HCV infections were averted (23.5%, 27.9% and 30.3% of the total). This resulted in gaining 1,586 (854-2,620 95% CR), 1,941 (1,066-3,014 95% CR) and 2,184 (1,232-3,277 95% CR) QALYS at a cost of £79.1 million (£12.5-£184.3 million 95% CR), £87.7 million (£12.1-£201.4 million 95% CR) and £105.0 million (£15.8-£223.2 million 95% CR), translating to mean ICERs of £49,204 (£2,043-£92,412 95% CR), £45,453 (£1,106-£87,323 95% CR) and £50,072 (£4,309-£91,927 95% CR).

The combined impact of screening HIV diagnosed MSM 6 monthly and PrEP users is larger than either alone, but results in a more cost-effective scenario than screening PrEP users alone. For example, screening PrEP users every 3 months and HIV diagnosed MSM every 6 months averted 4,438 (3,183-6,499 95% CR) HCV infections (41.6% of the total) and gained 2,716 (1,716-3,812 95% CR) QALYS. The costs of this scenarios compared to the baseline scenario is £51.9 million (±£31.3-£180.4 million 95% CR), resulting in a mean ICER of £18,400 (±£12,529-£61,101 95% CR).

In contrast to screening the higher risk subgroups, the impact of screening just HIV negative non-PrEP users every 5 or 2.5 years averted 1,748 (199-3,430 95% CR) and 4,451 (2,498-6,767 95% CR) HCV infections averted (13.2% of the total) and gained 640 (394-2,516 95% CR) QALYS while saving £79.1 million (£12.5-£184.3 million 95% CR), £87.7 million (£12.1-£201.4 million 95% CR) and £105.0 million (£15.8-£223.2 million 95% CR), translating to mean ICERs of £49,204 (£2,043-£92,412 95% CR), £45,453 (£1,106-£87,323 95% CR) and £50,072 (£4,309-£91,927 95% CR).
infections (16.4% and 41.7% of the total) and gained 1,195 (100-2,761 95% CR) and 3,132 (1,644-5,138 95% CR) QALYS. The costs of these scenarios compared to the baseline scenario are £65.3 million (£9.8-£205.0 million 95% CR) and £87.5 million (£2.9-£261.8 million 95% CR) resulting in a mean ICER of £36,593 (-£36065-£93,911 95% CR) and £29,324 (£1363-£61,928 95% CR), with the majority of this extra cost due to higher treatment costs.

Finally, we consider the two HCV elimination scenarios, both of which incorporate 3 monthly HCV screening in PrEP users and 6 Monthly in HIV diagnosed MSM, and then either additional screening of HIV negative non-PrEP users every 5 or 2.5 years. Within these scenarios, the number of HCV infections averted totals 5,525 (3,579-7,871 95% CR) and 7,112 (4,863-10,102 95% CR) respectively, corresponding to 51.8% and 66.7% of the total number of infections in the baseline scenario. We also gain 3,543 (2,040-5,643 95% CR) and 4,903 (3,008-7,276 95% CR) QALYS. The costs of these scenarios compared to the baseline scenario are £68.8 million (-£25.7-£262.2 million 95% CR) and £49.9 million (-£67.2-£263.5 million 95% CR) resulting in a mean ICER for these scenarios of £19,212 (-£10,360-£56,018 95% CR) and £10,263 (-£17,449-43,085). Results for the impact of all scenarios are displayed both in figure 5.2 and costs are also included in table 5.4.

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**Figure 5.2 - Impact of increased HCV screening interventions compared with current HCV screening coverage. Impact is measured in terms of (A) HCV infections averted, (b) QALYs gained. Error bars are 95% credible intervals from 1000 simulations. Elimination target refers to HCV screening rates of 6 months in HIV diagnosed MSM, 3 monthly in PrEP users and every *5 or **2.5 years for all other MSM to reach the target by 2030 or 2025 respectively.**
Table 5.4 - Impacts and costs of the intervention scenarios compared to the baseline. Including HCV infections averted, QALYS gained, costs of the intervention and mean ICERs (where the intervention is not cost saving) by 2030. Elimination target refers to HCV screening rates of 6 months in HIV diagnosed MSM, 3 monthly in PrEP users and every *5 or **2.5 years for all other MSM to reach the target by 2030 or 2025 respectively.

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<tbody>
<tr>
<td></td>
<td>Median and 95% CR interval values</td>
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<tr>
<td>HCV infections averted</td>
<td>1,417</td>
<td>2,510</td>
<td>2,978</td>
<td>3,229</td>
<td>3,783</td>
<td>4,195</td>
<td>4,438</td>
<td>1,748</td>
<td>4,452</td>
<td>5,525</td>
<td>7,112</td>
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<td></td>
<td>1,029</td>
<td>1,450</td>
<td>1,731</td>
<td>1,885</td>
<td>2,789</td>
<td>3,047</td>
<td>3,183</td>
<td>199</td>
<td>2,499</td>
<td>3,579</td>
<td>4,863</td>
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<td>1,794</td>
<td>4,193</td>
<td>5,079</td>
<td>5,575</td>
<td>5,235</td>
<td>6,062</td>
<td>6,499</td>
<td>3,431</td>
<td>6,767</td>
<td>7,871</td>
<td>10,102</td>
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<tr>
<td>QALYs gained</td>
<td>640</td>
<td>1,586</td>
<td>1,941</td>
<td>2,184</td>
<td>2,175</td>
<td>2,504</td>
<td>2,716</td>
<td>1,195</td>
<td>3,132</td>
<td>3,543</td>
<td>4,903</td>
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<tr>
<td></td>
<td>394</td>
<td>854</td>
<td>1,066</td>
<td>1,232</td>
<td>1,395</td>
<td>1,588</td>
<td>1,716</td>
<td>100</td>
<td>1,644</td>
<td>2,040</td>
<td>3,008</td>
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<tr>
<td></td>
<td>2,516</td>
<td>2,621</td>
<td>3,014</td>
<td>3,278</td>
<td>3,129</td>
<td>3,604</td>
<td>3,812</td>
<td>2,761</td>
<td>5,138</td>
<td>5,643</td>
<td>7,276</td>
</tr>
<tr>
<td>Cost of the intervention (millions £)</td>
<td>-44.5</td>
<td>79.1</td>
<td>87.7</td>
<td>105.0</td>
<td>27.5</td>
<td>36.3</td>
<td>51.9</td>
<td>65.3</td>
<td>87.5</td>
<td>68.8</td>
<td>49.9</td>
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<tr>
<td></td>
<td>-68.7</td>
<td>12.5</td>
<td>12.0</td>
<td>15.8</td>
<td>-42.9</td>
<td>-41.6</td>
<td>-31.3</td>
<td>9.9</td>
<td>3.0</td>
<td>-25.7</td>
<td>-67.2</td>
</tr>
<tr>
<td></td>
<td>-14.1</td>
<td>184.3</td>
<td>201.4</td>
<td>223.3</td>
<td>144.2</td>
<td>160.6</td>
<td>180.4</td>
<td>205.0</td>
<td>260.8</td>
<td>262.2</td>
<td>263.5</td>
</tr>
<tr>
<td>Mean ICER (E)</td>
<td>-</td>
<td>49,204</td>
<td>45,453</td>
<td>50,072</td>
<td>11,874</td>
<td>13,481</td>
<td>18,400</td>
<td>56,593</td>
<td>29,324</td>
<td>19,212</td>
<td>10,263</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2,043</td>
<td>1,106</td>
<td>4,309</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36,065</td>
<td>1,363</td>
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<tr>
<td></td>
<td>-</td>
<td>92,412</td>
<td>87,323</td>
<td>91,927</td>
<td>54,819</td>
<td>56,277</td>
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<td>93,911</td>
<td>61,928</td>
<td>56,018</td>
<td>43,085</td>
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<tr>
<td>Cost of HCV screening and care (millions £)</td>
<td>9.9</td>
<td>10.7</td>
<td>20.4</td>
<td>40.5</td>
<td>19.2</td>
<td>30.0</td>
<td>50.8</td>
<td>7.1</td>
<td>20.7</td>
<td>58.5</td>
<td>71.0</td>
</tr>
<tr>
<td>Cost of HCV treatment (millions £)</td>
<td>-54.4</td>
<td>68.4</td>
<td>67.2</td>
<td>64.5</td>
<td>8.3</td>
<td>6.4</td>
<td>1.1</td>
<td>58.1</td>
<td>66.8</td>
<td>10.3</td>
<td>-21.1</td>
</tr>
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</table>
Compared to the baseline scenario, the ordering of efficiency for the cost-effectiveness of these interventions is: (1) screening HIV diagnosed MSM 6 monthly as can be seen in the frontier analysis shown in figure 5.3. There was overlap however between the 95% CR uncertainty bounds between this scenario and screening PrEP users every 12 months plus screening HIV diagnosed MSM every 6 months. (2) The next most cost-effective is then to screen MSM at the frequencies needed to reach the 2025 HCV elimination target. However there was overlap within the 95% CR uncertainty bounds between this scenario and all others apart from simply screening HIV diagnosed MSM every 6 months.

![Figure 5.3 - QALYs gained and associated cost for increased HCV screening intervention scenarios compared to baseline HCV screening. Plotted points are medians for each intervention from 1000 parameter sets. The solid straight lines join the medians for the incrementally most cost-effective interventions as budget increases.](image)

**5.3.2 Sensitivity analysis**

From our univariate sensitivity analysis we see that the cost-effectiveness projections are improved by or robust to the uncertainties in the parameter assumptions, except for PrEP related risk compensation (figure 5.4). We project a modest cost-saving benefit from longer time horizon of 32 versus the 12 we use in our main analysis. However risk compensations, including condom use falling between PrEP users and their partners and equally less preferential mixing by HIV status, can mean that our HCV 2030 elimination scenario is much less cost-effective, with mean ICERS rising above the willingness-to-pay threshold in both cases.
Figure 5.4 - One-way sensitivity analysis on the mean ICERS achieved by the 2030 HCV elimination screening strategy. Baseline scenario is shown for reference. Point and error bars represent the median values along with the 2.5 to 97.5 percentiles of the model projections across the 10,000 baseline model fits.

From our ANOVA analysis, the main contributor to uncertainty in model projections for the mean ICER of the 2030 HCV elimination strategy the cost of care for stage F2 and F3 liver fibrosis, contributing 22.2% of the variation as described in table 5.5. With other main contributors to the uncertainty being the cost of care for individuals at stage F1 of liver fibrosis and the QALY scores of individuals who require a liver transplant which accounted for 16.9% and 9.4% of the variation, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The cost of care for stage F2 and F3 liver fibrosis</td>
<td>22.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 The cost of care for stage F1 liver fibrosis</td>
<td>16.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 The QALY score of individual’s who require a liver transplant</td>
<td>9.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 The cost of care for compensated cirrhosis</td>
<td>8.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 The QALYs score of individuals with F2 and F3 liver fibrosis</td>
<td>8.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 5.5 - ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the change in mean ICER observed by 2030 when screening HIV diagnosed MSM 6-monthly, PrEP users 3-monthly and all other MSM every 5 years for HCV, while treating all HCV diagnosed MSM within 6 months. This result is based on all cost and health utility parameters varied in the model over 10,000 runs.
5.4 Discussion

5.4.1 Overview

The current landscape of increasingly rapid treatment after diagnosis of HCV in MSM and expanding PrEP use proves to be extremely beneficial in reducing the number of HCV infections and raising the quality of life experienced in the MSM population. This observation supports another modelling study examining the rapid treatment of MSM during or following acute HCV infection, and rapid treatment is recommended as an HCV elimination strategy in a comprehensive review and discussion of the feasibility of HCV elimination in high risk groups, including MSM. Further halving the time to a completed course of HCV treatment from 6 to 3 months following diagnosis may even be possible with more widely accessible point of care testing for HCV, in which diagnosis and initiation of treatment can all be completed the same day as the clinical appointment. Tests with high levels of both speed and diagnostic accuracy are needed however, with OraSure being found to be the best choice from a comparative systematic review and meta-analysis. Point of care testing has also already been shown to be both cost saving and increase the quality of life impact for chlamydia and gonorrhoea, with current cost effectiveness analyses for HCV indicating it to be about equal to offsite laboratory testing in the general population and within PWID to be more efficient mainly due to less loss to follow-up.

Further to this already evolving state of HCV treatment, our analyses suggest that using routine appointments to perform additional screening or HCV can be highly cost-effective according to the NICE willingness-to-pay threshold of £20,000 per QALY gained in the UK. The most cost-effective scenario in isolation being he bi-annual screening for HCV in HIV diagnosed MSM. Indeed, even over our fairly short time horizon of 2030, screening HIV diagnosed MSM bi-annually saves on average £44.5 million. This sentiment has also been mirrored by an Australian modelling study, which found it highly cost-effective to screen HIV diagnosed MSM regularly for ALT levels and perform general HCV screening. However this intervention alone is limited in its overall impact on the epidemic as a whole. However the scale up of screening to that required for reaching the HCV elimination targets by 2025 and 2030 are both cost-effective interventions respectively, showing the benefit of regular HCV screening in HIV negative MSM in tandem with high risk groups, despite screening of this population alone not being cost-effective. It may in the future also be worth exploring more frequent screening of HIV negative MSM for HCV beyond the average current testing rate of 2.3 years, utilising easily accessible and cost-effective strategies for increased testing frequency such as online STI testing.
For example, to reach the WHO 2030 HCV elimination target would cost £68.8 million, but in doing so, not only do we reduce HCV incidence by 90% overall in all MSM, we would gain 5,525 QALYS, avert 51.8% of all new HCV infections compared to the baseline and generate a mean ICER of £19,212. What is more, by 2050 both elimination target interventions are cost-saving, with the 2030 strategy saving £31.2 million by 2050. Even more promisingly the 2025 scenario has an average ICER of £10,263, with over 90% of model runs indicating an ICER below £20,000 by 2030.

Our sensitivity analyses indicate that the model is extremely sensitive to the price of HCV DAAs, which being so high have been found to be a common barrier in many settings. Indeed, at half price, our 2030 HCV elimination scenario becomes cost saving even by 2030, saving a staggering £744.7 million. It is clear that negotiating the best deal possible on DAA drug price is key to a cost-effective journey towards the elimination of HCV for MSM in the UK.

I also observe that risk compensation associated with PrEP use has a noteworthy negative impact on the cost-efficiency of the suggested 2030 HCV elimination scenario. Indeed, reduced condom use and less preferential mixing by HIV status increase the mean ICER by £33,019 and £6,435 respectively, both of which push the mean ICER over the £20,000 per QALY willingness-to-pay threshold. Therefore risk compensation, especially falls in condom use, should be monitored and deterred where appropriate to ensure the repercussions of its impacts are minimised.

Overall, our findings support the economic feasibility of scaling up screening in UK MSM to reach HCV elimination targets. This analysis also provides strong evidence that utilising existing MSM sexual health appointments for HCV screening can be highly cost-effective in reducing HCV incidence, and could even be cost-saving by 2050.

5.4.2 Strengths and Limitations

I largely draw from the same strengths and limitations in section 4.4.3. The strengths of this analysis lie in modelling the full cost-effectiveness implications epidemic among all MSM in the UK, while accounting for heterogeneities in sexual risk, patterns of mixing by HIV-status, taking into account PrEP based risk compensation and using detailed UK data. A further strength of our analysis includes the robustness of our projections to financially based uncertainties which were included in the randomisation of parameter and sensitivity analysis of our projections. The benefit of mathematical
modelling for this cost-effectiveness analysis also has potential advantages in allowing us to consider the long-term health benefits of prevented infections. However, there is inevitably uncertainty surrounding the future which could affect these projections, especially once we reach the HCV elimination target dates, and the policy of future prescription and uptake of PrEP among MSM in the UK following the end of the IMPACT trial and PrEP related risk compensation.

One potential additional weakness of our analysis is that the cost-analysis portion of our model is more heavily UK-specific than the work performed in chapter 4, both making heavy use of UK specific MSM health appointment guidelines, and health utilities. Therefore this cost-analysis have limited generalisability to other settings. Although conversely, the premise of screening for HCV in existing structures of health care for MSM remains a strong premise to be considered given largely encouraging results.

5.4.3 Comparison with other modelling studies

This work is original in evaluating the cost-effectiveness of HCV screening in reaching HCV elimination targets explicitly over all MSM in the UK. However, other studies have considered the cost-effectiveness of HCV screening and treatment in HIV diagnosed MSM. A recent Dutch study found that immediate treatment, or treatment delayed until the period following the window for spontaneous clearance was cost saving over waiting to treat from stage F2 onwards,\(^{226}\) complimented by an Australian study which found regular screening for acute HCV prolonged the life expectancy of HV-positive MSM whilst also being cost-effective.\(^ {158}\) Both of which support our findings for faster treatment of all MSM for HCV and increased screening frequencies in HIV diagnosed MSM. A review study focusing on the feasibility of HCV elimination targets in HIV positive individuals also highlights these key changes to be needed to reach HCV elimination in high risk groups such as MSM in a cost-effective manner.\(^ {176}\) This study also supports our findings that the cost of DAAs is key to the cost-effectiveness of HCV elimination strategies, paired with the implementation of low cost regular screening, broad treatment access without restrictions and close monitoring of risk behaviours.\(^ {176}\)
Chapter 6 – Discussion

In this thesis, we have examined the pattern of the HCV epidemic in MSM with a focus on ascertaining the feasibility and cost-effectiveness of reaching the WHO and NHS HCV elimination targets. In this final chapter we review and discuss all the work from previous chapters, looking at the strengths and limitations of our work and outlining future directions this research could be developed.

Within chapter 3 we examined a range of known and theorised contributors to the HIV and HCV co-epidemic pattern within MSM. In dissecting a range of biological and behavioural factors, our work indicated that heterogeneity in sexual risk behaviours and preferential mixing by HIV status, known as serosorting, likely drive the HCV epidemic amongst MSM and cause the strongly concentrated prevalence among HIV positive MSM. The mechanism by which this occurs is the formation of a core group of MSM with HIV who also have high risk behaviours. This group form sexual partnerships more readily amongst themselves, which when paired with low condom use and more biological vulnerability to the HCV virus results in extreme amplified chances of HCV transmission. During this chapter, we also began to explore the role of targeted TasP specifically among HIV diagnosed MSM, which our model indicated could be an important tool for combating the current HCV epidemic in line with other modelling from the literature.\(^{179}\) HCV TasP for HIV diagnosed MSM however had less impact in settings that have a greater burden of HCV among HIV negative MSM; a scenario which could occur if sexual risk behaviours increase amongst HIV negative MSM as explored in chapter 4. The dependence of the HCV epidemic in HIV positive MSM is therefore something we must take into account, and it underscores the importance of monitoring HIV negative MSM’s full sexual health and behaviours to assess any shifts in the patterns of the HCV epidemic.

In chapter 4 we also modelled the introduction of PrEP, along with associated risk compensatory behaviour in the form of reduced condom use. We found that in the era of PrEP scale-up, the presence of 12, 6 or 3-monthly HCV screening of HIV diagnosed MSM and PrEP users, along with screening HIV negative non-PrEP users on average every 4.0, 5.2 or 6.1 years, respectively, could achieve the WHO elimination target for decreasing HCV incidence by 2030 in the UK, with the NHS target requiring
screening in HIV negative non-PrEP users to be twice as frequent. This demonstrates that these elimination targets are not possible through only screening HIV diagnosed MSM as some elimination initiatives are attempting, while the scale-up of PrEP provides a valuable opportunity for increasing HCV-screening among higher-risk MSM. Importantly, this added impact of screening PrEP users relies on the assumption that PrEP users are in regular contact with care, which may not be the case for MSM that acquire PrEP through other channels than the NHS. Our study has direct implications for the NHS-England commitment to eliminate HCV through giving specific screening targets for achieving this goal. This also emphasises the importance of making PrEP freely available through formal channels to ensure that the evolution of the HCV epidemic and indeed of other STIs can be screened for and treated effectively. For other countries with similar HCV epidemics in MSM, our findings highlight the need to look beyond just screening HIV diagnosed MSM, to also screening PrEP users and HIV negative non-PrEP users.

Within chapter 5 we expanded on the results presented in chapter 4, by considered the cost-effectiveness of our proposed screening strategies up to and including the strategies which would lead to HCV elimination, with cost-effective strategies defined as costing less than £20,000 per QALY gained. As the most cost-efficient addition to current screening, our modelling suggests that 6 monthly versus yearly screening of HIV diagnosed MSM for HCV would be cost-saving even by a short time horizon ending in 2030. Plus, if we are additionally screening PrEP users 12, 6 or 3-monthly, HCV screening with screening of HIV negative non-PrEP users on average every 5 or 2.5 years, respectively, we can achieve the 2030 WHO and 2025 NHS HCV elimination targets whilst also being cost-effective on a time horizon ending in 2030, and cost saving by a time horizon ending in 2050. Our study echoes the sentiments of current literature on HCV screening, but expands these statements to include HIV negative MSM. This has direct implications for our thinking about our routine screening practices for HCV, in both the UK and other countries with similar HCV epidemics in MSM, pointing towards HCV being routinely screened for along with all other STIs despite current policy not recommending this practice. Future work of interest to expand on this analysis could include examining different points of treatment commencement based on fibrosis stage and liver damage, to examine the benefit of early versus deferred treatment. This could easily be achieved by adding criteria to the model for HCV treatment eligibility dependant on the liver disease progression compartment of an individual.

Overall this work indicates the need to monitor and evaluate the changes in MSM behaviour over all subgroups in the coming years due to its influence on the patterns and transmissibility of HIV, HCV and other STIs. This is especially pertinent in the current era of PrEP, where many concerns exist.
around the ways in which PrEP may alter the landscape of sexual behaviours. Changes in attitudes driven by PrEP may be hugely beneficial to the MSM community: leading to reduction in HIV related stigma; allowing more MSM to have the kind of sex they desire; less fear and anxiety around sexual health; and provide an opportunity for regular sexual health check-ups for MSM who are generally at a higher level of STI risk. However some of these changes are accompanied by negative side-effects from a health care burden perspective, such as: lowered condom use leading to more STI infections; less preferential mixing by HIV status (which protects HIV negative MSM from STI transmission from higher risk core group); changes to sexual positioning; and increases in risky behaviours, all of which could make efforts to reduce the incidence of HCV and other STIs more difficult. This is mirrored by the past introduction of ART which, although a significant positive step to HIV management, came with its own hazards and changes which needed navigating. By learning from the past lessons of the era of ART, we can enter the era of widespread PrEP prepared and ready to reap the benefits and minimise the risks. Largely, our work has already indicated that even with these changes, our interventions remain feasible and may still be cost-effective, but may require more resource than would otherwise be expected, which we need to be ready to expend if necessary.

A central theme and strength of the work in this thesis was to be inclusive of all MSM, regardless of their HIV status. Largely this approach has been complementary to current work focusing on HIV diagnosed MSM, but has allowed an extra layer of perspective into the dynamics of HCV in UK MSM. For example, previous work examining the HCV epidemic amongst HIV diagnosed MSM has evaluated the impact of scaling-up HCV treatment in this group. While our analysis supports findings of these previous studies by indicating that scaling-up HCV treatment among HIV positive MSM could have substantial prevention benefits among HIV positive MSM, it additionally allowed us to assess how different behavioural and biological factors could result in the observed epidemic patterns, and discover the diminishing return of HCV TasP if HCV prevalence becomes higher in HIV negative MSM. Our analysis also allowed us to evaluate the HCV screening and treatment needed in all MSM subgroups. This was especially important in considering the effect of PrEP on HCV elimination targets and the subsequent cost-analysis, as PrEP will significantly shape the prevalence and incidence of HIV in the MSM population; change sexual risk landscapes; and be likely to attract a higher risk group of MSM in whom HCV is very likely to be more concentrated.

Equally, some of the main limitations of our work have highlighted the need for more comprehensive data collection or studies to contribute narrower parameter windows for future modelling which could be collected through empirical studies. Firstly, data regarding the time of HCV diagnosis in HIV
negative MSM, and secondly the prevalence of both HCV antibody and HCV RNA amongst HIV negative MSM are key to accurate modelling but are not readily available. These parameters are important to our modelling because of the major role that these parameters play in the variation of the outcomes of our model runs. Our estimate for increased HCV infectiousness amongst HIV positive MSM for sexual transmission to their partners is also very uncertain. There are no studies that explicitly measure this potentially key factor, although we can assume that higher HCV viral load in blood samples amongst HIV-positive MSM translates to increased infectivity. While data from vertical transmission studies suggests our assumption is reasonable, this may not be the case. It would be highly interesting and useful for modelling studies, if future studies could establish the exact biological mechanisms behind the sexual transmission of HCV. From this work we could more accurately place risky sexual behaviours into their full context and role in HCV transmission. Our work also assumes a 90% efficacy of DAAs, which has been since superseded by the next generation of DAAs boasting cure rates which can be upwards of 95%. This would likely increase the impact of our suggested interventions in controlling the HCV epidemic and consequently mean our interventions would have lower ICERs or become more cost-saving.

This model assumed fixed levels of risk through-out an individual’s lifetime, which is unlikely to be the case. However, data was unavailable to parametrise these changes over time. It is likely that with changing risk in the population our interventions would have less impact due to a more even spread of transmission over the population. Consequently, this would lead to less concentration of HCV/HIV infections in core high-risk groups, which we aim to target. We also cannot be certain of the exact scale-up of PrEP, nor the magnitude of risk compensation or behavioural changes that may occur among PrEP users or the general MSM population as a result of PrEP. Indeed, our sensitivity analyses show that if 25.0% PrEP coverage is achieved (instead of 12.5%) then the WHO HCV elimination targets (90% reduction in HCV incidence by 2030) could be reached without increasing HCV screening among HIV negative non-PrEP users. There are also forms of risk behaviour change, which we also have not explicitly modelled, such as the reduction in seropositioning, or a movement towards more sexual partners or to higher risk sexual activities amongst MSM due to PrEP. Further work into these areas would contribute well to the discussion on HIV and HCV policy.

I also utilised a simplified model of HCV and HIV transmission without explicitly recreating historical epidemic trends before 2010. This is largely due to the fact that this has been studied previously in great detail elsewhere. Our modelling in chapter 3 instead looks at the more general epidemic patterns, whilst in chapter 4 and 5, we project forward from an assumed stable HCV prevalence as
suggested would occur in the UK if DAA treatments were introduced without any scale-up. However, this was also partially due to the complexity of modelling two different diseases in the presence of a high number of biological and behavioural factors. Capturing the entire detailed history of both diseases would have meant an overly complex and unwieldy model that would have been computationally intensive and unnecessary for the purposes of our research questions.

Lastly, another significant limitation is our parameterisation of behavioural data to the EMIS-UK dataset. Conversely, compared to a national probability survey on sexual behaviours, the EMIS-UK dataset was biased towards higher-risk MSM due to their web-based convenience sampling approach, as well as MSM with higher education levels. These MSM may have a greater interest in HIV prevention and so increased propensity to mix preferentially by HIV status and use condoms with perceived serodiscordant partners. Also, because the model is UK-specific, it may have limited generalisability to other settings. Although most high income countries have a similar predominance of HCV in HIV diagnosed MSM, some epidemics are increasing or decreasing, while it is relatively stable in the UK. Additionally, our projections should not be generalised to lower and middle-income country settings which have different patterns of HIV and HCV prevalence among MSM.

Despite these limitations, our work has been important in providing modelling-based evidence towards indicating the main drivers of the HCV epidemic in MSM and subsequently examine how to cost-effectively reach the 2025 NHS and 2030 WHO HCV elimination targets. We hope that this work will contribute to the discussion of health policy, especially in regard to encouraging universal routine screening of HCV in HIV negative MSM, regular screening for HCV in PrEP users and consistent HCV testing as standard in health checks for those with HIV. This work supports the idea that HCV can be eliminated, and that along with PrEP’s impact on HIV, DAAAs can provide a healthier, less fearful and safer future for MSM in the UK.
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Additional Materials
Infectious Diseases

Behavioural, not biological, factors drive the HCV epidemic among HIV-positive MSM: HCV and HIV modelling analysis including HCV treatment-as-prevention impact

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Previous partial presentation of results of this study in meetings: INSHU 2015, AASLD 2015, IAS 2015, SCCS 2015.

Abstract

Background: Uncertainty surrounds why hepatitis C virus (HCV) is concentrated among HIV-positive men who have sex with men (MSM). We used mathematical modelling to explore reasons for these infection patterns, and implications for HCV treatment-as-prevention.

Methods: Using a joint MSM HIV/HCV transmission model parameterized with UK behavioural data, we considered how biological (heightened HCV infectivity and reduced spontaneous clearance among HIV-positive MSM) and/or behavioural factors (preferential sexual mixing by HIV status and risk heterogeneity) could concentrate HCV infection in HIV-positive MSM as commonly observed (5-20 times the HCV prevalence in HIV-negative MSM; defined as the HCV ratio). We explored how HCV treatment-as-prevention impact varies under differing HCV ratios.

Results: Biological factors produced low HCV ratios (< 3), not explaining the skewed epidemic. However, combining preferential mixing by HIV status with sexual risk behaviour heterogeneity produced high HCV ratios (> 10) that were highly sensitive to both factors. Irrespective of the HCV ratio or behavioural/biological factors, HCV treatment of HIV-diagnosed MSM markedly reduced the HCV prevalence among HIV-positive MSM, but less impact was achieved among all MSM for lower HCV ratios.

Conclusions: Sexual behaviour patterns likely drive observed HCV infection patterns among HIV-positive MSM. Changes in these patterns could disseminate HCV amongst HIV-negative MSM, limiting the impact of targeting HCV treatment to HIV-diagnosed MSM.
Introduction

An epidemic of hepatitis C virus (HCV) continues unfolding among HIV-positive men-who-have-sex-with-men (MSM) in the UK, Europe, the USA and Australia.\(^1\) HCV is a leading non-AIDS cause of death among MSM with HIV.\(^2\) The incidence of HCV among HIV-positive MSM is generally 5-20 times higher than in HIV-negative MSM.\(^1,3\) In the UK, the HCV seroprevalence among HIV-negative MSM was estimated to be 1.2% (0.6–2.1%) in 2009\(^4\) but was 9.9% among HIV-positive MSM in 2012.\(^5\)

Behavioural and biological factors have been proposed to account for the large discrepancy in HCV burden between HIV-positive and HIV-negative MSM.\(^6,7\) Biological factors include reduced chances of spontaneously clearing the HCV virus\(^8,9\) and higher HCV viral loads, potentially leading to greater infectivity in HIV-positive MSM.\(^10,11\) Behavioural factors include sexual partner selection based on HIV status and heterogeneity in sexual risk.\(^6,12\) Heterogeneities in risk and precautionary behaviours could incorporate differences in numbers of sexual partners and use of condoms, different preferences for ano-brachial insertion (fisting), and injecting illicit drugs.\(^5,13–15\) Additionally, partner selection and risk behaviours may interact, such as reduced condom use occurring between couples that assume they are sero-concordant.\(^12\) These heterogeneities in sexual risk and mixing could lead to groups with higher risk and thus greater sexually transmitted infection (STI) and HIV prevalences.

We developed a dynamic joint HIV/HCV transmission model among MSM to explore the contribution of behavioural and biological factors to why HCV is concentrated among HIV-positive MSM. We assessed how variations in these biological and behavioural factors may affect the HCV distribution, and evaluated the resulting implications for HCV treatment-as-prevention.\(^5\)

Key Messages

- Biological factors alone do not explain why the HCV epidemic is strongly concentrated among HIV-positive MSM.
- Sexual behavioural risk heterogeneity and HIV preferential mixing among sexual partners is likely to explain this observation. Changes in sexual mixing patterns could reshape the epidemic.
- Targeted HCV treatment-as-prevention among HIV-diagnosed MSM could be an important tool for combating the current HCV epidemic, but will have less impact in settings which have or develop a substantial burden of HCV among HIV-negative MSM, underscoring the importance of HCV monitoring in this population.

Methods

Model derivation

A dynamic, deterministic model of HIV and HCV transmission among MSM was developed. We divided MSM into compartments (model schematic in Supplementary Figure S1, available as Supplementary data at IJE online) defined by HIV status (susceptible, undiagnosed acute infection, undiagnosed chronic infection and diagnosed HIV infection), HCV status (susceptible, chronic HCV, chronic HCV treatment failure) and low and high sexual risk groups, based on annual numbers of partners that MSM have anal sex with. A simplified model was designed, that was not intended to rigorously simulate the historical HIV epidemic as done in other studies.\(^16\)

MSM enter the model when they reach sexual maturity and exit though death or ageing out of the model at 65 years of age. The model is dynamic, such that the risk of an individual acquiring HIV or HCV is related to the background prevalence of that infection, which can change over time. We assume that both diseases are transmitted through sexual episodes, which may involve unprotected anal intercourse, injecting drug use and fisting.\(^17–20\) Because individuals with more anal intercourse partners (whom we deem ‘high-risk’) also have a higher frequency of injecting drugs, fisting and other high-risk behaviours, high-risk MSM were assumed to have higher chances of HIV and HCV exposure.\(^6,13–15\)

Once HIV infected, individuals enter undiagnosed acute HIV infection, with heightened HIV infectivity,\(^21\) subsequently transitioning to undiagnosed chronic HIV infection. Individuals are assumed not to become HIV diagnosed during the short (2.6 months) acute phase of HIV infection.\(^21\) On diagnosis, MSM transition to diagnosed chronic HIV, where a proportion receive HIV antiretroviral treatment (ART) which we assume reduces HIV infectivity\(^22,23\) and increases survival.\(^24,25\)
Newly HCV-infected MSM that do not spontaneously clear HCV transition to chronic HCV. The HCV acute phase was not included due to its likely small contribution to HCV transmission.26 Those clearing HCV remain susceptible. When included in our analysis, HCV treatment is assumed to cure infection for a proportion of individuals but not to confer immunity. Successfully treated MSM remain at risk of reinfection. Unsuccessfully treated MSM move into the treatment failure class and remain infected with HCV.

To explore the implications of HIV infection for HCV infection/transmission patterns, we consider scenarios where HIV has no effect on HCV, and the alternative: where HIV infection increases HCV liver-related progression and mortality,27 reduces spontaneous clearance8,9 and increases HCV infectivity.10,11 We assume HCV does not impact on HIV disease progression or ART response.

Model parameterization
We modelled HIV and HCV transmission among sexually active MSM aged 15–65, parameterizing sexual behaviour with the UK component of the European MSM Internet Survey (EMIS-UK).28 EMIS was an online survey undertaken during June-August 2010, recruiting online and promoted offline through print media. Over 18,000 MSM living in the UK participated. From EMIS-UK data, we calculated the proportion of HIV-diagnosed MSM’s sexual partners they assumed were HIV-positive (36.2%) and condom use in these pairings (13.0% in latest sex act) compared with (68.0% in latest sex act) other MSM partnerships. EMIS-UK data also determined the heterogeneity in frequencies of sexual partnerships. When risk heterogeneity was explored, we divided the MSM population into categories of low and high risk by the annual number of casual sexual partnerships, 14 or less and 15 or greater, respectively, with 82.2% and 17.8% in the low- and high-risk groups, respectively. In some scenarios, an additional risk was also associated with MSM in the high-risk group due to EMIS-UK data suggesting that a greater proportion of these MSM either inject drugs (3.6% versus 1.0% among low-risk MSM), or undertake receptive (21.1% versus 8.6%) or insertive fisting (38.7% versus 14.0%) in the past year.5,13–15 Biological parameters were obtained from the literature. HCV treatment was not included in the baseline model because we were not aiming to closely model the precise HCV epidemic in the UK, and it was not considered to be an important determinant of observed epidemic patterns at existing treatment rates.5 All model parameters are outlined in Tables 1 and 2.

Model fitting and scenarios
For each different behavioural and biological risk factor scenario described below and in Table 2, the model was calibrated to a stable HIV and HCV prevalence. The model was run with a non-least-squares fitting algorithm which took point values of all parameters relevant to the scenario (shown in Table 2), except the transmission parameters for HCV and HIV which were used to fit the simulation. We calibrated the model to a 5% HIV prevalence among MSM29 and a chronic HCV prevalence of 10% among HIV-infected MSM.5 This approach gives a simplified characterization of the HIV and HCV epidemic among MSM in the UK. We did not fit the HCV prevalence among HIV-uninfected MSM. Instead, we explored the effect of the different scenarios on the HCV prevalence among HIV-uninfected MSM, while assuming a 10% HCV prevalence among HIV-infected MSM. The scenarios are as follows.

i. Baseline. No effect of HIV infection on HCV progression, transmissibility or spontaneous clearance; no heterogeneity in sexual risk behaviour or HIV preferential mixing among MSM.

ii. Biological factors only. Infection with HIV reduces HCV spontaneous clearance probability, increases HCV-related mortality and increases HCV infectivity.

iii. Mixing by HIV status with biological factors. MSM select partners preferentially based on HIV status with errors in judgement, with an additional sub-scenario assuming less condom usage among partnerships where HIV-diagnosed individuals think their partner is also HIV-positive (irrespective of whether right or not). Biological factors included as above.

iv. Heterogeneity in sexual risk behaviour with biological factors. Heterogeneity in sexual risk behaviour based on number of partners. Two additional sub-scenarios further assume that: (a) MSM select partners preferentially based on risk group; or (b) MSM select partners preferentially based on risk and assume further elevated transmission risk associated with high-risk MSM based on their higher prevalence of injecting drugs and fisting. Biological factors included as above.

v. All factors. Mixing is by HIV status and heterogeneity in sexual risk included as described above, with all associated effects from previous scenarios. Biological factors included as above.

Model analyses and sensitivity analyses
Impact on the HCV ratio: to explore the impact of these scenarios on the HCV relative burden among HIV-positive MSM, we define the HCV ratio as the chronic prevalence
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source reference</th>
<th>Details/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow and outflow rate due to entry and exit (annual)</td>
<td>0.02</td>
<td>–</td>
<td>Model age of sexual activity from 15 to 65</td>
</tr>
<tr>
<td>Excess death rate due to chronic HCV mono-infection (annual)</td>
<td>0.0014</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Excess death rate due to mono-infection with HIV untreated (annual)</td>
<td>0.089</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Decreased mortality hazard ratio for HIV mono-infection due to ART treatment</td>
<td>0.29</td>
<td>24, 25</td>
<td></td>
</tr>
<tr>
<td>Excess death rate due to HIV in HIV-HCV co-infection with no HIV treatment (annual)</td>
<td>0.089</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Excess death rate due to HCV in HIV-HCV co-infection with no HIV treatment (annual)</td>
<td>0.0035</td>
<td>27, 44</td>
<td>2.3 times higher than the excess death rate in HCV mono-infected individuals.</td>
</tr>
<tr>
<td>Excess death rate due to HIV in HIV-HCV co-infection with ART treatment (annual)</td>
<td>0.0024</td>
<td>27, 44</td>
<td>1.7 times higher than the excess death rate in HCV mono-infected individuals.</td>
</tr>
<tr>
<td>Transmission factor for HCV</td>
<td>Fit</td>
<td>5</td>
<td>Model calibrated to a 10% chronic HCV prevalence among HIV-positive MSM.</td>
</tr>
<tr>
<td>Efficacy of HCV treatment</td>
<td>90%</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Spontaneous clearance probability for HCV in HIV-negative MSM</td>
<td>0.25</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Odds ratio for spontaneous clearance probability for HCV in HIV-positive MSM compared with HIV-negative MSM</td>
<td>0.68</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HIV</td>
<td>Fit</td>
<td>29</td>
<td>Model calibrated to a 5% HIV prevalence among MSM.</td>
</tr>
<tr>
<td>Factor increase in HIV infectiousness during acute HIV phase compared with chronic HIV</td>
<td>26</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Duration in months of acute HIV phase of infection</td>
<td>2.9</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Relative transmissibility of HIV infection when on ART treatment compared with untreated HIV</td>
<td>0.1</td>
<td>23, 45</td>
<td></td>
</tr>
<tr>
<td>Percentage of diagnosed MSM on ART treatment</td>
<td>83.2%</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Diagnosis rate of HIV</td>
<td>1/3.2 years</td>
<td>29</td>
<td>Modelling approach to back-calculate diagnosis rates for HIV, range for 2010</td>
</tr>
<tr>
<td>Factor increase in HCV infectiousness due to HIV co-infection</td>
<td>2.35</td>
<td>10, 11</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Percentage of MSM who mix non-randomly with MSM they assume have the same HIV status as themselves. Other MSM mix randomly</td>
<td>35.2%</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Consistency of condom use between an HIV-diagnosed MSM and an assumed HIV-positive partner in latest sex act</td>
<td>13%</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Consistency of condom use between all other MSM sexual pairings in latest sex act</td>
<td>68%</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>70%</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Chance of error when evaluating HIV status of a sexual partnera</td>
<td>24.9%</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Percentage of individuals in the low-risk sexual behaviour groupa</td>
<td>82.2%</td>
<td>EMIS</td>
<td>EMIS data used to split the population into low- and high-risk, based on a number of partners for anal intercourse &gt; 15 or &lt; 15 in past year</td>
</tr>
<tr>
<td>Percentage of individuals in the high-risk sexual behaviour groupa</td>
<td>1-Low</td>
<td>EMIS</td>
<td></td>
</tr>
<tr>
<td>Mean number of sex partners for anal intercourse (when heterogeneity is turned on, low- and high-risk groups in brackets)a</td>
<td>7.4 [2.9, 29.1]</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Increased overall risk ratio of HIV and HCV transmission due to injecting drugs and fisting between low- and high-risk groupa</td>
<td>2.7</td>
<td>EMIS [6, 13–15]</td>
<td>See Supplementary material for details</td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by risk behaviour categorya</td>
<td>0.2</td>
<td>EMIS</td>
<td>See Supplementary material for details</td>
</tr>
</tbody>
</table>

*aSee Supplementary material for details, available at IJE online.*
Table 2. Parameterization of the scenarios with point values shown for each model parameter, showing values used for different sub-scenarios in Figures 1 and 4, with range in [ ] being the +/-100% range used in Figures 2, 3 and 5.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>HCV mono-infection excess annual death rate</th>
<th>Co-infection excess annual death rate without HAART</th>
<th>Co-infection excess annual death rate on HAART</th>
<th>Risk ratio for HCV infectivity if HIV+ compared with if HIV-</th>
<th>High-flow- risk partner ratio</th>
<th>High-flow- risk fisting/IDU risk ratio</th>
<th>Proportion MSM mixing by HIV status</th>
<th>Error in HIV status judgements of sex partners</th>
<th>Ratio difference in condom use between assumed sero-concordant HIV+ MSM partnerships and all other MSM partnerships</th>
<th>Proportion MSM mixing by risk status</th>
<th>Risk ratio of spontaneous clearance if HIV+ compared with HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Baseline</td>
<td>No effects present</td>
<td>0</td>
<td>0.089 (HIV-related death rate)</td>
<td>0.0258 (HIV-related death rate)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Biological factors</td>
<td>HCV death rates, HCV spontaneous clearance and infectivity are dependent on HIV status</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35 [1, 3.7]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>3. Mixing by HIV status</td>
<td>Biological factors with MSM preferentially selecting partners by HIV status, and sub-scenario with less condom use in assumed HIV+ pairings plus error in judgements of HIV status</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35 [1, 3.7]</td>
<td>1</td>
<td>1</td>
<td>35.2% [0%, 70.4%]</td>
<td>24.9%</td>
<td>1 or 5c [1, 9]</td>
<td>0</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>4. Heterogeneity in sexual risk behaviour</td>
<td>Biological factors with more sexual partners among high-risk MSM. Sub-scenarios consider effects of MSM selecting partners based on risk behaviour and including risk from fisting or IDU</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35 [1, 3.7]</td>
<td>10.0 [1, 20.0]</td>
<td>1 or 2.7b [1, 4.4]</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0 or 0.2a [0, 0.4]</td>
<td>0.68 [1, 0.36]</td>
</tr>
<tr>
<td>5. All effects</td>
<td>All the effects from the other scenarios</td>
<td>0.0014</td>
<td>0.0925</td>
<td>0.0282</td>
<td>2.35 [1, 3.7]</td>
<td>10.0 [1, 20.0]</td>
<td>2.7 [1, 4.4]</td>
<td>35.2% [0%, 70.4%]</td>
<td>24.9% [0%, 49.8%]</td>
<td>5 [1, 9]</td>
<td>0.2 [0, 0.4]</td>
<td>0.68 [1, 0.36]</td>
</tr>
</tbody>
</table>

Sub-scenarios within the main scenarios take the parameter values corresponding to the values given by a, b and c in the table where relevant. IDU, injecting drug use.
of HCV in HIV-positive MSM divided by the chronic prevalence of HCV in HIV-negative MSM. We first use point values for each parameter (Table 2) and assess whether each scenario produces an HCV ratio commonly observed in the UK and other settings (HCV ratio > 5). Then, to test the model’s sensitivity to parameter variation, for scenario 5 (all factors included) we undertook a univariate sensitivity analysis where we varied each scenario related parameter individually across +/−100% of their point value, and assessed the effect on the HCV ratio. These wide parameter uncertainty ranges were used to account for unknown biases and uncertainties in the data, with the same relative range being assumed for each parameter to see how each affected the results over the same relative range. We then performed bivariate sensitivity analyses on key parameters identified at the univariate level, quantifying their importance for three different levels of error in judgement of HIV status of sexual partners (+100%, 0% and +100% of point value).

Impact on HCV treatment-as-prevention initiatives: we explored the impact of HCV treatment-as-prevention for the different scenarios (Table 2). For each, we assessed the 10-year decrease in chronic HCV prevalence, among HIV-positive MSM and all MSM, achieved for an illustrative HCV treatment intervention that annually treated 10% of HIV-diagnosed HCV co-infected MSM. We assumed a 90% sustained viral response (SVR) with interferon-free direct acting antiviral therapy (DAA). By simultaneously sampling (5000 iterations) all the parameters varied for the univariate sensitivity analysis undertaken on scenario 5, we then considered the effect of variations in the HCV ratio on the impact of the illustrative HCV treatment-as-prevention strategy. Last, for scenario 5 (all factors), we individually varied key parameters across +/−100% of the point value, to assess their influence on the reduction in chronic HCV prevalence achieved with treatment.

Results

HCV ratio analysis

Model projections of the HCV ratio for the different scenarios in Table 2 are shown in Figure 1. If no biological or behavioural factors are included (scenario 1), the predicted HCV ratio is low but greater than one (1.39) due to MSM entering the model being susceptible to both diseases, so creating an increased proportion of HIV-negative MSM without HCV. Including biological factors only (scenario 2) marginally elevates the HCV ratio (1.41) because the greater HCV transmissibility in HIV-HCV co-infected MSM increases HCV transmission in both HIV-negative and HIV-positive MSM. Similarly, including preferential mixing by HIV status (scenario 3) cannot reproduce the high HCV ratio observed in the UK (HCV ratio of 5–20), with modelling projecting an HCV ratio of 1.7, which increases to 2.2 with inclusion of lower condom use in partnerships where HIV-diagnosed individuals assume their partner is HIV-positive.

In contrast, higher and more commonly observed HCV ratios (> 5) are achieved through including heterogeneity in sexual risk behaviour (scenario 4). For instance, stratifying MSM into low- and high-risk groups based on the number of sexual partners, with greater injecting drug use and fisting among high-risk individuals, and preferential mixing between these groups produces an HCV ratio of 9.7.

Last, combining all behavioural and biological factors (scenario 5) amplifies the HCV ratio to 19.7, with different factors acting synergistically to transmit HCV among HIV-positive MSM but not HIV-negative MSM.

Univariate and bivariate sensitivity analyses on the HCV ratio

Univariate variations of parameters in scenario 5 around their point values (+/−100%; Table 2) identified four key parameters that have most effect on the HCV ratio (Figure 2): (i) proportion of individuals preferentially mixing by HIV status (HCV ratio varies from 9.7 to 43.9); (ii) error in HIV status judgements (HCV ratio varies 16.2–24.4); (iii) ratio difference in numbers of partners between low- and high-risk MSM groups (HCV ratio varies 3.4–28.6); and (iv) additional relative risk for HCV transmission in high-risk MSM due to risky sexual behaviours (HCV ratio varies 8.3–33.5). Parameters that did not affect the HCV ratio as much are shown in Supplementary Figure S3, available as Supplementary data at IJE online.
The bivariate sensitivity analysis explored the relationship between the four most influential parameters from the univariate analysis (Figure 3). The two risk heterogeneity parameters were varied simultaneously, forming one combined measure. The HCV ratio is sensitive to levels of heterogeneity in sexual risk behaviour and preferential mixing by HIV status, which amplify each other. Indeed, the figures illustrate that HCV ratios of 5–20 are possible with high levels of risk heterogeneity alone, or moderate levels of both preferential mixing by HIV status and risk heterogeneity with any level of error in HIV status judgements. Greater error in HIV status judgements dampens the HCV ratio.

Impact of HCV treatment-as-prevention
Annually treating 10% of HIV-diagnosed HCV co-infected MSM for HCV over 10 years reduces HCV chronic prevalence among HIV-positive MSM by a relative 40.3–50.3%
across the different scenarios (Figure 4a). However, impact among the entire MSM population varies markedly, from a relative reduction in chronic HCV among MSM of 3.5% for scenario 1 to 29.3% for scenario 5 (Figure 4b). Figure 5 illustrates this effect further with the HCV ratio having a relatively small influence on the HCV treatment-as-prevention impact among HIV-positive MSM (Figure 5a), but a large influence among all MSM (Figure 5b). At higher HCV ratios, more of the epidemic is concentrated among HIV-positive MSM, so focusing treatment efforts on this population effectively combats the epidemic among all MSM. Univariate variations in parameters that have a large effect on the HCV ratio also affect the impact of HCV treatment among HIV-positive MSM on the overall HCV epidemic (Supplementary Figures S4 and S5, available as Supplementary data at IJE online).

**Discussion**

We find that biological factors alone (lower spontaneous clearance rate and higher HCV infectivity and mortality among HIV-infected MSM) are unable to explain why the HCV epidemic is concentrated among HIV-positive MSM. Instead, we suggest that behavioural factors (heterogeneity in sexual risk behaviour alone or combined with preferential mixing by HIV status) are highly likely to account for the higher HCV burdens among HIV-positive MSM. Thus, HCV infection and co-infection should be seen as a marker of high sexual risk behaviours, which are preferentially undertaken within partnerships with other HIV-positive MSM. This is likely to have been aided by the scale-up of effective HIV treatment improving the survival of higher-risk MSM, paired with possible increases in risk behaviour due to ‘treatment optimism’.

Importantly, these results highlight the possibility that changes in sexual behaviour or mixing patterns could reshape the HCV epidemic. For example, decreases in preferential mixing by HIV status could occur due to reductions in perceived risk resulting from widespread ART or pre-exposure prophylaxis (PrEP) use reducing HIV infectivity and susceptibility, which could increase HCV transmission among HIV-negative MSM. Alternatively, fewer high-risk MSM acquiring HIV (due to PrEP) might also raise the likelihood of HCV transmission among HIV-negative MSM, although this may be offset by increased HCV monitoring of MSM being prescribed PrEP.
Further, HCV treatment-as-prevention initiatives among HIV-diagnosed MSM will have greatest impact on overall levels of HCV transmission in settings where HCV is concentrated among HIV-positive MSM, as less of the epidemic is driven by HIV-negative MSM. Conversely, settings which have or develop a greater burden of HCV among HIV-negative MSM would also need to focus HCV treatment on the HIV-negative MSM.

Limitations

Our analysis has a number of limitations. First, we used a simplified model of HCV and HIV transmission and ART that was calibrated approximately to the UK without recreating historical epidemic trends, which suggest a slowly increasing HIV and HCV epidemic.\(^2,29\) This was done because our intention was to explore qualitatively how behavioural and biological factors contribute to HCV epidemic patterns, not make detailed predictions about the epidemics’ trajectory. Importantly, this simplification should not affect the degree to which HCV propagates preferentially among HIV-positive MSM. A further simplification of our model involved the incorporation of injecting drug use-related risk as an increased transmission risk among a subset of MSM\(^6,13-15\) instead of explicitly modelling injecting. We made this simplification because, although injecting drug use is a risk factor for HIV/HCV acquisition among MSM, it is unclear the degree to which this is due to injecting drug use itself or co-occurring high-risk sexual behaviours. Also, datasets such as EMIS only ask basic questions about undertaking injecting drug use in the past year, so preventing any explicit modelling of its role in HCV transmission among MSM.

Second, there exists uncertainty in our parameters and variation across settings, most notably amongst those related to self-reported behavioural data. We performed extensive sensitivity and scenario analyses to explore the effect of varying different behavioural factors. As such, our analyses form a platform from which to explore how variations in parameter assumptions affect observed epidemic patterns and treatment-as-prevention impact. However, care should be taken in generalizing our results to non-high-income settings where limited data suggest lower HCV-co-infection prevalences among MSM\(^32\) and where differences in sexual behaviour and the underlying HIV and HCV epidemic are likely to heavily effect the HCV epidemic that occurs.

Third, although parameterizing our model to EMIS-UK data produced realistic projections for the HCV ratio (\(~\sim\)20), we advise caution regarding potential over-interpretation of the quantitative accuracy of our model. For instance, the model did not incorporate all sources of HCV infection, such as among migrants with historic HCV infection. Conversely, compared with a national probability survey on sexual behaviours, the EMIS-UK dataset used to parameterize our model was biased towards higher-risk MSM due to their web-based convenience sampling approach,\(^34\) as well as MSM with higher education levels.\(^34\) These MSM may have a greater interest in HIV prevention and so increased propensity to mix preferentially by HIV status and use condoms with perceived sero-discordant partners.

Finally, our estimate for the increased HCV infectiousness among HIV-positive MSM is uncertain, although data from vertical transmission studies\(^11\) suggest our assumption is reasonable. We assume that higher HCV viral load in blood samples among HIV-positive MSM translates to increased infectivity,\(^10\) but this may not be the case. However this should not be a concern, because this parameter had little effect on the resulting model projections.

Comparison with other publications

To our knowledge, this is the first modelling analysis of the joint epidemics of HIV and HCV among MSM, although numerous previous analyses have modelled just HIV\(^17\) and some have also modelled other sexually transmitted infections (STI) among MSM.\(^17,34-37\) However, existing HIV and STI co-infection models generally considered different questions, focusing primarily on the degree to which STIs contribute to HIV transmission and the possible impact of STI treatment on HIV epidemics. Previous analyses have also modelled the transmission of HIV and HCV among people who inject drugs.\(^38-42\) Importantly, existing work by our group and others has modelled the HCV epidemic among HIV-diagnosed MSM, and evaluated the impact of scaling up HCV treatment in this group.\(^5,43\) These studies were limited because they did not explicitly include HIV transmission. Our new analysis supports findings of these previous two studies by indicating that scaling up HCV treatment among HIV-positive MSM could have substantial prevention benefits among HIV-positive MSM.\(^5\) Additionally, it extends previous work by dynamically modelling the transmission of HCV to and from the HIV-negative population, assessing how different behavioural and biological factors could result in the observed epidemic patterns, and evaluating the implications for HCV treatment-as-prevention.

Concluding remarks

Overall, our work indicates that sexual risk behaviour heterogeneity and HIV preferential mixing likely explain why the HCV epidemic amongst MSM is strongly concentrated among HIV-positive MSM, with HCV co-infection possibly signifying high-risk behaviours as suggested by others.\(^15\) Targeted HCV treatment-as-prevention among
HIV-diagnosed MSM could be an important tool for combating the current HCV epidemic, but will have less impact in settings which have or develop a substantial burden of HCV among HIV-negative MSM. This could occur if sexual risk behaviours increase among HIV-negative MSM or if higher-risk MSM do not become HIV-infected as readily. This underscores the importance of monitoring HCV among HIV-negative MSM, to assess any shifts in the patterns of the HCV epidemic.

Supplementary Data
Supplementary data are available at IJE online.

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Author Contributions
P.V. and N.K.M. designed the study. C.M. undertook preliminary model analyses. L.M. undertook the statistical analyses, model development, simulations and analyses. P.V., N.K.M. and L.M. wrote the first draft of the article. L.M., C.M., F.H., P.W., M.H., N.K.M. and P.V. interpreted the data, edited the article and approved the final version.

Conflict of interest: NKM and PV have received research grants from Gilead, and NKM has received honoraria from Merck, AbbVie, and Gilead. LM has nothing to report.

References


Supplementary Material to Behavioural, not biological, factors drive the HCV epidemic among HIV-positive MSM: HCV and HIV modelling analysis including HCV treatment-as-prevention impact

Details of the Mathematical Model

**Basic model compartments**

For a given compartment of our model, we represent the full disease and risk status of an individual by $X_{ij}$ where $X$ denotes the HIV status, $i$ denotes the HCV status, and $j$ the risk group.

The possible stages of HIV infection are set as $S$ for susceptible, $A$ for acute HIV infection, $C$ for chronic undiagnosed HIV infection and $D$ for diagnosed HIV infection.

We denote the stage of HCV infection (subscript $i$) where $S$ is susceptible, $I$ is HCV chronically infected, but not yet received treatment for HCV, and $F$ is HCV treatment attempted but failed. We also split the population into low and high-risk groups (subscript $j$), $L$ for low-risk and $H$ for high-risk. So for example $A_{SL}$ denotes low-risk group individuals who are acutely infected with HIV and susceptible to HCV.

All MSM enter the model at a rate $\theta_i$, and exit the model due to ageing, at a rate $\mu$. Additional mortality is included due to mono-infection of HCV $\mu_{HCV}$, undiagnosed HIV-infection where individuals are not on HAART $\mu_{HIV}^{undag}$, and diagnosed HIV-infection with a proportion of MSM on HAART $\mu_{HIV}^{diag}$. We also include mortality due to HCV and HIV co-infection with death rates of those with undiagnosed HIV status denoted by $\mu_{CO}^{undag}$ and diagnosed HIV status as $\mu_{CO}^{diag}$.

$\sigma_j$ is the force of infection for HIV, which is dependent on risk group denoted by $j = L$ or $H$.

Once HIV-infected, $a$ is the rate individuals move from the acute phase of HIV to chronic infection, and $d$ the subsequent rate at which chronically infected MSM with HIV are diagnosed.

$\lambda_{jk}$ is the force of infection for HCV, which is defined in greater detail later in this supplementary material, but is defined by risk group denoted by $j = L$ or $H$, and by the HIV infection and diagnosis status of the individuals in the compartment, which may either be $k=0$ for those which are still susceptible or HIV uninfected, $k=1$ for those that have undiagnosed HIV infection and $k=2$ for those with diagnosed HIV infection. Sometimes, $u$ for HIV undiagnosed or HIV susceptible may be used if $k=0$ or 1 and $d$ for HIV diagnosed if $k=2$.

$r_k$ is the rate of successful HCV treatment which returns HCV infected individuals to the susceptible category and $f_k$ for the rate of HCV treatment failure which moves individuals to the treatment failure compartment. These individuals are not retreated, and so stay in this group. These are also affected by the HIV infection and diagnosis status of the individuals in the compartment.

We assume individuals do not move from their respective risk groups ($j=L$ or $H$). This assumption is based on data from the EMIS and UK gay men’s survey that suggests MSM have a similar rate of unprotected sex, injecting drug use, and fisting from their 20s to their 50s[1], and data from MSM HCV incidence studies that suggests there is no clear relationship between age and HCV acquisition risk[2-4].

The way in which these parameters interact can be seen in figure S1 and is detailed in the compartmental equations.
Therefore, the overall model equations are as follows:

For $j = L$ or $H$,

\[
\frac{dS_{Sj}}{dt} = \theta_j + r_0 S_{ij} - \sigma_j S_{Sj} - \lambda_{j0} S_{Sj} - \mu S_{Sj}
\]

\[
\frac{dS_{ij}}{dt} = \lambda_{j0} S_{Sj} - r_0 S_{ij} - \sigma_j S_{ij} - f_0 S_{ij} - \mu S_{ij} - \mu_{HCV} S_{ij}
\]

\[
\frac{dS_{Fj}}{dt} = f_0 S_{ij} - \sigma_j S_{Fj} - \mu S_{Fj} - \mu_{HCV} S_{Fj}
\]

\[
\frac{dA_{Sj}}{dt} = r_1 A_{ij} + \sigma_j S_{Sj} - \lambda_{j1} A_{Sj} - a A_{Sj} - \mu A_{Sj} - \mu_{HIV} A_{Sj}
\]

\[
\frac{dA_{ij}}{dt} = \sigma_j S_{ij} + \lambda_{j1} A_{Sj} - f_1 A_{ij} - a A_{ij} - \mu A_{ij} - \mu_{HIV} A_{ij}
\]

\[
\frac{dA_{Fj}}{dt} = f_1 A_{ij} + \sigma_j S_{Fj} - a A_{Fj} - \mu A_{Fj} - \mu_{HIV} A_{Fj}
\]

\[
\frac{dC_{Sj}}{dt} = r_1 C_{ij} + a A_{Sj} - \lambda_{j1} C_{Sj} - d C_{Sj} - \mu C_{Sj} - \mu_{HIV} C_{Sj}
\]
\[
\frac{dC_{ij}}{dt} = \lambda_{j}C_{sj} + aA_{ij} - r_{1}C_{ij} - f_{1}C_{ij} - dC_{ij} - \mu_{C_{ij}} - \mu_{\text{un}diag,C_{ij}}
\]

\[
\frac{dC_{Fj}}{dt} = aA_{Fj} + f_{1}C_{ij} - dC_{Fj} - \mu_{C_{Fj}} - \mu_{\text{un}diag,C_{Fj}}
\]

\[
\frac{dD_{sj}}{dt} = r_{2}D_{sj} + dC_{sj} - \lambda_{sj}D_{sj} - \mu_{D_{sj}} - \mu_{\text{HIV},D_{sj}}
\]

\[
\frac{dD_{ij}}{dt} = \lambda_{ij}D_{ij} - r_{2}D_{ij} - f_{2}D_{ij} - \mu_{D_{ij}} - \mu_{\text{diag},D_{ij}}
\]

\[
\frac{dD_{Fj}}{dt} = dC_{Fj} + f_{2}D_{ij} - \mu_{D_{Fj}} - \mu_{\text{diag},D_{Fj}}
\]

**Forces of infection**

The forces of infection $\lambda_{jk}$ for HCV and $\sigma_{j}$ for HIV are dependent on the risk group ($j=\text{L or H}$) and HIV infection and diagnosis status ($k=0$ for uninfected, 1 for HIV infected but undiagnosed, and 2 for diagnosed, with $u$ sometimes being used if $k=0$ or 1 and $d$ being used if $k=2$). So for example, $\lambda_{H1}$ will denote the force of infection for HCV which applies to individuals who are in the high risk group, HIV infected but undiagnosed.

**Defining the mixing function**

For the HIV and HCV force of infection in our model, we must account for the fact that MSM mix preferentially by risk status and their assumed HIV status, and so must account for the HIV diagnosis and risk status of the primary individual and their potential partners. We therefore first formulate a function $m_{jklm}$ for the probability that an MSM in risk group $j$ and HIV diagnosis group $k$ forms a sexual partner with an MSM in risk group $l$ and HIV diagnosis group $m$. This probability varies depending on the HIV diagnosis status of the primary individual and partner and so we split the expressions as follows ($u$ is used to denote HIV undiagnosed or uninfected and $d$ is used to denote HIV diagnosed):

\[
m_{julu} = \delta_{jl}b \left( \zeta + (1 - \zeta) \frac{N_{ju}}{\sum_{all n} N_{jn}} \right) + (1 - b) \left( \zeta \frac{p_{l}N_{lu}}{\sum_{all n} p_{n}N_{nu}} + (1 - \zeta) \frac{p_{l}N_{lu}}{\sum_{all n,o} p_{n}N_{no}} \right)
\]

\[
m_{jdlu} = \delta_{jl}b \left( \zeta + (1 - \zeta) \frac{N_{jd}}{\sum_{all n} N_{jn}} \right) + (1 - b) \left( \zeta \frac{p_{l}N_{ld}}{\sum_{all n} p_{n}N_{nd}} + (1 - \zeta) \frac{p_{l}N_{ld}}{\sum_{all n,o} p_{n}N_{no}} \right)
\]

\[
m_{juid} = \delta_{jl}b (1 - \zeta) \frac{N_{jd}}{\sum_{all n} N_{jn}} + (1 - b)(1 - \zeta) \frac{p_{l}N_{ld}}{\sum_{all n,o} p_{n}N_{no}}
\]

\[
m_{jdlu} = \delta_{jl}b (1 - \zeta) \frac{N_{ju}}{\sum_{all n} N_{jn}} + (1 - b)(1 - \zeta) \frac{p_{l}N_{lu}}{\sum_{all n,o} p_{n}N_{no}}
\]

Where $N_{jk}$ is the number of individuals in risk group $j$ and HIV infection and diagnosis group $k$, $p_{j}$ is the number of partners on average per year dependant on low or high-risk group ($j=\text{L or H}$) $\delta_{jl}$ is the kronecker delta function that is 1 when $j=l$ and zero otherwise, $b$ is the probability that the primary individual consciously forms a partner with someone of the same risk behaviour, with the remainder formed with no preference for the same risk level, and $\zeta$ is the probability that the primary individual consciously mixes to form a partnership with someone of the same assumed HIV status, with the
remainder formed with no preference for HIV status. This can either involve someone who is HIV-infected and diagnosed mixing with someone they assume is also HIV-infected and diagnosed, or someone who is undiagnosed that assumes they are HIV-uninfected mixing with someone they assume is also HIV-negative. In words, the probability that an individual in risk group j has a sexual partner with someone in risk group l, is b if they are the same risk group plus if they don’t specifically choose someone in the same risk group (probability 1-b), then the probability that they choose an individual randomly from that group - this is assumed to be based on the relative number of sexual partnerships provided by individuals in that group compared to other groups. Similar assumptions are made for HIV mixing and then these two forms of mixing have to be combined so that we estimate the probability of choosing someone in risk group l and HIV infection and diagnosis group m as above.

The function $$m_{ijklm}$$ then has to be adapted because there is generally judgement errors when individuals choose partners by HIV status, and condom use is much lower if a HIV infected diagnosed MSM thinks their sexual partner is also HIV infected. We firstly adapt $$m_{ijklm}$$ to include error in choosing a partner of the same HIV status, where e is the chance an erroneous judgement about HIV status resulting in random mixing.

$$m_{julu} = \delta_{jl} b \left[ \zeta (1 - e) + (1 - \zeta (1 - e)) \frac{N_{ju}}{\sum_{a} n_j N_{jn}} \right] + (1 - b) \left[ \zeta (1 - e) \frac{p_l N_{lu}}{\sum_{a} n_p N_{nu}} + (1 - \zeta (1 - e)) \frac{p_l N_{lu}}{\sum_{a} n_o p_n N_{no}} \right]$$

$$m_{jldl} = \delta_{jl} b \left[ \zeta (1 - e) + (1 - \zeta (1 - e)) \frac{N_{ld}}{\sum_{a} n_j N_{jn}} \right] + (1 - b) \left[ \zeta (1 - e) \frac{p_l N_{ld}}{\sum_{a} n_p N_{nd}} + (1 - \zeta (1 - e)) \frac{p_l N_{ld}}{\sum_{a} n_o p_n N_{no}} \right]$$

$$m_{juld} = \delta_{jl} b (1 - \zeta (1 - e)) \frac{N_{jd}}{\sum_{a} n_j N_{jn}} + (1 - b) (1 - \zeta (1 - e)) \frac{p_l N_{jd}}{\sum_{a} n_o p_n N_{no}}$$

$$m_{jdlu} = \delta_{jl} b (1 - \zeta (1 - e)) \frac{N_{ju}}{\sum_{a} n_j N_{jn}} + (1 - b) (1 - \zeta (1 - e)) \frac{p_l N_{ju}}{\sum_{a} n_o p_n N_{no}}$$

This is then adapted to give a new function $$M_{ijklm}$$ that also includes the level of protection given by condom use, which is lower if a HIV diagnosed MSM thinks they are having sex with another HIV diagnosed MSM. The parameters $$c_0$$ and $$c_1$$ are the probabilities that condoms will not protect an individual from infection due to the consistency of condom use for that pairing type (see section below for how $$c_0$$ and $$c_1$$ are defined), with $$c_1$$ being for ‘HIV diagnosed MSM with an assumed HIV diagnosed partner’ pairings and $$c_0$$ for all other pairings. In the model, we have to remember that when a HIV diagnosed MSM thinks they have chosen a sexual partner that is HIV diagnosed, they will use condoms with lower consistency and so have protection $$c_1$$ irrespective of whether they were right or not in their assumption, so diagnosed MSM will sometimes use condoms at a lower consistency with MSM that may not be diagnosed.
\[
M_{jlu} = \delta_{jl} b c_0 \left[ \frac{\zeta(1-e)}{\sum_{\text{alt}} n N_{jn}} + (1 - \zeta(1-e)) \frac{N_{ju}}{\sum_{\text{alt}} n N_{jn}} \right] + (1 - b) c_0 \left[ \frac{\zeta(1-e)}{\sum_{\text{alt}} n p N_{nu}} + (1 - \zeta(1-e)) \frac{p_i N_{lu}}{\sum_{\text{alt}} n, o p N_{n0}} \right]
\]
\[
M_{jld} = \delta_{jl} b \left[ \frac{\zeta(1-e) c_1}{\sum_{\text{alt}} n N_{jn}} + (1 - \zeta(1-e)) c_1 \frac{N_{jd}}{\sum_{\text{alt}} n N_{jn}} \right] + (1 - b) \left[ \frac{\zeta(1-e) c_1}{\sum_{\text{alt}} n p N_{nd}} + (1 - \zeta(1-e)) c_1 \frac{p_i N_{ld}}{\sum_{\text{alt}} n, o p N_{n0}} \right]
\]
\[
M_{jlu} = \delta_{jl} b c_0 \left[ (1 - \zeta(1-e)) \frac{N_{ju}}{\sum_{\text{alt}} n N_{jn}} \right] + (1 - b) c_0 \left[ (1 - \zeta(1-e)) \frac{p_i N_{lu}}{\sum_{\text{alt}} n, o p N_{n0}} \right]
\]
\[
M_{jld} = \delta_{jl} b \left[ ((1 - \zeta) c_0 + \zeta c_1) \frac{N_{jd}}{\sum_{\text{alt}} n N_{jn}} \right] + (1 - b) \left[ ((1 - \zeta) c_0 + \zeta c_1) \frac{p_i N_{ld}}{\sum_{\text{alt}} n, o p N_{n0}} \right]
\]

Defining the HIV and HCV force of infection

To define the HIV and HCV force of infection, we also need to define some additional parameters:

\( \Omega \) is the increased HIV infectiousness of those in the acute phase of HIV,

\( \Delta \) is the reduced HIV infectiousness of HIV due to those on HAART,

\( \Lambda \) is the increased HCV infectivity of those with HIV,

\( \beta^{\text{hiv}} \) is the transmission factor for HIV

\( \beta^{\text{hcv}} \) is the transmission factor for HCV.

\( R \) is the additional risk associated with the high risk group due to more frequent fisting and IDU behaviours.

\( x_i \) is the chance an individual will spontaneously clear the virus with subscript \( i=n \) or \( p \) to denote their actual HIV status as negative or positive respectively.

Then for an HIV uninfected primary individual that is low or high risk (\( j = L \) or \( H \)), the HIV force of infection \( \sigma_{j} \) is:

\[
\sigma_{L} = \beta^{\text{hiv}} p_L \left[ M_{\text{Lulu}} \left( \frac{\sum_{\text{alt}} m (\Omega A_{ml} + C_{ml})}{\sum_{\text{alt}} m (S_{ml} + A_{ml} + C_{ml})} \right) + M_{\text{Lulu}} \left( \frac{\sum_{\text{alt}} n (\Omega A_{nh} + C_{nh})}{\sum_{\text{alt}} n (S_{nh} + A_{nh} + C_{nh})} \right) + \Delta M_{\text{LuxLd}} + \Delta M_{\text{LuLuD}} \right]
\]
\[
\sigma_{H} = \beta^{\text{hiv}} p_H \left[ M_{\text{HuLu}} \left( \frac{\sum_{\text{alt}} m (\Omega A_{ml} + C_{ml})}{\sum_{\text{alt}} m (S_{ml} + A_{ml} + C_{ml})} \right) + M_{\text{HuLu}} \left( \frac{\sum_{\text{alt}} n (\Omega A_{nh} + C_{nh})}{\sum_{\text{alt}} n (S_{nh} + A_{nh} + C_{nh})} \right) + \Delta M_{\text{HuLuD}} + \Delta M_{\text{HuHuD}} \right]
\]

Then for an HCV uninfected primary individual that is low or high risk (\( j = L \) or \( H \)), and are either HIV-negative (\( k=0 \)), or HIV infected and undiagnosed (\( k=1 \)) or HIV infected and diagnosed (\( k=2 \)), the HCV force of infection \( \lambda_{jk} \) is:
\[
\begin{align*}
\lambda_{L0} &= \beta_{hcV} \ p_L(1 - x_p) \left[ M_{Lulu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Luhu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Ludh} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Ldhf} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right] \\
\lambda_{L1} &= \beta_{hcV} \ p_L(1 - x_p) \left[ M_{Lulu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Luhu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Ludh} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Ldhf} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right] \\
\lambda_{L2} &= \beta_{hcV} \ p_L(1 - x_p) \left[ M_{Ldlu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Ldhu} \left( \frac{\sum_{m=1}^{mL} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mL} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Ldud} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Lhdh} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right] \\
\lambda_{H0} &= \beta_{hcV} \ R_{P}{H}(1 - x_p) \left[ M_{Hulu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Huhu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Hudh} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Huhf} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right] \\
\lambda_{H1} &= \beta_{hcV} \ R_{P}{H}(1 - x_p) \left[ M_{Hulu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Huhu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Hudh} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Huhf} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right] \\
\lambda_{H2} &= \beta_{hcV} \ R_{P}{H}(1 - x_p) \left[ M_{Hdlu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) + M_{Hdhu} \left( \frac{\sum_{m=1}^{mH} (S_{ml} + \Lambda A_{ml} + \Lambda C_{ml})}{\sum_{m=1}^{mH} (S_{ml} + A_{ml} + C_{ml})} \right) \\
&\quad + \Lambda M_{Hdud} \left( \frac{D_{lh} + D_{fL}}{D_{sl} + D_{lh} + D_{fL}} \right) + \Lambda M_{Hhdh} \left( \frac{D_{ih} + D_{fH}}{D_{sh} + D_{ih} + D_{fH}} \right) \right]
\end{align*}
\]

**Condom usage terms**

As used in the formulation for \( M_{ijkm} \) above, and so the forces of infection, the model parameters \( c_0 \) or \( c_2 \) are denoted as the probability that condoms will not protect an individual from infection due to the consistency of condom use for that pairing type, where \( c_1 \) is for ‘HIV diagnosed MSM with an assumed HIV diagnosed partner’ pairings and \( c_2 \) for the other pairings. The protection a condom offers when used is denoted as \( P \) (HCV and HIV). HIV diagnosed MSM with an assumed HIV diagnosed partner are assumed to use condoms with consistency \( D \), whereas all other partnerships are assumed to use condoms with equal consistency \( U \). The parameters \( c_0 \) and \( c_1 \) are therefore defined as:

\[
\begin{align*}
c_0 &= 1 - UP \\
c_1 &= 1 - DP
\end{align*}
\]

Or if we change these equations to incorporate the ‘the relative risk of using condoms amongst ‘other pairings’ compared to partnerships between HIV diagnosed MSM with an assumed HIV diagnosed partner’ as \( g=U/D \), then \( D = U/g \), so

\[
c_0 = 1 - UP
\]
Treatment Equations for HCV

$\psi_k$ is the rate of HCV treatment which varies by HIV diagnosis status.

$y_i$ is the efficacy of the treatment which varies by HIV infection status, $i=n$ for HIV negative and $i=p$ for HIV positive.

$r_k$ is the rate of successful treatments for HCV and $f_k$ is the rate of unsuccessful treatments for HCV ($k=0$ for those which are still susceptible or HIV uninfected, $k=1$ for those that have undiagnosed HIV infection and $k=2$ for those with diagnosed HIV infection, although $u$ for undiagnosed may be used if $k=0$ or 1 and $d$ for diagnosed if $k=2$), which we formulate from $\psi_k$ and $y_i$, resulting in:

\[
\begin{align*}
r_0 &= \psi_u y_n \\
r_1 &= \psi_u y_p \\
r_2 &= \psi_d y_p \\
f_0 &= \psi_u (1 - y_n) \\
f_1 &= \psi_p (1 - y_n) \\
f_2 &= \psi_d (1 - y_p)
\end{align*}
\]
EMIS Derived Parameter Calculations

Mixing of MSM by HIV Status

Q69. What do you think your current HIV status is (whether or not you've ever tested for HIV)?
1=Definitely negative (I don't have HIV) 2=Probably negative 3=Not sure / I don't know 4=Probably positive 5=Definitely positive (I do have HIV)

This question above provides the perceived HIV status of the individual in question. Only a confirmed diagnosis i.e. answer 5 (10.4% report this) is counted as being ‘HIV Diagnosed’. The number of individuals is very small who answered with response 4 (0.5%). The other categories (including answer 4) are classed as ‘HIV Negative or Undiagnosed’ (89.6%). This is potentially an over-estimate of HIV prevalence as EMIS is likely to have attracted more participants of HIV positive status than found in the general MSM population.

Q185. What did you know or think about his HIV status before having sex? 1=I knew or thought he was HIV negative 2=I knew or thought he was HIV positive 3=I don’t remember 4=I didn’t have any thoughts about his HIV status

This question allows us to identify perception of the HIV status of their last sexual partner. For individuals that perceived themselves to be HIV diagnosed or not, we estimated the proportion of each that thought their last partner to be HIV positive, HIV-negative, and for those that said they did not think about it we assumed that a proportion were HIV-positive based on the UK prevalence of HIV infection. Assuming their judgements are correct, this allowed us to estimate the likely proportion of sexual partners that were HIV-infected and the proportion that were not. For example in our data 36.2% of HIV diagnosed MSM thought their last partner was HIV positive, 16.9% thought they were HIV-negative, and 46.9% hadn’t thought about it when selecting a partner. Assuming their judgement is correct and a 5% HIV prevalence in the UK, we estimate that (36.2% + 0.05 × 46.9%) = 38.5% of HIV positive MSM made pairings with positive partners. Conversely, because 16.9% thought their partner was HIV negative we estimate that (16.9% + (1 − 0.05) × 46.9%) = 61.5% of HIV positive MSM made pairings with HIV negative partners.

From EMIS, we used these point estimates to construct a single parameter for the degree of like-with like mixing of MSM by HIV diagnosis status. We refer to MSM who are HIV undiagnosed or negative as non-diagnosed. Firstly, we assume that:

\[ Y = 0.05 \] is the proportion of MSM with HIV;

\( e \) is the chance of errors in HIV judgements; and

\( \zeta \) is the probability that an individual will preferentially seek a partner of the same HIV diagnosis status

If we define \( \text{mix}_{km}^{\text{HIV}} \) as the probability that an individual of HIV diagnosis state \( k=u \) or \( d \) (where \( u \) is undiagnosed or HIV negative MSM and \( d \) is HIV diagnosed MSM) has a sexual partner of HIV diagnosis state \( m=u \) or \( d \), then we can estimate \( \text{mix}_{km}^{\text{HIV}} \) as follows:
\[ \text{mix}^{HIV}_{uu} = \zeta(1 - e) + (1 - \zeta(1 - e))(1 - Y) \]
\[ \text{mix}^{HIV}_{ud} = (1 - \zeta)Y + \zeta eY \]
\[ \text{mix}^{HIV}_{du} = (1 - \zeta)(1 - Y) + \zeta e(1 - Y) \]
\[ \text{mix}^{HIV}_{dd} = \zeta(1 - e) + (1 - \zeta(1 - e))Y \]

The EMIS data indicates that this mix function should have the following values:

\[ \text{mix}^{HIV}_{uu} = 94.3\% \]
\[ \text{mix}^{HIV}_{ud} = 5.7\% \]
\[ \text{mix}^{HIV}_{du} = 61.5\% \]
\[ \text{mix}^{HIV}_{dd} = 38.5\% \]

Of these values, we aim to capture the best fit for \( \text{mix}^{HIV}_{dd} \) as this is our main effect of interest. When we fit \( \zeta \) to give these values for \( \text{mix}^{HIV}_{km} \) from EMIS values, assuming \( e = 0 \) and that the prevalence of HIV is 5% as in the UK, then we estimate that \( \zeta = 0.352 \) is the best fit, which results in the following mixing:

\[ \text{mix}^{HIV}_{uu} = 96.8\% \]
\[ \text{mix}^{HIV}_{ud} = 3.2\% \]
\[ \text{mix}^{HIV}_{du} = 61.5\% \]
\[ \text{mix}^{HIV}_{dd} = 38.5\% \]

**Chance of error when evaluating HIV status of a sexual partner**

The following question in EMIS was used to get an estimation of the likelihood of error when evaluating the HIV status of a sexual partner, following from question 185, which asked what people thought about the HIV status of their last casual partner.

**Q186.** [if Q185=1 or 2] Why did you think this? Please read the list below and tick the answer that best applies. 1=He told me some time ago / I had known for some time 2=He told me (online or in person) before or during sex 3=I knew it from his profile on the Internet 4=He made it clear without actually telling me 5=Someone else told me 6=We were at an event where everyone was HIV positive 7=We were at an event where everyone was HIV negative 8=I guessed 9=Other reason

If guessing a partner was HIV negative, we assumed that answers 2 and 3 were likely to be correct assumptions, it was uncertain whether answers 1, 4, 5, 7 and 9 could yield errors in judgement and that answer 6 (very few answered to this for partners thought to be negative) and 8 were highly likely to be unable to determine the HIV status of your partner accurately.

If guessing a partner was HIV positive we assumed that answers 1, 2, 3 and 6 were likely to be correct assumptions, it was uncertain whether answers 4, 7 and 9 could yield errors in judgement and that answers 5 and 8 were highly likely to be unable to determine the HIV status of partners accurately.
Therefore, the proportion of assumptions likely to be correct were 54.3% and 68.7% when a partner was assumed HIV negative or HIV positive MSM respectively. The proportion of assumptions which were correct or uncertain amounted to 84.9% and 87.9% when a partner was assumed HIV negative or HIV positive MSM, respectively. This allows us calculate the error range as between 15.1-45.7% (midpoint 30.6%) when an MSM thought their partner was HIV negative, and 12.1-31.3% (midpoint 19.2%) when an MSM thought their partner was HIV positive. These midpoints are close enough that we combine them together, averaging to 25%.

We also note that in this instance guessing a partner’s actual HIV status is akin to guessing if they are diagnosed or not, as if the partner in question was unaware of their HIV infection, then they could not communicate if they were HIV positive to their partners.

**Condom usage by perceived HIV Status**

The following questions are used to determine whether a condom was used for a specific sexual contact with a partner:

Q187. Did you have anal intercourse (fuck) on that occasion? 1=No 2=Yes, he fucked me 3=Yes, I fucked him 4=Yes, we fucked each other

Q188. [if Q187=2 or 4] Did he use a condom when he was active in anal intercourse (when he fucked you)? 1=No 2=Yes 3=I don’t remember/I don’t know

Q190. [if Q187=3 or 4] Did you use a condom when you were "active" in anal intercourse? 1=No 2=Yes 3=I don’t remember/I don’t know

If an individual responds to Q187 with answer 4, then we require a yes to both Q188 and Q190 to decide that a condom has been used. Otherwise, we need a yes to Q188 if they answered 2 for Q187, and a yes to Q190 if they answered 3 to Q187.

We found that when HIV diagnosed MSM have sex with a partner they assume to be HIV positive there is a 13% chance of condom usage, whereas all other pairings had similar levels of condom usage of approximately 68% in last sex act.

**Defining the high/low-risk sexual behaviour group**

For this parameter, we combine the number of casual and long term partners an individual reports in the last year. To do this, we use the following questions:

Q157. [if Q155=2] How many steady male partners have you had anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 or more

Q165. [if Q163=2] How many non-steady partners did you have anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 12=11-20 13=21-30 14=31-40 15=41-50 16=More than 50

For both the question on steady and non-steady partners, we find the midpoint for each categorical response and add them together to determine the average number of partners across the MSM. For the last category of each question (more than 10 steady partners and more than 50 casual partners) we use the shape of the distribution to estimate the average number of partners for those who answered in this final range (11.85 and 64.5 for respectively). This produced an average number of partners for all MSM of 7.4.
We also used this distribution to determine a cut-off for defining the high and low risk group. We chose the cut-off for high risk as greater than 15 partners in the last year due to the shape of the histogram in figure S2. Using this cut-off 82.6% of MSM fall into the low risk group and 17.4% in the high risk group. The average number of partners in the last year was 2.9 in the low risk group and 29.1 in the high risk group.

![Histogram of the distribution of total sexual partners in the last year as given by the EMIS data.](image)

**Figure S2**: Histogram of the distribution of total sexual partners in the last year as given by the EMIS data

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**Calculation of relative risk (risk ratio) of HIV and HCV transmission due to injecting drugs and fisting between low and high risk group**

We used the following EMIS questions to assess the prevalence of injecting drug use and fisting behaviours in the low and high risk group, as defined by number of sexual partners in last year (see last section).

Q221. Have you ever injected any drug other than anabolic steroids or medicines? 1=No, never 2=Yes, within the last 12 months 3=Yes, more than 12 months ago

- Percentage of low-risk MSM reporting injecting drug use in last 12 months - 1.0% (0.8-1.1%)
- Percentage of high-risk MSM reporting injecting drug use in last 12 months - 3.6% (3.0-4.2%)

Q174. When did you last put your hand into a man's rectum (do the fist-fucking)? [recency response set]

- Percentage of low-risk MSM reporting fisting (receptive) in last 12 months - 8.6% (8.0-9.0%)
Percentage of high-risk MSM reporting fisting (receptive) in last 12 months - 21.1% (19.7-22.7%)

Q175. When did you last have a man's hand in your rectum (get fist-fucked)? [recency response set]

Percentage of low-risk MSM reporting fisting (insertive) in last 12 months - 14.0% (13.2-14.6%)

Percentage of high-risk MSM reporting fisting (insertive) in last 12 months - 38.7% (37.0-40.6%)

Using findings from previously published studies that have considered the degree to which HIV and HCV acquisition risk is elevated amongst MSM reporting these risk behaviours, we are then able to multiply the prevalence of these activities in each group with the odds ratio associated with these acts increasing HCV and HIV acquisition risk. Combining these products gives us an estimate of the average amount these behaviours as a whole may be elevating HIV and HCV acquisition risk in low and high risk MSM.

Added risk of HIV acquisition from injecting drugs in last 12 months— OR 2.23 (1.49-3.33) [20]

Added risk of HCV transmission from injecting drugs in the last 12 months— OR 2.05 (0.72-5.82) [22]

Added risk of HIV acquisition from fisting (receptive) in last 12 months— OR 3.10 (1.46, 6.60) [24]

Added risk of HIV acquisition from fisting (insertive) in last 12 months— OR 1.58 (0.85, 2.95) [24]

Added risk of HCV acquisition from fisting (receptive) in last 12 months— OR 4.75 (2.14-10.57) [22]

Added risk of HCV acquisition from fisting (insertive) in last 12 months— OR 5.53 (2.59-11.81) [22]

The following calculation is used to estimate the combined increased acquisition risk for HIV and HCV in the low and high-risk groups:

Elevated acquisition risk in low-risk group=∑(Prevalence of Activity in Low group x Activity OR)

Elevated acquisition risk in low-risk group=∑(Prevalence of Activity in High group x Activity OR)

The summations are over the different risk behaviours – injecting drug use, insertive and receptive fisting.

To estimate the increased relative risk (RR) in high-risk MSM due to these behaviours, the elevated acquisition risk in high-risk MSM is divided by the elevated acquisition risk in low risk MSM. To estimate the likely uncertainty range around the RR for HIV and HCV, we randomly sample (n=100,000) from the uncertainties ranges using a uniform distribution for the ORs and proportions reporting each risk behaviour, and for each set of sampled values re-estimate the RR. This gives the following ranges for the RR for HIV and HCV:

HIV RR = 2.69 (2.33-3.04)

HCV RR= 2.71 (2.36-3.06)

Given the RRs are similar for each infection, we assume a point value of 2.7 for increased risk and vary both equally in the sensitivity and uncertainty analyses.

Like-with-like mixing by risk group

Little data exists on the degree of like with like mixing occurs amongst MSM in the UK. The data from EMIS comes from the following question that asks about where an individual met their last sexual
partner, which can be used to see if high risk MSM mainly meet partners in venues that other high-risk men meet partners but not low risk partners.

Q182. Where did you first meet him? 1=A gay community centre, gay organisation or gay social group 2=A gay café or gay bar 3=A gay disco or nightclub 4=A backroom of a bar, gay sex club, a public gay sex party 5=A gay sex party in a private home 6=A gay sauna 7=A porn cinema 8=A cruising location (street, roadside service area, park, beach, baths, lavatory) 9=A website for gay or bisexual men 10=Elsewhere

For this we specify:

\( p_j \) as the number of partners per year in the high or low risk group, \( j = L \) or \( H \)

\( N_j \) as the proportion of the population in the high or low risk group, \( j = L \) or \( H \)

\( V_j^x \) as the proportion of individuals from the high or low risk group, \( j = L \) or \( H \), who met their last partner in venue \( x \) from the answer selections above. We exclude venues 9 as it is impossible to tell how MSM will mix based on online information from our data set, and whether it will be preferentially or not. For example hook-up apps may cause high risk individuals to mix preferentially and websites for MSM seeking relationships may also promote mixing between MSM with less partners. We also exclude 10 as we don’t have specific information about the venue type. Venues 1-8 however we can assume that once present, will ensure even mixing for all individuals there.

If we define that \( m_{ij}^{risk} \) as the probability that an individual of risk group \( j \) (L or H) will mix with an individual of risk group \( l \) (L or H), then \( m_{ij}^{risk} \) can be estimated as follows:

\[
m_{ij}^{risk} = \sum_{x=1}^{8} V_j^x \left( \frac{V_j^x p_l N_l}{V_L^x p_l N_L + V_H^x p_H N_H} \right)
\]

Using this equation we therefore predict with our EMIS data that:

\[
m_{HH}^{risk} = 0.7012 \]
\[
m_{HL}^{risk} = 0.2988 \]
\[
m_{LH}^{risk} = 0.6643 \]
\[
m_{LL}^{risk} = 0.3357 \]

Based on the overall frequency of partnerships provided by MSM from the low and high risk group, we expect that:

\[
m_{HH}^{risk} = 0.6898 \]
\[
m_{HL}^{risk} = 0.3102 \]
\[
m_{LH}^{risk} = 0.6898 \]
\[
m_{LL}^{risk} = 0.3102 \]

So, to calculate the proportion of MSM who preferentially mix by risk status (\( b \), as defined earlier) we use the equations:

\[
m_{HH}^{risk} = b + (1 - b)0.6898
\]
\[ mix_{HL}^{\text{risk}} = (1 - b)0.3102 \]
\[ mix_{LH}^{\text{risk}} = (1 - b)0.6898 \]
\[ mix_{LL}^{\text{risk}} = b + (1 - b)0.3102 \]

The closest fit we have to the data is when \( b = 0.03675 \) - so an estimated 3.7% of MSM preferential mix by risk status. However, 56% of individuals said they met their last partner on the internet, which may also result in mixing by risk status (people often state their sexual preferences and risk behaviour), but could not be estimated with the available data from EMIS. Therefore, preferential mixing by risk status could be greater than we estimated, and so we assumed a larger value that 20% of MSM preferentially mix by risk status, and explored its potential role through uncertainty and sensitivity analysis. However this is certainly a limitation of our data and better data collection for this parameter would be advantageous for future modelling.

References

Figure S3. Effect of univariate changes in individual parameters which did not substantially affect the HCV ratio (A-D) for the “All effects” scenario 5. All other parameters are set to their point values in Table 2 within the main article. Numbers shown on x-axis are -100% of the point value, the point value and +100% of point value.
Figure S4. Effect of univariate changes in individual parameters on the impact of HCV treatment on reducing HCV chronic prevalence in HIV-positive MSM within the “All effects” scenario. All other parameters are set to their point values unless varied. Numbers shown on x axis are -100% of the point value, the point value and +100% of point value.
**Figure S5.** Effect of univariate changes in individual parameters on the impact of HCV treatment on reducing HCV chronic prevalence in all MSM within the “All effects” scenario. All other parameters are set to their point values unless varied. Numbers shown on x axis are -100% of the point value, the point value and +100% of point value.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow and Outflow for the model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of initiation of sexual activity</td>
<td>15</td>
<td>EMIS</td>
<td>EMIS data backs up that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Exit age for the model due to sexual cessation</td>
<td>65</td>
<td>EMIS</td>
<td>EMIS data backs up that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Standard exit rate</td>
<td>0.02</td>
<td>EMIS</td>
<td>$1/(\text{period of sexual activity})=1/50=0.02$</td>
</tr>
<tr>
<td>Inflow of population to the model</td>
<td>0.02</td>
<td>EMIS</td>
<td>A steady population was assumed in absence of HIV mortality and so we equated the inflow rate to the exit rate.</td>
</tr>
<tr>
<td>Excess death rate due to chronic HCV mono-infection</td>
<td>0.0014</td>
<td>[5]</td>
<td></td>
</tr>
<tr>
<td>Excess death rate due to mono-infection with HIV untreated</td>
<td>0.089</td>
<td>[6]</td>
<td>Untreated HIV in MSM results in 11.2 (10.4-12.2) years until death. Death rate is the reciprocal.</td>
</tr>
<tr>
<td>Decreased mortality hazard ratio for HIV mono-infection due to HIV treatment</td>
<td>0.29</td>
<td>[6, 7]</td>
<td>If infected with HIV but on treatment live to 73, so 38 years compared to 11.2 without HAART. 11.2/38</td>
</tr>
<tr>
<td>Excess death rate due to HIV for HIV-HCV co-infection with no HIV treatment</td>
<td>0.089</td>
<td>[6]</td>
<td>Meta-analysis of studies of co-infection death rates, 10 pre-HAART, 27 post HAART suggested that pre-HAART death rate largely only affected by HIV progression. So then we defer to the death rate for when HIV in untreated.</td>
</tr>
<tr>
<td>Excess death rate due to HCV for HIV-HCV co-infection with no HIV treatment</td>
<td>0.0035</td>
<td>[5, 8]</td>
<td>2.5 times higher than the excess death rate in HCV mono-infected individuals = 2.5*0.0014</td>
</tr>
<tr>
<td>Excess death rate due to HCV for HIV-HCV co-infection with ART treatment</td>
<td>0.00238</td>
<td>[5, 8]</td>
<td>1.7 times higher than the excess death rate in HCV mono-infected individuals = 1.7*0.0014</td>
</tr>
<tr>
<td><strong>HCV related parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HCV</td>
<td>Fit to Model</td>
<td>-</td>
<td>Meta-analysis of new direct acting antiviral Sofosbuvir treatment in various combinations. Point estimate used in this case for easy comparison of interventions over different scenarios.</td>
</tr>
<tr>
<td>Efficacy of HCV treatment</td>
<td>90%</td>
<td>[9]</td>
<td></td>
</tr>
<tr>
<td>Spontaneous clearance probability for HCV in HIV negative MSM</td>
<td>0.25</td>
<td>(0.22-0.29)</td>
<td>[10]</td>
</tr>
<tr>
<td>Odds ratio for spontaneous clearance probability for HCV in HIV positive MSM compared to HIV negative MSM</td>
<td>0.68 (0.46-1)</td>
<td>[11]</td>
<td>Clearance rates of HIV positive MSM versus HIV negative MSM.</td>
</tr>
<tr>
<td><strong>HIV related parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HIV</td>
<td>Fit to Model</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Increased HIV infectiousness during acute HIV phase</td>
<td>26 (10-67)</td>
<td>[12]</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, stage of virus estimated for passing on infection, all couples start negative.</td>
</tr>
<tr>
<td>Duration of acute HIV infection</td>
<td>2.9 (1.23-6) months</td>
<td>[12]</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, infectiousness monitored over the duration of infection.</td>
</tr>
<tr>
<td>OR for transmission of HIV infection on HAART compared to untreated HIV</td>
<td>0.1 (0.01-0.27)</td>
<td>[13, 14]</td>
<td>A meta-analysis of varying ART regimes looking at the transmission of HIV virus on treatment.</td>
</tr>
</tbody>
</table>
**Proportion of diagnosed MSM on HAART treatment**

| Proportion of diagnosed MSM on HAART treatment | 0.832 (0.829-0.834) | [15] | UK report of all HIV diagnosed cases, what proportion were receiving treatment that year (2011). |

**Diagnosis rate of HIV**

| Diagnosis rate of HIV | 3.2 (2.6-3.8) | [16] | Modelling approach to back calculate the diagnosis rates for HIV, range for 2010. |

**Increased HCV infectiousness due to HIV infection**

| Increased HCV infectiousness due to HIV infection | 2.35 (1-3.7) | [17, 18] | Various estimates from elevated amounts of HCV viral load in those with HIV of 2.88 times, 3.02 and 3.7 times more likely. Range depicts that higher viral load might not translate to higher infectivity up to highest estimate. |

### Behavioural parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing parameter for choosing partners by HIV diagnosis status</td>
<td>0.352</td>
<td>EMIS</td>
</tr>
<tr>
<td>Condom usage between two diagnosed MSM</td>
<td>13.0 (10.4-15.6%)</td>
<td>EMIS</td>
</tr>
<tr>
<td>Condom usage between other MSM pairings</td>
<td>65 (52-78%)</td>
<td>EMIS</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>0.7 (0.6-0.8)</td>
<td>[19]</td>
</tr>
<tr>
<td>Chance of error when evaluating HIV status of a sexual partner</td>
<td>24.9% (12.1% - 45.7%)</td>
<td>EMIS</td>
</tr>
<tr>
<td>Proportion of individuals in the Low risk group</td>
<td>82.6%</td>
<td>EMIS</td>
</tr>
<tr>
<td>Proportion of individuals in the High risk group</td>
<td>17.4%</td>
<td>EMIS</td>
</tr>
<tr>
<td>Mean number of partners for anal intercourse. (When heterogeneity is turned on, low and high risk group in brackets)</td>
<td>7.4 [2.9, 29.1]</td>
<td>EMIS</td>
</tr>
<tr>
<td>Increased overall risk ratio of HIV and HCV transmission due to injecting drugs and fisting between low and high risk group</td>
<td>2.7 (2.35-3.05)</td>
<td>EMIS [20-23]</td>
</tr>
<tr>
<td>Mixing parameter for choosing partners by risk behaviour category</td>
<td>0.2</td>
<td>EMIS</td>
</tr>
</tbody>
</table>

**Table S1**: Parameters with ranges and details of estimation included (time unit of years unless otherwise stated).
Title: Scaling up screening and treatment for elimination of hepatitis C among men who have sex with men in the era of HIV pre-exposure prophylaxis.

Running Head: Modelling the elimination of hepatitis C in men who have sex with men

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Word count: 4014;

Tables: 2    Figures: 5

Abbreviations: PrEP, pre-exposure prophylaxis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; DAA, direct acting antiviral; PLHIV, people living with HIV; ART, anti-retroviral treatment; STIs, sexually transmitted infections; WHO, World Health Organisation; NHS, National Health Service; EMIS The European Men-Who-Have-Sex-With-Men Internet Survey; UK CHIC, UK Collaborative HIV Cohort.
Declaration of interests: NKM and PV have received unrestricted research grants from Gilead, and honoraria from Gilead. NKM has also received honorarium of Merck. LM, FH and PW have nothing to report.

Author contributions: PV and LM designed the study. LM undertook the statistical analyses, model development, simulations and analyses with supervision from PV. LM and PV wrote the first draft of the article. LM, FH, PW, MD, JN, MH, NKM, and PV interpreted the data, edited the article, and approved the final version.

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ABSTRACT word count 300

Background: Routine HIV pre-exposure prophylaxis (PrEP) and HIV care appointments provide opportunities for screening men who have sex with men (MSM) for hepatitis C virus infection (HCV). However, levels of screening required for achieving the WHO elimination target of reducing HCV incidence by 90% by 2030 among all MSM are unknown.

Methods: An HCV/HIV transmission model was calibrated to UK prevalence of HIV among MSM (4.7%) and chronic HCV infection among HIV-positive MSM (9.9%) and HIV-negative MSM (1.2%). Assuming 12.5% coverage of PrEP among HIV-negative MSM, we evaluated the relative reduction in overall HCV incidence by 2030 (compared to 2018 levels) of HCV screening every 12/6-months (alongside completing treatment within 6-months of diagnosis) in PrEP users and/or HIV-diagnosed MSM. We estimated the additional screening required among HIV-negative non-PrEP users to reduce overall incidence by 90% by 2030. The effect of 50% reduction in condom use among PrEP users (risk compensation) was estimated.

Results: Screening and treating PrEP users for HCV every 12 or 6-months decreases HCV incidence by 67.3% (uncertainty range 52.7-79.2%) or 70.2% (57.1-80.8%), respectively, increasing to 75.4% (59.0-88.6%) or 78.8% (63.9-90.4%) if HIV-diagnosed MSM are also screened at same frequencies. Risk compensation reduces these latter projections by <10%. To reduce HCV incidence by 90% by 2030 without risk compensation, HIV-negative non-PrEP users require screening every 5-6 (3.8-9.2) years if MSM on PrEP and HIV-diagnosed MSM are screened every 6-months, shortening to 4.4 (3.1-6.6) years with risk compensation. For 25.0% PrEP coverage, the HCV elimination target can be reached without screening HIV-negative MSM not on PrEP, irrespective of risk compensation.

Conclusion: At low PrEP coverage, increased screening of all MSM is required to achieve the WHO HCV-elimination targets for MSM in the UK, whereas at higher PrEP coverage this is possible through just screening HIV-diagnosed MSM and PrEP users.

Funding: NIHR, ESPRC

Key words: Pre-exposure prophylaxis, hepatitis C virus, HIV, men who have sex with men, antiviral treatment, prevention, risk compensation
**Key messages**

HIV-negative MSM using HIV pre-exposure prophylaxis are an important target for hepatitis C screening.

Achieving the WHO target of a 90% reduction in incident hepatitis C by 2030 will require improved hepatitis C screening among all MSM, unless PrEP coverage is high (~25%) when HIV-negative MSM not on PrEP may not need to be screened.

Decreases in condom use among HIV-negative MSM on PrEP could greatly increase HCV transmission among PrEP users. However, the reductions in HCV incidence gained through additional HCV screening are not affected substantially by this risk compensation.
Research in context

Evidence before this study

We reviewed current literature on studies that have evaluated interventions required to reach the WHO HCV elimination targets among MSM by 2030. Searches were performed in PubMed with the terms ("MSM" or "men who have sex with men" or "homosexual") and ("HCV" or "hepatitis C") and ("elimination" or "world health organisation" or "WHO target" or "WHO aim" or "WHO goal" or "2030"). We excluded any papers which exclusively discussed low/middle-income countries, as HCV infection patterns among MSM are different in these settings. Eight papers were identified that have investigated or modelled the interventions needed to reach HCV elimination in MSM in high income countries.

In a 2016 modelling study, Salazar-Vizcaya et al explore the transmission of HCV within a Swiss cohort of HIV-diagnosed MSM using a dynamic compartmental transmission model, finding that under stable levels of risk behaviour and treatment for HCV within 1 year of diagnosis, HCV incidence would reduce by 77% by 2030 among HIV-diagnosed MSM. However, reductions in risk behaviour would be needed to reach the 2030 elimination target whereas increases in risk behaviours will lead to much higher overall HCV incidence. Similar conclusions were drawn by a modelling study by Martin et al concerning the HIV-positive MSM population in Berlin, with HCV treatment initiation within 3 months of diagnosis and behavioural interventions both being required to reach the HCV elimination target. A later 2018 modelling study by Scott et al. for Victoria, Australia considered a dynamic compartmental and two agent-based HCV transmission models. This work considered the impact of faster linkage to treatment within 6 months of HCV diagnosis amongst HIV-positive MSM, which lowered HCV prevalence by 80% in just over 2 years in all models.

A further dynamic compartmental HCV transmission model in a 2017 study by Virlogeux et al. based on a French population indicated that an 80% reduction in HCV prevalence could be reached in high risk HIV-positive MSM over 10 years by treating 70% of HCV infections in this group yearly. Further to these modelling studies, several review articles summarise the likely conditions needed for HCV elimination in HIV-positive populations. Both the 2017 and 2018 reviews of modelling and clinical evidence by Martin et al. supported the modelling studies, indicating that HCV elimination is possible amongst people living with HIV (including MSM) provided both HCV treatment and behaviour risk reduction among HIV-positive MSM occurs. Lastly, a 2017 review by Hajarizadeh et al. highlighted the potential drawbacks of treatment as prevention for HCV in MSM due to high re-infection rates, and so raised concerns about attaining the 2030 elimination targets.

Added value of this study

Our study is an important addition to this literature because it is the first to examine HCV elimination targets for the entire population of MSM, not just HIV-positive MSM. We also consider how HCV screening and treatment needs to evolve with the scale-up of PrEP, and should incorporate the possible effect of risk compensation on HCV elimination targets. These additions are useful for policy-makers working towards the WHO 2030 HCV elimination targets of reducing HCV incidence by 90% among MSM. Importantly, at low PrEP coverage our modelling suggests it will be difficult to reach these elimination targets among MSM without also including screening and treatment interventions for HIV-negative MSM, with frequent screening of MSM on PrEP being an important addition to ongoing HCV management strategies. However, at higher PrEP coverage, the elimination targets may be possible through just improving HCV screening in HIV-diagnosed MSM and MSM on PrEP.
Implications of all the available evidence

Our work supports the current literature, showing that the 2030 HCV elimination targets for incidence are achievable among MSM. However, this target may require increased HCV screening of all MSM with faster linkage of diagnosed individuals to HCV treatment. Elimination efforts that are currently only focussing on HIV-diagnosed MSM need to expand their scope to include other MSM groups.
Introduction

Globally, men who have sex with men (MSM) experience a high burden of HIV, with elevated levels of hepatitis C (HCV) co-infection occurring among HIV-positive MSM in high-income countries, but much lower transmission occurring among HIV-negative MSM. This recent MSM HCV epidemic has been associated with sexual and drug-related behaviours, with the polarised pattern of HCV in HIV-infected MSM likely due to heterogeneity in risk behaviours and HIV seroadaptive behaviours. Over 2012-2017, HIV incidence has halved in the UK mainly due to the UK achieving very high levels of ART coverage and HIV viral suppression.

HIV pre-exposure prophylaxis (PrEP) is a pre-emptive anti-retroviral medication, which has high efficacy for preventing HIV acquisition. Many countries are expanding the availability of PrEP among MSM. However, as occurred with the expansion of anti-retroviral treatment (ART), there are concerns that PrEP use could result in increased sexual risk taking, thus increasing the transmission of sexually transmitted infections (STIs), including HCV. Recent studies have confirmed this, giving a consistent picture that the incidence of STIs increases following initiation of PrEP.

Although PrEP is freely available in Wales and Scotland, it has limited availability in England, with PrEP being restricted to individuals enrolled in the IMPACT trial. In all these settings, PrEP is only available to individuals meeting specific eligibility criteria. In England, this mainly involves reporting on-going condomless sex or other factors posing similar HIV-risk. The full IMPACT trial eligibility criteria is included in the supplementary material, with there being similar eligibility criteria in Scotland and Wales.

The World Health Organisation (WHO) recently developed a Global Health Strategy to eliminate HCV, aiming to reduce HCV incidence by 90% by 2030. Elimination initiatives are attempting to achieve this goal among MSM, mainly targeting HIV-diagnosed MSM. In the UK, HIV-diagnosed MSM are advised to be screened for HCV each year, while HIV-negative MSM are rarely tested and there are no HCV testing guidelines for MSM using PrEP.
Previous modelling has considered what is required to eliminate HCV among HIV-diagnosed MSM\textsuperscript{20,21}, but none have accounted for the HCV transmission dynamics among HIV-negative MSM. In this study, we use modelling to determine what HCV testing and treatment strategies are needed to reduce the overall incidence of HCV among MSM by 90\% by 2030 in the UK. We assess how PrEP and any associated changes in condom use may affect the impact achieved, and determine the need for HCV screening among PrEP users and other HIV-negative MSM to help inform future policy and guidelines.

Methods

Model Derivation

We adapt a previous model of HIV and HCV transmission among MSM\textsuperscript{5} to include PrEP use (details in supplementary material). The model (supplementary figure S1) stratifies MSM by: HIV and PrEP status (susceptible on/off PrEP, acute HIV infection on/off PrEP, undiagnosed or diagnosed chronic HIV infection); HCV-status (susceptible, acute HCV infection, undiagnosed and diagnosed chronic HCV infection); and either low- or high-risk sexual behaviour, defined by the annual number of anal sex partners (high-risk defined as $\geq 15$). Individuals are not assumed to change their risk.

Individuals enter the model susceptible to HIV and HCV, not using PrEP, and either low- or high-risk. HIV and HCV transmission occurs at rates related to an individuals’ sexual risk and prevalence of HIV and HCV among their sexual partners. HCV infectivity is elevated for HIV-HCV co-infected individuals based on evidence for vertical HCV transmission (details in supplementary materials).\textsuperscript{22} MSM also mix preferentially, more commonly choosing partners of the same sexual risk and HIV-status (see supplementary materials).

Depending on the PrEP scenario being modelled, HIV-negative individuals may initiate using PrEP, which confers protection to acquiring HIV.\textsuperscript{7,8,23} PrEP was assumed to scale-up from 2018, with
the coverage of PrEP reaching 12.5% of HIV-negative MSM by 2020 with the average duration on PrEP being 8-2 months. PrEP users are screened quarterly for HIV and upon a positive diagnosis stop using PrEP. This frequent HIV-testing means PrEP users are diagnosed before reaching chronic HIV infection. Non-PrEP users who acquire acute HIV infection, firstly transition to undiagnosed HIV infection and are then diagnosed at current UK HIV-testing rates (2-3 years between infection and diagnosis). Acute HIV is assumed to have elevated HIV transmission risk (26-fold). A proportion of HIV-diagnosed MSM are on ART, which increases survival 3.4-fold, with a proportion being virally suppressed and having negligible HIV transmission risk (see supplementary materials).

Newly HCV-infected individuals develop acute HCV infection, following which they either develop chronic HCV infection or spontaneously clear their infection and become susceptible again. The baseline model assumes HIV-negative MSM are diagnosed for HCV based upon symptomatic presentation after 5-15 years. Conversely, undiagnosed HIV-positive MSM receive testing for HCV following HIV diagnosis, with 88% of HIV-diagnosed MSM being screened annually in the UK. At baseline, we assume 2.2 years from diagnosis to completing HCV treatment, consistent with UK data for pre-DAA treatments. Before 2015, we assume different cure rates for HIV-positive (sustained viral response or SVR of 35-42%) and HIV-negative MSM (SVR of 59-69%) based on pre-DAA treatments, but then assume higher cure rates from 2015 for DAA therapies (SVR of 90-100%). From 2018, we then consider the impact of various scenarios of improved HCV screening with faster linkage-to-treatment following diagnosis (6 months to treatment completion); more consistent with current treatment rates. This assumes a 3-month waiting time and an HCV treatment duration of 8-12 weeks. MSM failing treatment are retreated at the same rate as initial HCV treatment.

Parameterization of sexual risk behaviour

Sexual risk behaviours were parameterized using data from the UK component of the European MSM Internet Survey (EMIS-UK); EMIS was a pan-European internet survey on
knowledge, attitudes, needs and behaviour regarding HIV and STI transmission among MSM.\textsuperscript{5} Individuals could complete the survey online during Summer 2010. Over 180,000 men took part from 38 countries, including 18,000 in the UK.\textsuperscript{31} From EMIS, we calculated the level of preferential mixing by HIV-status; proportion of MSM in the low and high-risk groups; prevalence of chem-sex; and levels of condom use stratified by the assumed HIV sero-concordancy. These model parameters are detailed in supplementary Table S3, and summarised in Table 1. Briefly, EMIS data suggests 17.4\% of MSM are high-risk, amongst whom the prevalence of chem-sex in last year is higher than among low-risk MSM (22.6\% versus 11.5\%). The baseline model assumed that MSM have sex more often with others of the same perceived HIV-status, with perceived HIV-positive concordant partnerships having lower condom use (13\%) than other partnerships (68\%).\textsuperscript{5}

\textit{Baseline model calibration}

Assuming historic levels of HCV screening and pre-DAA SVR rates with no PrEP, the model was firstly calibrated to give a stable HIV and HCV epidemic in 2012, in line with prevalence data from the UK Collaborative HIV Cohort (UK CHIC) study.\textsuperscript{28,32,33} UK CHIC involved a collaboration of UK centres providing care for people living with HIV (PLHIV). The study gathered data relating to clinical care of PLHIV since 1996, including data on HCV incidence and prevalence among HIV-diagnosed MSM.\textsuperscript{2}

To calibrate the model, we firstly randomly sampled parameter sets from their uncertainty ranges in Table S3. We then used non-linear least-squares fitting (see supplementary) to estimate transmission parameters for HIV and HCV that result in each model run giving an overall HIV prevalence within the range 4.3-5.3\%\textsuperscript{32} and a chronic HCV prevalence within the range 9.6-10.2\% for HIV-infected MSM at equilibrium.\textsuperscript{28} Model runs were only accepted if they also projected a prevalence of HCV among HIV-negative MSM within the range of 0.6-2.1\%.\textsuperscript{34} In total, we performed 668 runs to obtain 500 fits (75\% acceptance rate). For our results, we present the 2.5\% to 97.5\% percentile range from these 500 model fits, denoted as the 95\% central range (95\% CR).
For each model fit, we then assume that over 2012-2017 there is an increase in: (1) proportion of HIV-diagnosed MSM on ART from 85% to 98%; (2) proportion of those on ART that are virally suppressed from 72% to 97%; and (3) HIV testing frequency from every 3·2 years to 2·3 years. The resulting model projections (supplementary figures S7-S12) were then validated against data suggesting a 55·5% (95% CI 34·4-72·7%) decrease in the annual rate of new HIV infections among MSM over 2012-2017 in the UK. HCV prevalence and incidence also decrease over this period due to an increase to DAA SVR rates from 2015. Despite being not fit to this data, our model projections for HCV incidence among HIV-diagnosed MSM and HIV-negative MSM off PrEP for 2012 are comparable to UK data estimates from that period, as shown in supplementary figures S7-S12.

**PrEP Intervention Scenarios**

The calibrated model was used to estimate the impact of initiating a PrEP programme, with the coverage of PrEP scaling-up to 12·5% of HIV-negative MSM over the period 2018-2020 while assuming the average duration on PrEP was 8.2 months. This coverage assumption was based on NHS-eligibility criteria, where only MSM recently participating in unprotected sex are eligible for PrEP. The relative coverage of PrEP among low- and high-risk MSM reflects this eligibility criteria (see supplementary materials). The efficacy of PrEP for reducing the risk of HIV acquisition was assumed to be 91.5% (86-97%).

PrEP driven risk compensation was also modelled. However, because of inconclusive data on how sexual behaviours may change, we only considered reductions in condom use among MSM using PrEP. In our modelling, we either assume no risk compensation (Scenario S0) or that all PrEP users halve their consistency of condom use from 68% to 34% with all partners (Scenario S1). This assumption is varied in our sensitivity analyses.
**Model analyses**

The main aim of the analysis is to determine what level of HCV screening and treatment is needed among different MSM sub-populations to eliminate HCV in all MSM, while incorporating the possible effects of PrEP scale-up. However, we firstly considered the possible impact of using DAAs as the new standard of care from 2015, and the effect that PrEP alone could have on the number of new HIV and HCV infections, as well as HCV prevalence and incidence in 2030 compared to 2018 levels.

We then evaluated the impact of different HCV screening and treatment scenarios initiated from 2020, to see what is needed to achieve the WHO elimination target. We firstly evaluated the impact of more frequent HCV screening for HIV-diagnosed MSM or PrEP users, with PrEP users otherwise having the same low level of HCV screening as HIV-negative MSM. The impact on HCV incidence among MSM using PrEP was estimated, with the relative change being compared to what the incidence was in those MSM in 2018. Similarly, the impact on HCV incidence in other groups was estimated. For these scenarios, we also assumed improved linkage-to-treatment for those MSM sub-groups with enhanced screening, with MSM completing treatment within 6 months of diagnosis. Lastly, we considered whether improved screening and linkage-to-treatment for HIV-negative MSM not using PrEP was needed to reach the elimination targets. For MSM using PrEP and HIV-diagnosed MSM, 3, 6 or 12-monthly screening were considered, while the screening frequency for HIV-negative MSM not using PrEP was fitted to give an overall 90% reduction in HCV incidence by 2030.

**Uncertainty analysis**

To ascertain which parameters are important for determining variability in the impact projections across the 500 baseline model fits, a linear regression analysis of covariance (ANCOVA) was performed on the projected decrease in overall HCV incidence (2018-2030) of undertaking 6
monthly screening among HIV-diagnosed MSM and MSM using PrEP (no risk compensation). The proportion of the sum of squares contributed by each parameter was calculated to determine each parameters’ importance to the variability in our projections.

We also performed a series of sensitivity analyses where we varied the following: (1) 4 versus 6 months between HCV diagnosis and treatment completion; (2) 25% versus 12.5% coverage of PrEP; (3) condom use among PrEP users decreases to 13% instead of 34% with risk compensation; (4) PrEP is distributed evenly between high and low-risk MSM, or to (5) just low-risk MSM or (6) just high-risk MSM; (7) no increased infectiousness of HCV with HIV co-infection; (8) 50% less mixing by HIV-status following PrEP introduction; (9) no increased risk associated with chem-sex; (10) HCV transmission rate decreased by 20% from 2012 to simulate a decreasing HCV epidemic before the introduction of DAA treatments, or conversely (11) increased by 20% to simulate an increasing HCV epidemic.

Results

Impact of PrEP on HIV

A 12.5% coverage of PrEP among HIV-negative MSM translates to 27.6% of high-risk HIV-negative MSM and 10.3% of low-risk HIV-negative MSM receiving PrEP. Over 2018-2030, this PrEP coverage results in 44.7% (95%CR 30.4-66.7%) of new HIV infections being prevented if sexual behaviours remain unchanged (scenario S0). This large impact on HIV is due to PrEP being targeted to high-risk MSM resulting in the basic reproductive rate decreasing close to one. Less HIV-impact is achieved if PrEP is not targeted to high-risk MSM (figure S5).

Impact of PrEP on HCV

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Due to switching to DAA therapies from 2015, HCV incidence will decrease by 42.1% (95%CR 20.8%-61.9%) over 2018-2030, even without the introduction of PrEP or enhanced HCV screening. With 12.5% coverage of PrEP, an additional small decrease in HCV incidence occurs (by 45.1% (95%CR 16.8%-67.2%) - figure 1 and table 1) if sexual behaviours remain unchanged (S0) and HCV screening remains the same. This decrease is due to PrEP reducing the number of HIV-infected MSM, among whom HCV is concentrated, thus translating to less HIV/HCV co-infections. Interestingly, the HCV prevalence and incidence among HIV-negative MSM using PrEP are both about 3-fold higher than other HIV-negative MSM (figure 1) due to many PrEP users being high-risk (supplementary figure S3). However, although HIV-positive MSM and MSM on PrEP have the highest prevalence of HCV, HIV-negative MSM not using PrEP on average harbour 73.1% of all HCV infections (supplementary figure S4).

With a halving in condom use among PrEP users (S1), HCV incidence now only decreases by 5.9% (95%CR -59.4%-49.5%) over 2018-2030.

Impact of increasing HCV screening in PrEP users

In the previous section, no additional HCV screening of PrEP users occurred. Assuming 12.5% coverage of PrEP and no risk compensation (S0), screening PrEP users every 12, 6 or 3-months (and reducing time to completing treatment to 6-months) reduces the HCV incidence among PrEP users by 65.7% (95%CR 51.1%-77.5%), 68.8% (95%CR 55.9%-79.7%) or 70.4% (95%CR 58.4%-80.7%), respectively, all compared to 2018 levels (figure 2), and the HCV incidence among all MSM decreases by 67.3% (95%CR 52.7%-79.2%), 70.2% (95%CR 57.1%-80.8%) or 71.8% (95%CR 59.5%-81.6%) (figure 3). This sizeable impact is due to HCV transmission being primarily driven by high-risk MSM, which predominate among PrEP users, with the large impact of HCV treatment in PrEP users having a large subsequent impact among other high-risk MSM (especially HIV-positive MSM) due to them.
preferentially mixing with each other (supplementary materials). Risk compensation (S1) reduces the impact of screening PrEP users by about half (figure 3).

**Screening requirements for reaching WHO HCV elimination targets**

Figure 3 shows that screening HIV-diagnosed MSM and/or PrEP users more often (3, 6 or 12-monthly) and reducing the time to completing treatment (6 months) can dramatically reduce the overall incidence of HCV by 2030. For instance, without risk compensation if we improve screening to 3-monthly in only HIV-diagnosed MSM then incidence will decrease by 57·1% (95%CR 27·0-80·1%) by 2030, whereas it will decrease by 80·4% (95%CR 66·6-91·2%) if we also undertake 3-monthly screening in PrEP users. With risk compensation, less impact is achieved, although this is small (10% reduction) when both PrEP users and HIV-diagnosed MSM are screened and treated.

Although considerable impact can be achieved from screening HIV-diagnosed MSM and PrEP users, at 12.5% PrEP coverage it is unlikely to achieve a 90% decrease in overall incidence by 2030 unless we also enhance HCV screening and linkage-to-treatment among HIV-negative MSM not using PrEP. Without risk compensation, screening HIV-negative non-PrEP users every 4·8 (95%CR 3·4-8·0) years will result in a 90% reduction in incidence by 2030 if PrEP users and HIV-diagnosed MSM are screened yearly (figure 4). These screening frequencies reduce if PrEP users and HIV-diagnosed MSM are screened more frequently but increase with risk compensation.

**Uncertainty analysis**

Uncertainty in the increased infectiousness of HCV due to HIV co-infection and the ratio of the number of high-risk MSM on PrEP compared to low-risk MSM accounted for 71.8% of the overall variation in the projected impact on HCV incidence (2018-2030) of undertaking 6-monthly screening among HIV-diagnosed MSM and HIV-negative MSM on PrEP (Supplementary tables S5-S6).
Otherwise, the efficacy of condoms and the probability of condom usage between pairings other than a HIV-diagnosed MSM and a partner perceived to be HIV-positive accounted for 9-0% and 7-7% of the variation, respectively.

Figure 5 shows the effect of our sensitivity analyses, with higher coverage of PrEP among HIV-negative MSM (25-0% instead of 12-5%) resulting in the biggest increase in impact aside from giving PrEP to all high-risk MSM. Indeed, in these two scenarios just screening HIV-diagnosed MSM and MSM on PrEP can now result in HCV elimination. Otherwise, impact was reduced by 15-20% if either there was a higher level of risk compensation (to 13% condom use among PrEP users) or PrEP was equally used by low- and high-risk MSM. Other changes in the model assumptions had a small effect, including shorter time to HCV treatment completion after diagnosis (4 instead of 6 months) and a 50% decrease in preferential mixing by HIV-status after the introduction of PrEP. Importantly, none of the sensitivity analyses resulted in the HCV screening frequency of HIV-negative MSM being more frequent than the average screening frequency for HIV in this group (every 2-3 years).

**Discussion**

Our results highlight that PrEP users as well as HIV-diagnosed MSM are important and convenient groups for targeting HCV screening and treatment initiatives because of their higher risk and frequent health check-ups, which are normally every 3 and 6 months, respectively.\(^{25}\) Indeed, with 12-5% coverage of PrEP among HIV-negative MSM, yearly screening of MSM on PrEP with rapid linkage-to-treatment could reduce the overall HCV incidence among MSM by up to 67-3% (95%CR 52-7-79-2%), with this increasing to 79-6% (95% CR 64-6-91-0%) if HIV-diagnosed MSM also receive equivalent screening and treatment. However, although considerable impact is possible from just reaching these groups, at this lower PrEP coverage (12.5%) the WHO HCV elimination targets cannot be reached without also improving screening (and linkage-to-treatment) among HIV-negative MSM not on PrEP to every 3-8 years. This changes, though, at higher PrEP coverage (25-0%), where only

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HIV-diagnosed MSM and PrEP users will require improved screening to reach the elimination target. Importantly, the required HCV screening frequencies in all MSM groups for achieving elimination are greater than their average frequency of HIV testing in the UK, suggesting that these increases in HCV testing should be feasible if done at the same time as existing HIV testing using the same blood samples.

Our projections also highlight the importance of maintaining condom use among PrEP users, possibly through including counselling on STI and HCV risk for PrEP users as part of routine healthcare visits. Otherwise, reductions in condom use among PrEP users will increase HCV and STI transmission, especially among PrEP users and HIV-diagnosed MSM. Importantly, though, enhanced HCV screening in PrEP users may offset these additional HCV risks with our modelling suggesting similar impact can be achieved from our screening activities irrespective of the level of risk compensation.

**Strengths and limitations**

The strength of our analysis is in modelling the full epidemic of HIV and HCV among MSM in the UK, while accounting for heterogeneities in sexual risk, patterns of mixing by HIV-status, and using detailed UK data. Despite these strengths, there are limitations.

Firstly, because the model is UK-specific, it may have limited generalisability to other settings. Although most developed countries have a similar predominance of HCV in HIV-diagnosed MSM, some epidemics were increasing or decreasing before the introduction of DAAs, while it was relatively stable in the UK in 2012. Our sensitivity analyses suggest that it will be harder to control an increasing HCV epidemic, with a greater frequency of HCV screening being needed among HIV-negative MSM not on PrEP to reach the elimination targets than for a stable or decreasing HCV epidemic. Unfortunately, more precise parameterisation to specific settings is needed to form more
detailed conclusions about the impact of our interventions’ in other settings. Additionally, our projections should not be generalised to lower and middle-income country settings which have different patterns of HIV and HCV prevalence among MSM.²

Secondly, to simplify our modelling we did not attempt to recreate the entire historical HCV epidemic among MSM in the UK;²⁸,³³ rather we assumed a stable HCV epidemic from 2012 (before the introduction of DAA treatments) as suggested by data from that time. We also did not explicitly model the role of chem-sex; which we simplified by assuming a factor increase in transmission risk, reflective of what is found in the literature (see supplementary materials). MSM were also assumed to have similar risk behaviour over their entire lifetime³⁹ due to insufficient data to parameterise transitions between risk groups over time.

Lastly, uncertainty exists in the data used by the model which propagates to uncertainty in our model projections. For instance, as with all large MSM datasets which include detailed sexual behavioural, the EMIS dataset is likely to be biased towards more highly educated and higher risk MSM due to the need to perform convenience sampling to obtain a large number of respondents.⁴⁰ However, because EMIS was widely distributed and undertaken by 18,000 men in UK, these biases should be less than much smaller surveys undertaken in gay venues.⁴⁰ Our uncertainty analyses show the model is most sensitive to the increased infectiousness of HCV among HIV co-infected MSM and the level of heterogeneity in risk in the two risk groups. Better data on these parameters would improve our model projections. Importantly, we also cannot be certain of the exact scale-up of PrEP, nor the level of risk compensation that may occur among PrEP users. Our model projections suggest that uncertainty in the coverage of PrEP could have a large effect on our findings, while encouragingly, uncertainty in levels of risk compensation has little effect on the impact of large increases in screening.

Comparison with other studies
Several modelling studies have projected the impact of HCV treatment among HIV-diagnosed MSM, but none have modelled the full HCV transmission dynamics and HCV treatment elimination requirements for all MSM.\textsuperscript{20,21,41,42} Our analysis builds on these previous studies by evaluating the level of HCV screening and treatment needed in all MSM sub-groups. Our analysis is novel in considering the effect of PrEP on HCV elimination targets, and the additional screening opportunities this provides. Our work compliments recent modelling from the US showing the beneficial impact that PrEP scale-up could have on STI transmission through more frequent STI screening at routine PrEP check-ups.\textsuperscript{43}

**Conclusions and implications**

In the era of PrEP scale-up, our modelling suggests that at low PrEP coverage, 12, 6 or 3-monthly HCV screening of HIV-diagnosed MSM and PrEP users, alongside less frequent screening (every 3-8 years) of HIV-negative non-PrEP users, could achieve the WHO elimination target for decreasing HCV incidence by 2030 in the UK. At higher PrEP coverage, this may be achievable with just increased screening in HIV-diagnosed MSM and PrEP users. Importantly, these elimination targets are not possible through only screening HIV-diagnosed MSM (as most elimination initiatives are doing), with the scale-up of PrEP providing a valuable opportunity for increasing HCV-screening among higher-risk MSM. Importantly, though, this added impact of screening PrEP users relies on the assumption that PrEP users are in regular contact with care, which may not be the case if MSM acquire PrEP through unofficial channels. This emphasises the importance of making PrEP freely available through formal channels to ensure that HCV and other STIs can be tested and treated effectively.

Lastly, our study has direct implications for the NHS-England commitment to eliminate HCV through giving specific screening targets for achieving this goal. For other countries with similar HCV
epidemics in MSM, our findings highlight the need to look beyond just screening HIV-diagnosed MSM, to also screening PrEP users and HIV-negative non-PrEP users.
References

44. BHIVA Guidelines for the treatment of management of coinfection with HIV-1 and hepatitis viruses 2013.
### Tables

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Value and uncertainty range</th>
<th>References</th>
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<tr>
<td><strong>HCV related parameters</strong></td>
<td></td>
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<td>Efficacy of HCV treatment with DAAs – after 2015</td>
<td>95% (90-100%)</td>
<td>[35,36]</td>
<td>Efficacy is the sustained viral response</td>
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<td>Duration of HCV treatment in years</td>
<td>0.19 (0.15-0.23)</td>
<td>[15]</td>
<td>Duration of DAA treatment generally 8 to 12 weeks</td>
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<td>Rate of HCV screening in HIV-diagnosed MSM at baseline</td>
<td>1.13 person-years</td>
<td>[28]</td>
<td>88% of HIV-diagnosed MSM are HCV tested each year during routine HIV check-up appointments from UK-CHIC data</td>
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<tr>
<td>Rate of HCV screening in HIV-negative MSM at baseline</td>
<td>0.10 (0.07-0.20) person-years</td>
<td>[44]</td>
<td>HIV-negative MSM not normally diagnosed with HCV until they have symptoms unless they are high-risk, so assume 5-15 years</td>
</tr>
<tr>
<td>Average delay from HCV diagnosis to initiation of treatment.</td>
<td>2.2 years</td>
<td>[28]</td>
<td>UK-CHIC data for HIV-diagnosed MSM and assume same for other MSM</td>
</tr>
<tr>
<td><strong>Behavioural parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of MSM that are low-risk</td>
<td>0.83 (0.79-0.86)</td>
<td>EMIS</td>
<td>Proportion of MSM with &lt;15 anal sex partners in the last year.</td>
</tr>
<tr>
<td>Proportion of MSM that are high-risk</td>
<td>0.17 (0.21-0.14)</td>
<td>EMIS</td>
<td>Proportion of MSM with ≥15 anal sex partners in the last year.</td>
</tr>
<tr>
<td>Number of anal sex partners in each year</td>
<td></td>
<td>EMIS</td>
<td>Average number of anal sex partners in each group with a +/-20%. Uncertainty range added to each</td>
</tr>
<tr>
<td>Low-risk</td>
<td>2.9 (2.3-3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>29.1 (23.3-34.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional elevated risk of HCV and HIV acquisition among high-risk MSM compared to low-risk MSM (based on chem-sex participation in last year)</td>
<td>HIV: 1.3 (1.1-1.5) HCV: 1.5 (1.1-1.9)</td>
<td>EMIS and [45,46]</td>
<td>EMIS data on prevalence of chem-sex in last year for low and high risk MSM combined with estimated increased risk of HIV and HCV acquisition due to chem sex in MSM studies. Relative risk is difference between low and high risk MSM. [47]</td>
</tr>
<tr>
<td>The proportion of MSM who mix like with like by HIV-status</td>
<td>0.35 (0.28 -0.42)</td>
<td>EMIS</td>
<td>EMIS data on proportion of partnerships chosen between people of the same HIV-status assuming no errors in judgement.</td>
</tr>
<tr>
<td>Probability of error in serosorting judgement (random mixing otherwise)</td>
<td>24.9% (12.1-45.7%)</td>
<td>EMIS</td>
<td>EMIS data on proportion of individuals who make assumptions about partner’s HIV-status based on unreliable reasons</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td>Source</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Probability of condom usage between HIV diagnosed MSM and a partner assumed to be HIV-positive</td>
<td>13.0% (10.4-15.6%)</td>
<td>EMIS</td>
<td>EMIS data on condom use with last casual partner when both sides of partnership are thought to be HIV-positive. Assume range +/- 20% either side.</td>
</tr>
<tr>
<td>Probability of condom usage in other MSM partnerships (not ones thought to be both HIV-positive)</td>
<td>68.0% (54.4-81.6%)</td>
<td>EMIS</td>
<td>EMIS data on condom use with last casual partner when partnerships not thought to be sero-concordant. Assume range +/- 20% either side.</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>0.91 (0.69-1.00)</td>
<td>48</td>
<td>Per act protection provided by condom use during anal sex</td>
</tr>
<tr>
<td>The proportion of MSM who mix like with like by risk status</td>
<td>0.25 (0.00-0.50)</td>
<td>EMIS</td>
<td>EMIS data on whether individuals in each risk group meet their partners in the same places. Assume large uncertainty.</td>
</tr>
<tr>
<td><strong>PrEP related parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of MSM taking up PrEP by 2020</td>
<td>12.5% or 25.0%</td>
<td>EMIS 25</td>
<td>12.5% coverage estimated from EMIS data using basic element of eligibility criteria from NHS England – recent condomless sex. Higher value assumed to encompass uncertainty.</td>
</tr>
<tr>
<td>Relative increase in coverage of PrEP in high-risk MSM versus low-risk MSM</td>
<td>2.6 (2.4-2.8)</td>
<td>EMIS 25</td>
<td>EMIS data applied to NHS England eligibility criteria for low and high-risk MSM</td>
</tr>
<tr>
<td>Efficacy of PrEP in reducing HIV incidence</td>
<td>91.5% (86.0-97.0%)</td>
<td>8,49</td>
<td>Range in efficacy from UK PROUD study and real-world study of PrEP use among MSM in France and Canada.</td>
</tr>
<tr>
<td>Rate of HIV testing for PrEP users</td>
<td>Every 3 months</td>
<td>8</td>
<td>Standard of care for HIV testing in PrEP users in UK</td>
</tr>
<tr>
<td>Rate of HCV testing for PrEP users</td>
<td>Every 3-12 months; baseline same as HIV-negative MSM</td>
<td></td>
<td>Varied in different model scenarios</td>
</tr>
</tbody>
</table>

**Table 1:** Key model parameters with ranges and details of estimation included. (For the full version see supplementary table S3).
<table>
<thead>
<tr>
<th>PrEP scenario</th>
<th>Relative change (%) in new infections from 2018 to 2030 compared to no PrEP scenario</th>
<th>HCV prevalence by 2030</th>
<th>HCV Incidence by 2030 (per 100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PrEP</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>12.5% coverage of PrEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario S0 – no risk compensation</td>
<td>-44.7%</td>
<td>-1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Scenario S1 – condom use in PrEP users falls from 68% to 34%</td>
<td>-40.5%</td>
<td>42.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>25.0% coverage of PrEP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario S0 – no risk compensation</td>
<td>-67.3%</td>
<td>-1.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Scenario S1 – condom use in PrEP users falls from 68% to 34%</td>
<td>-63.1%</td>
<td>80.7%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Table 2: Model projections of the impact of PrEP on HCV prevalence, incidence and the relative change in new HIV and HCV infections for 12.5% and 25.0% PrEP coverage with and without risk compensation. The risk compensation scenario assumes condom use among PrEP users reduces from 68% to 34%. *PrEP users in ‘No PrEP’ scenario are assumed to be representative of MSM who are eligible for PrEP in 2018.
Figures

A. Hepatitis C prevalence

<table>
<thead>
<tr>
<th>Subpopulations of men who have sex with men</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MSM</td>
</tr>
<tr>
<td>HIV-positive MSM</td>
</tr>
<tr>
<td>PrEP users</td>
</tr>
<tr>
<td>HIV-negative non-PrEP users</td>
</tr>
</tbody>
</table>

B. Hepatitis C incidence

<table>
<thead>
<tr>
<th>Subpopulations of men who have sex with men</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MSM</td>
</tr>
<tr>
<td>HIV-positive MSM</td>
</tr>
<tr>
<td>PrEP users</td>
</tr>
<tr>
<td>HIV-negative non-PrEP users</td>
</tr>
</tbody>
</table>

Figure 1: Projections of HCV (A) prevalence and (B) incidence among different subgroups of MSM by 2030 for the baseline ‘no PrEP’ scenario and due to the introduction of PrEP both with and without risk compensation. The projections assume 12.5% coverage of PrEP in HIV-negative MSM and no additional HCV screening. The risk compensation scenario assumes condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with the whiskers representing the 2.5 to 97.5 percentiles from our 500 model fits. *PrEP users at baseline are assumed to be representative of MSM who are eligible for PrEP in 2018.
**Figure 2:** Relative reduction in HCV (A) prevalence and (B) incidence by 2030 compared to 2018 levels among PrEP users when they are screened for HCV every 3, 6 or 12 months and complete HCV treatment within 6 months of diagnosis. Projections are given with and without risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. The projections with no additional screening are also shown for comparison. Point estimates are the median of our model projections with the whiskers representing the 2.5 to 97.5 percentiles from our 500 model fits. *This is compared to the prevalence of HCV in MSM who are eligible for PrEP in 2018.*
Figure 3: Relative decrease in overall HCV incidence by 2030 due to different HCV screening and treatment scenarios among MSM on PrEP and/or HIV-diagnosed MSM. MSM subgroups with enhanced screening also complete HCV treatment within 6 months of diagnosis. Projections are given (A) without and (B) with risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with whiskers representing the 2.5 to 97.5 percentile range from our 500 model fits.
Figure 4: Required duration between HCV screening tests among HIV-negative MSM not on PrEP (assuming 12.5% PrEP coverage) in order to reach a 90% HCV incidence reduction by 2030 compared to 2018 levels. HIV-diagnosed MSM and/or MSM on PrEP are screened every 3, 6 or 12 months, with all MSM subgroups completing HCV treatment within 6 months of diagnosis. Projections are given with and without risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with whiskers representing the 2.5 to 97.5 percentile range from our 500 model fits.
Figure 5: One-way sensitivity analysis on the (A) percentage reduction in HCV incidence by 2030, and (B) the frequency of screening needed in HIV-negative non-PrEP users to reach an overall 90% reduction in HCV among MSM by 2030, given 6 monthly HCV screening in HIV-positive MSM and PrEP users. Scenario 0 shown for reference as point and whisker and grey vertical line. Point and whiskers represent the median values along with the 2.5 to 97.5 percentiles of the model projections across the 500 baseline model fits. *Note*: the 25% PrEP coverage scenario and distribution of PrEP to only high-risk MSM is not shown in figure 5b because it does not require any screening in HIV-negative MSM not on PrEP to reach an overall 90% reduction in HCV among MSM by 2030.
Supplementary Material to:

‘Scaling up screening and treatment for elimination of hepatitis C among men who have sex with men in the era of HIV pre-exposure prophylaxis’

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   4.4 Central range of the main results
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1. Model Structure

1.1 Basic model compartments

In our model, individuals enter the model at age 15 and leave the model at age 65 or through HIV or HCV related death. New individuals enter the model susceptible to both HCV and HIV. We denote the proportion of the population in each disease state by using compartments, $X_{ij}$, where $X$ denotes the HIV-status, $i$ denotes the HCV-status, and $j$ the risk group.


We denote the stages of HCV infection (subscript $i$) where $S$-susceptible, $A$-acute infection, $C$-chronic infection and $D$-diagnosed chronic infection.

We also split the population into low and high-risk groups (subscript $j$), $L$ for low-risk and $H$ for high-risk. So for example $A_{SL}$ denotes low-risk group individuals who are acutely infected with HIV, not currently on PrEP and susceptible to HCV. Therefore compartments are divided based on; risk group; one of four possible HCV states; one of six possible HIV states. This creates a total of $4 \times 6 \times 2 = 48$ compartments. MSM are assumed not to change risk group over their lifetime.

For HIV and HCV, the different possible transitions between disease states are shown in figure S1. The rates of transitions however may vary depending on factors we will address subsequently.

![HIV Progression](image)

**Figure S1**: Model schematic for the HIV and HCV model components.
1.2 Entry, exit and mortality

A set amount of MSM enter the model each year $\theta$, with a proportion of MSM exiting the model due to ageing at a rate $\mu$. Additionally, mortality rates are included due to mono-infection of HCV $\mu_{HCV}$, undiagnosed HIV-infection where individuals are not on HAART $\mu_{HIV}^{\text{undiag}}$, and diagnosed HIV-infection, where a proportion of MSM are assumed to be on HAART thus reducing the rate of death $\mu_{HIV}^{\text{diag}}$. We also include mortality due to HCV and HIV co-infection with death rates of those with undiagnosed HIV-status denoted by $\mu_{CO}^{\text{undiag}}$ and diagnosed HIV-status $\mu_{CO}^{\text{diag}}$.

1.3 Forces of infection

The force of infection for HIV $\sigma$ is based on the individual’s PrEP status and risk group, where we denote $l = 0$ or $1$ for ‘not taking PrEP’ or ‘taking PrEP’, respectively, and risk group by $j = L$ or $H$ for ‘low-risk’ and ‘high-risk’, respectively. Therefore, the force of infection is written as $\sigma_{jl}$.

The force of infection terms for HCV however also depend on the individual’s HIV infection status $k$ (due to seroadaptive behaviours), and so is written $\lambda_{jkl}$ with the HIV infection/diagnosis status of the individual being: $k = 0$ for MSM which are HIV uninfected; $k = 1$ for MSM who are HIV-positive but with undiagnosed HIV infection; and $k = 2$ for HIV-positive MSM with a diagnosed HIV infection. Sometimes we also denote $k = u$ to indicate a person who has never had an HIV diagnosis. This corresponds to individuals who are HIV-positive but undiagnosed or simply HIV-negative (i.e. $k = 0$ or $1$). Similarly, we denote $k = d$ for MSM who have received an HIV diagnosis (i.e. $k = 2$).

1.4 HCV/HIV Diagnosis, PrEP and HCV treatment

We also include a rate to denote spontaneous recovery from HCV $a^{HCV}$ and the chance of spontaneous recovery, $x_k$, which depends on the HIV-status $k$ of the individual.

People move from the acute phase of HIV at rate $a^{HIV}$ to undiagnosed chronic HIV infection if not on PrEP but move directly to a diagnosed state of HIV if on PrEP due to three monthly HIV screening.

We also have the rate of HCV diagnosis $d_{k}^{HCV}$ which depends on the HIV and PrEP status of the individual but can occur at both chronic and acute stages of HCV. However, those with acute or undiagnosed HIV infection are assumed to not be screened for HCV as this would occur in tandem with an HIV test, so it does not make sense for these individuals to be only diagnosed for HCV alone. Similarly, the rate of HIV diagnosis $d_{l}^{HIV}$ depends on whether the individual is currently on PrEP or not ($l = 0$ or $1$).

$r_{kl}$ is the rate at which MSM are successfully treated for HCV once diagnosed, which returns HCV diagnosed MSM to the HCV susceptible category. At baseline we assume this rate is equal in all MSM. However, over our intervention scenarios we vary this parameter by the HIV infection/diagnosis status and PrEP status of MSM, to reflect different HCV treatment strategies employed.

For MSM not currently on PrEP, but still susceptible to HIV, we denote the rate of PrEP uptake as $\pi_j$. For MSM who are on PrEP, we similarly have a cessation rate of PrEP use, which we denote by $\eta_j$. Both of these parameters depend on the risk group of the MSM. This is because the coverage of PrEP use for each risk group must reach different equilibrium values after the scale-up of PrEP.
2. Model equations

2.1 Compartmental differential equations

We begin by a comprehensive listing all the parameters found within our differential equations in Table S1.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subscripts</strong></td>
<td></td>
</tr>
<tr>
<td>( j )</td>
<td>Denotes the risk group. This can take values ( L ) for low-risk and ( H ) for high-risk.</td>
</tr>
<tr>
<td>( k )</td>
<td>Denotes HIV-status. This can take the values 0 for HIV-negative, 1 for HIV-positive but undiagnosed and 2 for HIV-diagnosed. Sometimes we use ( u ) to denote either ( k = 0 ) or 1 and ( d ) to denote ( k = 2 ).</td>
</tr>
<tr>
<td>( l )</td>
<td>Denotes current PrEP usage. This can take values 0 for not using PrEP and 1 for using PrEP.</td>
</tr>
<tr>
<td><strong>Parameters</strong></td>
<td></td>
</tr>
<tr>
<td>( a_{\text{HCV}} )</td>
<td>The rate at which HCV infections progress from acute to chronic</td>
</tr>
<tr>
<td>( a_{\text{HIV}} )</td>
<td>The rate at which HIV infections progress from acute to chronic</td>
</tr>
<tr>
<td>( d_{\text{HCV}} )</td>
<td>The rate at which individuals are screened for HCV</td>
</tr>
<tr>
<td>( d_{\text{HIV}} )</td>
<td>The rate at which individuals are screened for HIV</td>
</tr>
<tr>
<td>( r_{kl} )</td>
<td>The rate of successful treatment of individuals with diagnosed HCV, returning them to being susceptible to HCV</td>
</tr>
<tr>
<td>( x_k )</td>
<td>The proportion of individuals who spontaneously clear HCV infection</td>
</tr>
<tr>
<td>( \eta )</td>
<td>The rate at which individuals currently on PrEP stop using PrEP</td>
</tr>
<tr>
<td>( \pi_j )</td>
<td>The rate at which HIV-negative susceptible individuals start using PrEP</td>
</tr>
<tr>
<td>( \theta_j )</td>
<td>The amount of new individuals ‘aging in’ to the population per year</td>
</tr>
<tr>
<td>( \lambda_{jkl} )</td>
<td>The rate at which individuals are infected with HCV</td>
</tr>
<tr>
<td>( \sigma_l )</td>
<td>The rate at which individuals are infected with HIV</td>
</tr>
<tr>
<td>( \mu )</td>
<td>The rate at which people leave the model due to aging out of the model</td>
</tr>
<tr>
<td>( \mu_{\text{HCV}} )</td>
<td>The additional death rate due to HCV mono-infection</td>
</tr>
<tr>
<td>( \mu_{\text{HIV}}^{\text{Diag}} )</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV-diagnosed</td>
</tr>
<tr>
<td>( \mu_{\text{HIV}}^{\text{Undiag}} )</td>
<td>The additional death rate due to HIV mono-infection where the individual is HIV-undiagnosed</td>
</tr>
<tr>
<td>( \mu_{\text{CO}}^{\text{Diag}} )</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV-diagnosed</td>
</tr>
<tr>
<td>( \mu_{\text{CO}}^{\text{Undiag}} )</td>
<td>The additional death rate due to HCV and HIV co-infection where the individual is HIV-undiagnosed</td>
</tr>
</tbody>
</table>

**Table S1**: Parameters included in the differential modelling equations with descriptions and symbolic denotation.
The overall model equations are as follows:

For \( j = L \) or \( H \):

**S** - Susceptible to HIV and not on PrEP

\[
\frac{dS_j}{dt} = \theta_j + r_{00}S_{DJ} + a_{UCV}x_0S_{A_j} + \eta_jS_jP_{SJ} - \pi_jS_j - \sigma_jP_{SJ} - \lambda_j00S_{SJ} - \mu S_j
\]

\[
\frac{dS_{A_j}}{dt} = \lambda_j00S_{SJ} + \eta_jS_jP_{A_j} - \sigma_jS_{A_j} - \sigma_jS_{AJ} - a_{UCV}x_0S_{A_j} - a_{UCV}(1 - x_0)S_{A_j} - d_{00}^{UCV}S_{A_j} - \mu S_{A_j} - \mu_{HCV}S_{A_j}
\]

\[
\frac{dS_c}{dt} = a_{UCV}(1 - x_0)S_{A_j} + \eta_jS_jP_{c j} - \pi_jS_c - \sigma_jS_{c j} - \sigma_jS_{cj} - \mu S_{c j} - \mu_{HCV}S_{c j}
\]

\[
\frac{dS_{D_j}}{dt} = d_{00}^{UCV}S_{A_j} + d_{00}^{UCV}S_{c j} - \pi_jS_{D_j} - \sigma_jS_{D_j} - r_{00}S_{D_j} - \mu S_{D_j} - \mu_{HCV}S_{D_j}
\]

**S** - Susceptible to HIV and on PrEP

\[
\frac{dS_{P_j}}{dt} = r_{01}S_{P_j} + a_{UCV}x_0S_{P_j} + \pi_jS_{P_j} - \eta_jS_{P_j} - \sigma_jS_{P_j} - \lambda_j01S_{P_j} - \mu S_{P_j}
\]

\[
\frac{dS_{P_{A_j}}}{dt} = \lambda_j01S_{P_j} + \eta_jS_jP_{A_j} - \sigma_jS_{P_j} - \sigma_jS_{A_j} - a_{UCV}x_0S_{P_j} - a_{UCV}(1 - x_0)S_{P_j} - a_{UCV}(1 - x_0)S_{A_j} - d_{01}^{UCV}S_{P_j} - \mu S_{P_j}
\]

\[
\frac{dS_{P_c}}{dt} = a_{UCV}(1 - x_0)S_{P_j} + \eta_jS_jP_{c j} - \pi_jS_c - \sigma_jS_{P_c} - \sigma_jS_{cj} - \mu S_{P_c} - \mu_{HCV}S_{P_c}
\]

\[
\frac{dS_{P_{D_j}}}{dt} = d_{01}^{UCV}S_{P_j} + d_{01}^{UCV}S_{c j} + \pi_jS_{P_{D_j}} - \eta_jS_{P_{D_j}} - \sigma_jS_{P_{D_j}} - r_{01}S_{P_{D_j}} - \mu S_{P_{D_j}} - \mu_{HCV}S_{P_{D_j}}
\]

**A** - Acute HIV infection and not on PrEP

\[
\frac{dA_j}{dt} = r_{10}A_{DJ} + \sigma_jS_{A_j} + a_{HIV}x_0A_{A_j} - \lambda_j10A_{A_j} - a_{HIV}A_{A_j} - \eta_jA_{P_j} - \mu_{HIV}A_{A_j} - \mu_{HIV}A_{S_j}
\]

\[
\frac{dA_{A_j}}{dt} = \sigma_jS_{A_j} + \lambda_j10A_{A_j} - a_{HIV}A_{A_j} - a_{HIV}x_1A_{A_j} - a_{HIV}(1 - x_1)A_{A_j} + \eta_jA_{P_j} - \mu_{HIV}A_{A_j} - \mu_{HIV}A_{A_j}
\]

\[
\frac{dA_{c j}}{dt} = a_{HIV}(1 - x_1)A_{A_j} + \eta_jA_{P_{cj}} - \pi_jA_{c j} - \eta_jA_{P_{cj}} - \mu_{HIV}A_{c j} - \mu_{HIV}A_{c j}
\]

\[
\frac{dA_{D j}}{dt} = \sigma_jS_{D_j} - a_{HIV}A_{D_j} - r_{10}A_{D_j} + \eta_jA_{P_{D_j}} - \mu_{HIV}A_{D_j} - \mu_{HIV}A_{D_j}
\]

**A** - Acute HIV infection and on PrEP

\[
\frac{dA_{P_j}}{dt} = r_{11}A_{P_j} + \sigma_jS_{P_j} + a_{HIV}x_1A_{P_j} - \lambda_j11A_{P_j} - d_{11}^{HIV}A_{P_j} - \eta_jA_{P_j} - \mu_{HIV}A_{P_j} - \mu_{HIV}A_{P_j}
\]

\[
\frac{dA_{P_{A_j}}}{dt} = \sigma_jS_{P_j} + \lambda_j11A_{P_j} - d_{11}^{HIV}A_{P_j} - a_{HIV}x_1A_{P_j} - a_{HIV}(1 - x_1)A_{P_j} - a_{HIV}(1 - x_1)A_{P_j} - \eta_jA_{P_j} - \mu_{HIV}A_{P_j}
\]

\[
\frac{dA_{P_{c j}}}{dt} = a_{HIV}(1 - x_1)A_{P_j} + \eta_jA_{P_{cj}} - \pi_jA_{P_{cj}} - \eta_jA_{P_{cj}} - \mu_{HIV}A_{P_{cj}} - \mu_{HIV}A_{P_{cj}}
\]

\[
\frac{dA_{P_{D j}}}{dt} = d_{11}^{HIV}A_{P_j} + d_{11}^{HIV}A_{P_{cj}} + \sigma_jS_{P_{D_j}} - d_{11}^{HIV}A_{P_{D_j}} - r_{11}A_{P_{D_j}} - \eta_jA_{P_{D_j}} - \mu_{HIV}A_{P_{D_j}} - \mu_{HIV}A_{P_{D_j}}
\]
\[ \frac{dC_{sj}}{dt} = a^{HIV}A_{sj} + r_{10}C_{sj} + a^{HCV}x_{1}C_{Aj} - \lambda_{j10}C_{sj} - a_{0}^{HIV}C_{sj} - \mu_{C_{sj}} - \mu_{Undiag}^{HIV}C_{sj} \]

\[ \frac{dC_{cJ}}{dt} = \lambda_{j20}C_{sj} + a^{HIV}C_{cJ} - a^{HCV}(1 - x_{1})C_{cJ} - a_{0}^{HIV}C_{cJ} - \mu_{C_{cJ}} - \mu_{Undiag}^{HIV}C_{cJ} \]

\[ \frac{dC_{dJ}}{dt} = a^{HIV}C_{dJ} - d_{0}^{HIV}C_{dJ} - r_{10}C_{dJ} - \mu_{C_{dJ}} - \mu_{Undiag}^{CO}C_{dJ} \]

\[ \frac{dD_{sj}}{dt} = r_{20}D_{dJ} + d_{0}^{HIV}C_{sj} + d_{1}^{HIV}A_{pJ} + a^{HCV}x_{1}D_{AJ} - \lambda_{j20}D_{sj} - \mu_{D_{sj}} - \mu_{Undiag}^{HIV}D_{sj} \]

\[ \frac{dD_{dJ}}{dt} = \lambda_{j20}D_{dJ} + a^{HIV}D_{dJ} + \lambda_{j20}D_{dJ} - x_{1}D_{dJ} - d_{0}^{HIV}D_{dJ} - \mu_{D_{dJ}} - \mu_{Undiag}^{CO}D_{dJ} \]

\[ \frac{dD_{CJ}}{dt} = a^{HCV}(1 - x_{1})D_{A_{J}} + d_{0}^{HIV}C_{C_{J}} + d_{1}^{HIV}A_{P_{C_{J}}} - d_{0}^{HIV}D_{C_{J}} - \mu_{D_{C_{J}}} - \mu_{Undiag}^{CO}D_{C_{J}} \]

\[ \frac{dD_{D_{J}}}{dt} = d_{0}^{HIV}C_{D_{J}} + d_{1}^{HIV}A_{P_{D_{J}}} + d_{0}^{HIV}D_{D_{J}} + \mu_{P_{D_{J}}} - \mu_{D_{D_{J}}} - \mu_{Undiag}^{CO}D_{D_{J}} \]

**2.2 Mixing matrix**

We show the parameters found within our mixing equations for reference purposes in Table S2.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subscripts</strong></td>
<td></td>
</tr>
<tr>
<td>(j)</td>
<td>Denotes the risk group. This can take values (L) for low-risk and (H) for high-risk.</td>
</tr>
<tr>
<td>(k)</td>
<td>Denotes HIV-status. This can take the values (0) for HIV-negative, (1) for HIV-positive but undiagnosed and (2) for HIV-diagnosed. Sometimes we use (a) to denote either (k = 0) or (1) and (d) to denote (k = 2).</td>
</tr>
<tr>
<td>(l)</td>
<td>Denotes current PrEP usage. This can take values (0) for not using PrEP and (1) for using PrEP.</td>
</tr>
</tbody>
</table>

| Sub-populations | |
| \(N_{jkl}\) | \(N\) Represents the entire population. Presence of subscripts slice the total population by the subscript. For example, \(N_{j}\) refers to everyone of the member of the population who is in risk category \(j\). |
| \(u_{0}\) | Refers to non-PrEP users who are either HIV-negative/HIV-undiagnosed. |
| \(u_{1}\) | Refers to PrEP users who are either HIV-negative/HIV-undiagnosed. |
| \(d_{0}\) | Refers to HIV-diagnosed individuals. |

| Parameters | |
| \(M_{ij}^{Risk}\) | Denotes the mixing equations for MSM of type \(j\) with type \(j'\). |
| \(M_{ij}^{HIV/Undiag}\) | Denotes the mixing equations for MSM of type \(jkl\) with type \(j'k'l'\) in the presence of no HIV serosorting errors. |
| \(M_{ij}^{HIV/HIV}\) | Denotes the mixing equations for MSM of type \(jkl\) with type \(j'k'l'\) in the presence of HIV serosorting errors. |
| \(M_{ij}^{HIV/HCV}\) | Denotes the mixing equations for MSM of type \(jkl\) with type \(j'k'l'\) in the presence of HIV serosorting errors and protection provided by condoms. |
| \(b\) | The proportion of MSM who mix with like by risk status \(j\). |
| \(p_{t}\) | Number of yearly partners with which there was anal intercourse by risk group \(j\). |
| \(\xi\) | The proportion of MSM who mix with like by HIV-status \(k\). |
| \(e\) | Chance of a serosorting judgement being incorrect. An incorrect judgement leads to random mixing. |
| \(c_{0}\ & c_{1}\) | \(c_{1}\) represents the proportion of HIV and HCV infections we expect to transmit through the protection offered by condom use between a serosorting HIV-diagnosed MSM and a partner they also assume is HIV-positive. \(c_{0}\) is between all other sexual partnerships. |
| \(y\) | This factor represents a modifier for the chance that a sexual encounter involving at least one MSM on PrEP will have a lower chance to use a condom and hence less condom protection provided (\(y \leq 1\)). However, condom use between any two partners is equal to \(c_{1}\) at minimum. So that \(c_{2} \leq c_{0}y\) and \(c_{0}y \leq c_{2}\). |

Table S2: Parameters included in the mixing equations with descriptions and symbolic notation.
MSM mix preferentially by risk status and their assumed HIV-status. We therefore account for the HIV infection/diagnosis and risk status of the primary individual and their potential partners. Because of the complexity in doing this, we build the mixing equations in stages for clarity.

Firstly, we define the probability of mixing between two individuals that is only based on their risk group, denoted $M_{jj'}^{Risk}$ (one individual from risk group $i$ with their partner from risk group $j'$. $b$ is the proportion of individuals who mix exclusively with partners of the same risk group, with other partnerships assumed to form randomly. The random portion of this mixing is weighted by the proportion of all sexual partnerships provided by each risk group. $N_j$ is used to represent the entire population in risk group $j$. $p_j$ is the average number of partnerships which individuals in risk group $j$ form over a year, and $\delta_{jj'}$ is the kronecker delta function that is equal to 1 when $j = j'$ and equal to zero otherwise.

Next, we build on this, considering mixing by HIV infection/diagnosis status and formulate a function $M_{jj'k'l}^{HIV}$. This calculates the probability that an MSM in risk group $j$, HIV-status group $k$ and PrEP status $l$, forms a sexual partner with an MSM in risk group $j'$, HIV-status group $k'$ and PrEP status $l'$. This probability varies depending on the HIV diagnosis status of the primary individual and their partner. Therefore, we express $k$ as follows $-k = u$ is used to denote HIV susceptible or HIV-positive but undiagnosed MSM and $k = d$ is used to denote HIV-positive and diagnosed MSM.

We denote $N_{ijkl}$ as the number of individuals in risk group $j$, HIV-status group $k$ with PrEP status $l$. $\zeta$ is the proportion of MSM who specifically mix to form a partnership with someone of the same HIV-status. We weight the chance that each partnership is with a specific subgroup by the number of MSM in that subgroup and their average number of partners. The remaining proportion of MSM $(1 - \zeta)$ that do not mix by HIV-status are assumed to mix randomly with individuals in all subgroups, again weighted by the number of individuals in each of those MSM subgroups and the average number of partnerships formed by each of those subgroups.

MSM who are HIV-positive but undiagnosed are assumed to prefer mixing with other undiagnosed/susceptible MSM. We also assume PrEP users having the same mixing preferences as other HIV-negative/undiagnosed MSM.

The following is an example showing the mixing equations for HIV-negative/undiagnosed MSM with each other:

This function $M_{ijkl}^{HIV}$ then has to be adapted because there is generally judgement errors when individuals choose partners by their assumed HIV-status. We adapt $M_{ijkl}^{HIV}$ to include a chance of error in choosing a partner of the same HIV-status, denoted by $e$. Where there is an error in judgement, the primary individual who intended to mix with a specific type of MSM, will instead mix randomly.
This is then finally adapted to give a final function \( M_{jkl,k'l} \), that also includes condom use; which varies by pairings of MSM. The parameters \( c_0 \) and \( c_1 \) are used to denote the chance an infection will be able to transmit through the protection offered by condom use. \( c_0 \) being used for MSM when they are not mixing by HIV-status or when undiagnosed MSM are mixing by HIV-status, and \( c_1 \) being used between diagnosed MSM when they are mixing by HIV-status (see section 2.3 for how \( c_0 \) and \( c_1 \) are defined in more detail). In the model, we also have to remember that when an MSM preferentially mixes, they will use condoms with a probability based on the assumption of their partner’s HIV and/or PrEP status, even where this judgement is incorrect.

![Math equation](https://via.placeholder.com/500)

To illustrate the use of \( c_1 \) we also show the cases of \( M_{jdo,j'u0} \) and \( M_{jdo,j'd0} \):

![Math equation](https://via.placeholder.com/500)

To also model the potential risk compensation in the form of a reduction in condom use by PrEP users, we include the modifier \( y \), which represents the potential reduction in condom use between PrEP users and their partners. The functionality of \( y \) is described subsequently in the section 2.3 and is only applied in cases where one or more partners are using PrEP. Other terms in mixing scenario 1 follow similarly and thus the full mixing equations are:

![Math equation](https://via.placeholder.com/500)
\[
M_{ju0,j'\!u1} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 y \varepsilon_{ju1} \sum_{i=1}^{N_{ju1}} + (1 - \zeta) + \zeta_e c_0 y \frac{N_{ju1}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (\zeta - \zeta_e) c_0 y \frac{p_{ij} N_{j'\!u1}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} + (1 - \zeta) + \zeta_e c_0 y \frac{p_{ij} N_{j'\!u1}}{\sum_{i=1}^{n} p_{n}(N_{nu0} + N_{nu1} + N_{nd0})} \right]
\]

\[
M_{ju0,j'\!d0} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 + \zeta e_{1} \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (1 - \zeta) c_0 + \zeta e_{1} \frac{p_{ij} N_{j'\!d0}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} \right]
\]

\[
M_{ju1,j'\!u0} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 y \frac{N_{ju0}}{\sum_{i=1}^{N_{ju0}} + (1 - \zeta) + \zeta_e c_0 y \frac{N_{ju0}}{N_{ju0} + N_{ju1} + N_{jd0}}} \right] + (1 - b) \left[ (\zeta - \zeta_e) c_0 y \frac{p_{ij} N_{j'\!u0}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} + (1 - \zeta) + \zeta_e c_0 y \frac{p_{ij} N_{j'\!u0}}{\sum_{i=1}^{n} p_{n}(N_{nu0} + N_{nu1} + N_{nd0})} \right]
\]

\[
M_{ju1,j'\!d0} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 y + \zeta e_{1} \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (1 - \zeta) c_0 y + \zeta e_{1} \frac{p_{ij} N_{j'\!d0}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} \right]
\]

\[
M_{jd0,j'\!u0} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 + \zeta e_{1} \frac{N_{ju0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (1 - \zeta) c_0 + \zeta e_{1} \frac{p_{ij} N_{j'\!u0}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} \right]
\]

\[
M_{jd0,j'\!u1} = \delta_{jj,b} \left[ (1 - \zeta) c_0 + \zeta e_{1} \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (1 - \zeta) c_0 + \zeta e_{1} \frac{p_{ij} N_{j'\!u1}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} \right]
\]

\[
M_{jd0,j'\!d0} = \delta_{jj,b} \left[ (\zeta - \zeta_e) c_0 + (1 - \zeta) c_0 + \zeta e_{1} \frac{N_{jd0}}{N_{ju0} + N_{ju1} + N_{jd0}} \right] + (1 - b) \left[ (\zeta - \zeta_e) c_0 + (1 - \zeta) c_0 + \zeta e_{1} \frac{p_{ij} N_{j'\!d0}}{\sum_{i=1}^{nq} p_{n} N_{nuq}} \right]
\]

2.3 Condom usage terms

As used in the formulation for \(M_{jkj'\!k'b}\) above the model parameters \(c_0\) and \(c_1\) denote the chance an infection will be able to transmit through the protection offered by condom use at a given consistency. This is calculated from the consistency in which a pairing uses a condom and the efficacy of condoms: where \(c_1\) is for ‘HIV-diagnosed MSM with an assumed HIV-positive partner’ and \(c_0\) for ‘HIV-negative or HIV-positive but undiagnosed MSM with any partner or a pairing of a HIV-positive MSM with an assumed HIV-negative partner’. The efficacy of a condom when used is denoted as \(P\) (assumed equal for both HCV and HIV).
We start in the absence of PrEP related risk compensation, by assuming HIV-diagnosed MSM with an assumed HIV-diagnosed partner are assumed to use condoms with consistency $D$, whereas all other partnerships are assumed to use condoms with equal consistency $U$. The parameters $c_0$ and $c_1$ are therefore defined as:

$$c_0 = 1 - UP$$
$$c_1 = 1 - DP$$

The exception to the above setup is that any pairing involving a person on PrEP with a partner who is not diagnosed for HIV, will have condom usage term $c_0y$. The $y$ factor ($y \geq 1$), is the modifier for the condom term $c_0$. It represents the notion that less condoms may be used by people on PrEP and their partners, as a risk compensation behaviour. If $y = 1$, this results in individuals on PrEP using condoms with the same consistency as people who are HIV-negative or undiagnosed HIV-positive who are not on PrEP.

### 2.4 HIV and HCV force of infection

The forces of infection $\lambda_{jkl}$ for HCV and $\sigma_{jH}$ for HIV are dependent on; the sexual risk group ($j = L \ or \ H$): HIV infection/diagnosis status ($k = 0$ for uninfected, $k = 1$ for HIV infected but undiagnosed, and $k = 2$ for diagnosed, with $u$ sometimes being used if $k = 0 \ or \ 1$ and $d$ being used if $k = 2$); and the PrEP status of individuals ($l = 0 \ or \ 1$ to denote if the individuals are not on PrEP or are on PrEP). So for example, $\lambda_{HL0}$ will denote the force of infection for HCV which applies to individuals who are in the high-risk group, HIV infected but undiagnosed but not currently using PrEP.

However, additional biological or risk-based influences also affect transmission, for which we define some additional parameters:

$\Omega$ is the increased HIV infectiousness of those in the acute phase of HIV,

$\Delta$ is the reduced HIV infectiousness of HIV due to ART

$\Lambda$ is the increased HCV infectivity of those with HIV co-infection

$\beta^{HIV}$ is the transmission factor for HIV in the chronic phase of infection with no ART treatment

$\beta^{HCV}$ is the transmission factor for HCV

$R^{HIV}$ is the additional multiplicative risk factor associated with HIV acquisition among the high-risk group due to more frequent chem-sex participation

$R^{HCV}$ is the additional multiplicative risk factor associated with HCV acquisition among the high-risk group due to more frequent chem-sex participation

$p_L$ and $p_H$ are the number of annual sexual partners for low and high-risk MSM

$\omega$ is the efficacy of PrEP. Thus, the proportion of infections that will not be mitigated by taking PrEP is denoted by $(1 - \omega)$

For low or high-risk ($j = L \ or \ H$), with PrEP status ($l = 0 \ or \ 1$) and HCV infection stage $n$, the HIV force of infection $\sigma_{jH}$ is:

$$\sigma_{L0} = \beta^{HIV} p_L \left[ \sum_{all \ j} M_{L_{0}j_{0}u_{0}} \left( \frac{\sum_{all \ n} (\Omega A_{nj} + C_{nj})}{\sum_{all \ n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \ j} M_{L_{0}j_{1}u_{1}} \left( \frac{\sum_{all \ n} (\Omega P_{nj})}{\sum_{all \ n} (S_{nj} + A_{nj} + C_{nj})} \right) \right]$$

$$\sigma_{L1} = \beta^{HIV} (1 - \omega) p_L \left[ \sum_{all \ j} M_{L_{1}j_{0}u_{0}} \left( \frac{\sum_{all \ n} (\Omega A_{nj} + C_{nj})}{\sum_{all \ n} (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all \ j} M_{L_{1}j_{1}u_{1}} \left( \frac{\sum_{all \ n} (\Omega P_{nj})}{\sum_{all \ n} (S_{nj} + A_{nj} + C_{nj})} \right) \right]$$
\[ \sigma_{H0} = \beta^{HIV} R^{HIV} \rho_H \left( \sum_{all\ j} M_{H]\to\j u0} \left( \frac{\sum n (\Omega A_{nj} + C_{nj})}{\sum n (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{H]\to\j u1u1} \left( \frac{\sum n (\Omega A^p_{nj})}{\sum n (S^p_{nj} + A^p_{nj})} \right) \right) + \sum_{all\ j} M_{H]\to\j ud0} \left( \frac{\sum n (\Delta D_{nj})}{\sum n (D_{nj})} \right) \]

\[ \sigma_{H1} = \beta^{HIV} (1 - \omega) R^{HIV} \rho_H \left( \sum_{all\ j} M_{H1]\to\j u0} \left( \frac{\sum n (\Omega A_{nj} + C_{nj})}{\sum n (S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{H1]\to\j u1u1} \left( \frac{\sum n (\Omega A^p_{nj})}{\sum n (S^p_{nj} + A^p_{nj})} \right) \right) + \sum_{all\ j} M_{H1]\to\j ud0} \left( \frac{\sum n (\Delta D_{nj})}{\sum n (D_{nj})} \right) \]

For low or high-risk (\( j = L \) or \( H \)), and HIV-negative (\( k = 0 \)), HIV infected and undiagnosed (\( k = 1 \)), HIV infected and diagnosed (\( k = 2 \)), with PrEP status (\( l = 0 \) or \( 1 \)) the HCV force of infection \( \lambda_{kl} \) is:

\[ \lambda_{L0l} = \beta^{HCV} \rho_L \sum_{all\ j} M_{L]\to\j u0} \left( \frac{\sum n=:\text{A, C, D}(S_{nj} + A_{nj})}{\sum n=:\text{S, A, C, D}(S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{L]\to\j u1} \left( \frac{\sum n=:\text{A, C, D}(S^p_{nj} + A^p_{nj})}{\sum n=:\text{S, A, C, D}(S^p_{nj} + A^p_{nj})} \right) \]

\[ \lambda_{L1l} = \beta^{HCV} \rho_L \sum_{all\ j} M_{L}\to\j u0} \left( \frac{\sum n=:\text{A, C, D}(S_{nj} + A_{nj})}{\sum n=:\text{S, A, C, D}(S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{L}\to\j u1} \left( \frac{\sum n=:\text{A, C, D}(S^p_{nj} + A^p_{nj})}{\sum n=:\text{S, A, C, D}(S^p_{nj} + A^p_{nj})} \right) \]

\[ \lambda_{L20} = \beta^{HCV} \rho_L \sum_{all\ j} M_{Ld0}\to\j u0} \left( \frac{\sum n=:\text{A, C, D}(S_{nj} + A_{nj})}{\sum n=:\text{S, I, F, n=:\text{S, A, C, D}(S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{Ld0}\to\j u1} \left( \frac{\sum n=:\text{A, C, D}(S^p_{nj} + A^p_{nj})}{\sum n=:\text{S, A, C, D}(S^p_{nj} + A^p_{nj})} \right) \]

\[ \lambda_{H0l} = \beta^{HCV} \rho_H \sum_{all\ j} M_{H}\to\j u0} \left( \frac{\sum n=:\text{A, C, D}(S_{nj} + A_{nj})}{\sum n=:\text{S, A, C, D}(S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{H}\to\j u1} \left( \frac{\sum n=:\text{A, C, D}(S^p_{nj} + A^p_{nj})}{\sum n=:\text{S, A, C, D}(S^p_{nj} + A^p_{nj})} \right) \]

\[ \lambda_{H1l} = \beta^{HCV} \rho_H \sum_{all\ j} M_{H}\to\j u0} \left( \frac{\sum n=:\text{A, C, D}(S_{nj} + A_{nj})}{\sum n=:\text{S, A, C, D}(S_{nj} + A_{nj} + C_{nj})} \right) + \sum_{all\ j} M_{H}\to\j u1} \left( \frac{\sum n=:\text{A, C, D}(S^p_{nj} + A^p_{nj})}{\sum n=:\text{S, A, C, D}(S^p_{nj} + A^p_{nj})} \right) \]
\[
\lambda_{H20} = \beta^{HCV} R^{HCV} p_H \left[ \sum_{a \in \{D\}} M_{Hd0ju0} \frac{\left( \sum_{n=A,C,D} \left( S_{nj} + AA_{nj} + AC_{nj} \right) \right)}{\sum_{n=S,A,C,D} \left( S_{nj} + A_{nj} + C_{nj} \right)} \right] \\
+ \sum_{a \in \{D\}} M_{Hd0ju1} \frac{\left( \sum_{n=A,C,D} \left( S_{nj}^P + AA^P_{nj} \right) \right)}{\sum_{n=S,A,C,D} \left( S_{nj}^P + A_{nj} + C_{nj} \right)} + \sum_{a \in \{D\}} M_{Hd0ju0} \frac{\left( \sum_{n=A,C,D} AD_{nj} \right)}{\sum_{n=S,A,C,D} \left( D_{nj} \right)}
\]

### 2.5 Treatment equations for HCV

\(\psi_k\) is the efficacy of HCV treatment, (which is based on HIV status \(k\) pre-DAA treatment). \(z^{\text{treat}}\) denotes the duration of a course of HCV treatment. Further to this, MSM have a delay between diagnosis and starting treatment. We denote the waiting time as \(z^{\text{delay}}\), which can vary depending on the PrEP status \(l\) and HIV infection/diagnosis status \(k\) of MSM.

These factors combine to form \(r_{kl}\), the rate of successful treatments for HCV once diagnosed is therefore:

\[ r_{kl} = \frac{\psi_k}{z^{\text{delay}} + z^{\text{treat}}} \]

### 2.6 Death rates

MSM exit the model at age 65, which is represented by the exit rate \(\mu\). However, there are additional rates which cause an exit from the model due to HIV and HCV related death. There are several death rates in our model which are affected by both the disease status and treatment status of an individual. Individuals can be completely susceptible to both diseases in which case the additional death rate associated with disease is 0. Individuals also may have HCV or HIV mono or co-infection, as well as being on ART, or not, for their HIV infection.

We use the following parameters to construct our compartmental death rates:

- **\(\mu_{HCV}\)** The additional death rate due to HCV mono-infection

- **\(h_{HCV}^{\text{No ART}}\)** Increased mortality hazard ratio for HCV mono-infection due to an untreated HIV infection

- **\(h_{HCV}^{\text{ART}}\)** Increased mortality hazard ratio for HCV mono-infection due to ART treated HIV infection

- **\(\mu_{HIV}\)** The additional death rate due to untreated HIV mono-infection

- **\(h_{HIV}^{\text{ART}}\)** Decreased mortality hazard ratio for HIV mono-infection due to ART treatment

- **\(\nu^{\text{ART}}\)** Proportion of HIV-diagnosed MSM currently receiving ART treatment

Where our compartmental death rates are then calculated as follows:

- **\(\mu_{HCV}^{\text{Undiag}}\)** = \(\mu_{HIV}\)

- **\(\mu_{HIV}^{\text{Diag}}\)** = \((1 - \nu^{\text{ART}})\mu_{HIV} + \nu^{\text{ART}} h_{HIV}^{\text{ART}} \mu_{HIV}\)

- **\(\mu_{CO}^{\text{Undiag}}\)** = \(\mu_{HCV} + \mu_{HIV}\)

- **\(\mu_{CO}^{\text{Diag}}\)** = \((1 - \nu^{\text{ART}}) h_{HCV}^{\text{No ART}} \mu_{HCV} + \nu^{\text{ART}} h_{HIV}^{\text{ART}} h_{HCV}^{\text{ART}} \mu_{HCV} + (1 - \nu^{\text{ART}}) \mu_{HIV} + \nu^{\text{ART}} h_{HIV}^{\text{ART}} \mu_{HIV}\)
3. Parametrisation and data extraction

In this section, we rely primarily on data extracted from the European Men’s Internet Survey (EMIS) 2010. Where relevant, we have displayed the question from the survey, along with the possible responses before justifying our use of this data to parametrise our model. Where EMIS 2010 is not the primary data source we give clear indication.

3.1 Mixing of MSM by HIV Status

*EMIS Q69. What do you think your current HIV-status is (whether or not you've ever tested for HIV)?*
1=Definitely negative (I don’t have HIV) 2=Probably negative 3=Not sure / I don’t know 4=Probably positive 5=Definitely positive (I do have HIV)

This question above provides the perceived HIV-status of the individual. Only a confirmed diagnosis i.e. answer 5 is counted as being ‘HIV-diagnosed’ (of which 10.4% of MSM responded). This is supported by the number of individuals who answered response 4 being very small (0.5%). For this reason the other categories (including answer 4) are classed as ‘HIV-negative or HIV-positive but undiagnosed’ (89.6%). We acknowledge the estimate of HIV prevalence from EMIS is higher than expected, but a limitation of EMIS is that it was more likely to have attracted more participants of HIV-diagnosed status than found in the general MSM population. We do not calibrate our model to this HIV prevalence estimate, but do use the behavioural traits of these HIV-diagnosed MSM to inform our behavioural parameters

*EMIS Q185. What did you know or think about his HIV-status before having sex? 1=I knew or thought he was HIV-negative 2=I knew or thought he was HIV-positive 3=I don’t remember 4=I didn’t have any thoughts about his HIV-status*

This question allows us to identify perception of the HIV-status of MSM’s last sexual partner. For individuals that perceived themselves to be HIV-diagnosed or not, we estimated the proportion of each that thought their last partner to be HIV-positive or HIV-negative. For those that said they did not think about their partner’s HIV-status, we assumed that a proportion were HIV-positive based on the UK prevalence of HIV infection used in the model.

Assuming these judgements are correct, this allowed us to estimate the likely proportion of sexual partners that were HIV-infected and the proportion that were not. For example in our data 36.2% of HIV-diagnosed MSM thought their last partner was HIV-positive, 16.9% thought they were HIV-negative, and 46.9% hadn’t thought about it when selecting a partner. Assuming their judgement is correct and a 5.9% HIV prevalence in the UK, we would estimate that (36.2% + 0.059 x 46.9%) = 38.5% of HIV-positive MSM made pairings with HIV-positive partners. Conversely, because 16.9% thought their partner was HIV-negative we estimate that (16.9% + (1 – 0.059) x 46.9%) = 61.5% of HIV-positive MSM made pairings with HIV-negative partners.

From EMIS, we used these point estimates to construct a single parameter for the degree of like-with like mixing of MSM by HIV diagnosis status. We refer to MSM who are HIV-undiagnosed or negative as non-diagnosed. Firstly, we assume that:

\[ Y = 0.059 \]  

is the proportion of MSM with HIV;

\[ e \]  

is the chance of errors in HIV judgements; and

\[ \zeta \]  

is the probability that an individual will preferentially seek a partner of the same HIV-diagnosis status.

If we define \( mix_{km}^{HIV} \) as the probability that an individual of HIV diagnosis state \( k = u \ or \ d \) (where \( u \) is an HIV-positive but undiagnosed MSM or HIV-negative MSM and \( d \) is HIV-diagnosed MSM) has a sexual partner of HIV diagnosis state \( m = u \ or \ d \), then we can estimate \( mix_{km}^{HIV} \) as follows:

\[
\begin{align*}
mix_{uu}^{HIV} &= \zeta(1-e) + (1-\zeta(1-e))(1-Y) \\
mix_{ud}^{HIV} &= (1-\zeta)Y + \zeta e Y \\
mix_{du}^{HIV} &= (1-\zeta)(1-Y) + \zeta e (1-Y) \\
mix_{dd}^{HIV} &= \zeta(1-e) + (1-\zeta(1-e))Y
\end{align*}
\]

The EMIS data indicates that this mix function should have the following values:
\[ mix_{uu}^{HIV} = 94.3\% \]
\[ mix_{ud}^{HIV} = 5.7\% \]
\[ mix_{du}^{HIV} = 61.5\% \]
\[ mix_{dd}^{HIV} = 38.5\% \]

Of these values, we aim to capture the best fit for \( mix_{dd}^{HIV} \) as this is our main effect of interest. When we fit \( \zeta \) to give these values for \( mix_{dd}^{HIV} \) from EMIS values, assuming \( e = 0 \) and that the prevalence of HIV is 5.9% as in the UK, then we estimate that \( \zeta = 0.352 \) is the best fit, which results in the following mixing:

\[ mix_{uu}^{HIV} = 96.8\% \]
\[ mix_{ud}^{HIV} = 3.2\% \]
\[ mix_{du}^{HIV} = 61.5\% \]
\[ mix_{dd}^{HIV} = 38.5\% \]

### 3.2 Chance of error when evaluating HIV-status of a sexual partner

The following question in EMIS was used to get an estimation of the likelihood of error when evaluating the HIV-status of a sexual partner, following from question Q185 above, which asked what people thought about the HIV-status of their last casual partner.

**EMIS Q186. [if Q185=1 or 2] Why did you think this? Please read the list below and tick the answer that best applies.**

1. He told me some time ago / I had known for some time
2. He told me (online or in person) before or during sex
3. I knew it from his profile on the Internet
4. He made it clear without actually telling me
5. Someone else told me
6. We were at an event where everyone was HIV-positive
7. We were at an event where everyone was HIV-negative
8. I guessed
9. Other reason

If guessing a partner was HIV-negative, we assumed that answers 2 and 3 were likely to be correct assumptions, it was uncertain whether answers 1, 4, 5, 7 and 9 could yield errors in judgement and that answer 6 (very few answered to this for partners thought to be negative) and 8 were highly likely to be unable to determine the HIV-status of your partner accurately.

If guessing a partner was HIV-positive we assumed that answers 1, 2, 3 and 6 were likely to be correct assumptions, it was uncertain whether answers 4, 7 and 9 could yield errors in judgement and that answers 5 and 8 were highly likely to be unable to determine the HIV-status of partners accurately.

Therefore, the proportion of assumptions likely to be correct were 54.3% and 68.7% when a partner was assumed HIV-negative or HIV-positive, respectively. The proportion of assumptions which were correct or uncertain amounted to 84.9% and 87.9% when a partner was assumed HIV-negative or HIV-positive MSM, respectively. This allows us calculate the error range as between 15.1-45.7% (midpoint 30.6%) when an MSM thought their partner was HIV-negative, and 12.1-31.3% (midpoint 19.2%) when an MSM thought their partner was HIV-positive. These midpoints are close enough that we combine them together, averaging to 25% errors in judgement on average.

We also note that in this instance guessing a partner’s HIV-status is akin to guessing if they are HIV-diagnosed or not, as if the partner in question was unaware of their HIV infection, then they could not communicate if they were HIV-positive to their partners and have previously set up the mixing equations to accommodate this factor.

### 3.3 Condom usage by perceived HIV Status

The following questions are used to determine whether a condom was used for a specific sexual contact with a partner:

**EMIS Q187. Did you have anal intercourse (fuck) on that occasion?**

1. No
2. Yes, he fucked me
3. Yes, I fucked him
4. Yes, we fucked each other

**EMIS Q188. [if Q187=2 or 4] Did he use a condom when he was active in anal intercourse (when he fucked you)?**

1. No
2. Yes
3. I don’t remember
4. I don’t know
EMIS Q190. [if Q187=3 or 4] Did you use a condom when you were “active” in anal intercourse? 1=No 2=Yes 3=I don’t remember/I don’t know

If an individual responds to Q187 with answer 4, then we require a yes to both Q188 and Q190 to decide that a condom has been used. Otherwise, we need a yes to Q188 if they answered 2 for Q187, and a yes to Q190 if they answered 3 to Q187.

We found that when HIV-diagnosed MSM have sex with a partner they assume to be HIV-positive there is a 13% chance of condom usage, whereas all other pairings had similar levels of condom usage of approximately 68% in last sex act.

3.4 Defining the high/low-risk sexual behaviour group

For this parameter, we combine the number of casual and long term partners an individual reports in the last year. To do this, we use the following questions:

EMIS Q157. [if Q155=2] How many steady male partners have you had anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 or more

EMIS Q165. [if Q163=2] How many non-steady partners did you have anal intercourse with in the last 12 months? 1=0 2=1 ... 11=10 12=11-20 13=21-30 14=31-40 15=41-50 16=More than 50

For both the question on steady and non-steady partners, we find the midpoint for each categorical response and add them together to determine the average number of partners across all MSM. For the last category of each question (more than 10 steady partners and more than 50 casual partners) we use the shape of the distribution to estimate the average number of partners for those who answered in this final range (11.85 and 64.5 for respectively). This produced an average number of partners for all MSM of 7.4.

We also used this distribution to determine a cut-off for defining the high and low-risk group. We chose the cut-off for high-risk as greater than 15 partners in the last year due to the shape of the histogram in figure S2. Using this cut-off 82.6% of MSM fall into the low-risk group and 17.4% in the high-risk group. The average number of partners in the last year was 2.9 in the low-risk group and 29.1 in the high-risk group.

![Figure S2: Histogram of the distribution of total sexual partners in the last year as given by the EMIS data](image-url)
3.5 Chem-sex risk

We used the following EMIS questions to assess the prevalence of chem-sex behaviours in the low and high-risk group. We characterised the use of crystal methamphetamine or gamma-hydroxybutyrate or mephedrone within the last 12 months to be the most indicative measure of chem-sex behaviour.1

EMIS Q233. When was the last time you consumed crystal methamphetamine (crystal, meth, Tina)?

EMIS Q235. When was the last time you consumed mephedrone (4-MMC, meow, methylene, bubbles)?

EMIS Q236. When was the last time you consumed GHB/GBL (liquid ecstasy)?

\[ L_{\text{Chem}} = \text{Proportion of low-risk MSM reporting chem-sex in last 12 months} = 0.115 \]

\[ H_{\text{Chem}} = \text{Proportion of high-risk MSM reporting chem-sex in last 12 months} = 0.226 \]

Using findings from previously published studies that have considered the degree to which HIV and HCV acquisition risk is elevated amongst MSM reporting these risk behaviours, we were then able to multiply the prevalence of each behaviour in each group with the relative risk associated with HCV and HIV acquisition risk.

We use ORs from the literature as our relative risks as in this case the ORs are largely similar to relative risk as incident infections with HIV over a year are rare events:2

\[ OR_{\text{HIV}}^{\text{Chem}}, \text{OR of HIV acquisition from chem-sex in last 12 months} = 5.06 (95\% \text{ CI 2.56-10.02})^1 \]

\[ OR_{\text{HCV}}^{\text{Chem}}, \text{OR of HCV acquisition from chem-sex in the last 12 months} = 11.3 (95\% \text{ CI 1.9-68.2})^3 \]

The following calculation is used to estimate the combined increased acquisition risk for HIV and HCV in the low and high-risk groups due to chem-sex:

Elevated HIV acquisition risk in low-risk group is:

\[ R_L^{\text{HIV}} = (1 - L_{\text{Chem}}) + OR_{\text{HIV}}^{\text{Chem}} \times L_{\text{Chem}} = 1.5 (1.2 - 2.0) \]

Elevated HIV acquisition risk in low-risk group is:

\[ R_H^{\text{HIV}} = (1 - H_{\text{Chem}}) + OR_{\text{HIV}}^{\text{Chem}} \times H_{\text{Chem}} = 1.9 (1.4 - 3.0) \]

Elevated HCV acquisition risk in low-risk group is:

\[ R_L^{\text{HCV}} = (1 - L_{\text{Chem}}) + OR_{\text{HCV}}^{\text{Chem}} \times L_{\text{Chem}} = 3.3 (1.2 - 16.2) \]

Elevated HCV acquisition risk in low-risk group is:

\[ R_H^{\text{HCV}} = (1 - H_{\text{Chem}}) + OR_{\text{HCV}}^{\text{Chem}} \times H_{\text{Chem}} = 2.2 (1.1 - 8.7) \]

Then to calculate the increased factor of relative risk between the two groups, we combine these results:

\[ \frac{R_H^{\text{HIV}}}{R_L^{\text{HIV}}} = 1.3 (1.1 - 1.5) \]

\[ \frac{R_H^{\text{HCV}}}{R_L^{\text{HCV}}} = 1.5 (1.1 - 1.9) \]

3.6 Increased infectiousness of HCV within HIV co-infected MSM

There is evidence to suggest that HIV positive individuals are at higher risk of onward transmission of HCV infection, although current evidence is only available for vertical transmission from mother to child,4,5 along with some weak evidence from needle-stick injuries suggesting a similar increased risk of transmission.6 These increased risks of HCV transmission are generally postulated to be due to the observed increase in HCV viral load occurring during HIV infection,7,8 with one study finding a direct link between vertical transmission and higher HCV viral load.9 During ART, HCV viral load remains similar, or possibly increases compared to other HIV infected individuals,10,12 although very limited data suggest the chance of vertical transmission for HIV-positive women may decrease if they are on ART.13 Because there is no direct evidence suggesting that sexual HCV transmission increases with HIV co-infection, we now consider a wide plausible range in line with vertical transmission of HCV under HIV co-infection, regardless of ART status.5 We use the most up to date systematic review and meta-analysis of the increased risk in vertical transmission for this value of 2.6 (1.5-4.4 95\% CI).
3.7 Mixing of MSM by risk group

Little data exists on the degree of like with like mixing occurs amongst MSM in the UK based on sexual risk behaviour other than serosorting. The value we use is based on data from EMIS, from the following question that asks about where an individual met their last sexual partner, which can be used to see if high-risk MSM mainly meet partners in venues that other high-risk men meet partners but not low-risk partners.

**EMIS Q182. Where did you first meet him?**
1=A gay community centre, gay organisation or gay social group
2=A gay café or gay bar
3=A gay disco or nightclub
4=A backroom of a bar, gay sex club, a public gay sex party
5=A gay sex party in a private home
6=A gay saunas
7=A porn cinema
8=A cruising location (street, roadside service area, park, beach, baths, lavatory)
9=A website for gay or bisexual men
10=Elsewhere

For this we specify:

\[ p_j \] as the number of partners per year in the high or low-risk group, \( j = L \) or \( H \)

\[ N_j \] as the proportion of the population in the high or low-risk group, \( j = L \) or \( H \)

\[ V_j^x \] as the proportion of individuals from the high or low-risk group, \( j = L \) or \( H \), who met their last partner in venue \( x \) from the answer selections above. We exclude venue 9 as it is impossible to tell how MSM will mix based on online information from our data set, and whether it will be preferentially or not. For example hook-up apps may cause high-risk individuals to mix preferentially and websites for MSM seeking relationships may also promote mixing between MSM with less partners. We also exclude 10 as we don’t have specific information about the venue type. Venues 1-8 however we can assume that once present, will ensure even mixing for all individuals there.

If we define that \( \text{mix}^{\text{risk}}_{jl} \) as the probability that an individual of risk group \( j \) (L or H) will mix with an individual of risk group \( l \) (L or H), then \( \text{mix}^{\text{risk}}_{jl} \) can be estimated as follows:

\[
\text{mix}^{\text{risk}}_{jl} = \sum_{x=1}^{8} V_j^x p_j N_l \left( \frac{V_l^x p_l N_l + V_H^x p_H N_H}{V_l^x p_l N_l + V_H^x p_H N_H} \right)
\]

Using this equation we therefore predict with our EMIS data that:

\[
\text{mix}^{HH}_{HH} = 0.7012
\]
\[
\text{mix}^{HL}_{HH} = 0.2988
\]
\[
\text{mix}^{HH}_{HH} = 0.6643
\]
\[
\text{mix}^{HH}_{HH} = 0.3357
\]

Based on the overall frequency of partnerships provided by MSM from the low and high-risk group, we expect that:

\[
\text{mix}^{HH}_{HH} = 0.6898
\]
\[
\text{mix}^{HL}_{HH} = 0.3102
\]
\[
\text{mix}^{HH}_{HH} = 0.6898
\]
\[
\text{mix}^{HH}_{HH} = 0.3102
\]

So, to calculate the proportion of MSM who preferentially mix by risk status (\( b \), as defined earlier) we use the equations:

\[
\text{mix}^{\text{risk}}_{HH} = b + (1 - b) 0.6898
\]
\[
\text{mix}^{\text{risk}}_{HL} = (1 - b) 0.3102
\]
\[
\text{mix}^{\text{risk}}_{HH} = (1 - b) 0.6898
\]
\[
\text{mix}^{\text{risk}}_{LL} = b + (1 - b) 0.3102
\]
The closest fit we have to the data is when $b=0.03675$ - so an estimated 3.7% of MSM preferential mix by risk status. However, 56% of individuals said they met their last partner on the internet, which may also result in mixing by risk status (people often state their sexual preferences and risk behaviour), but could not be estimated with the available data from EMIS. Therefore, preferential mixing by risk status could be greater than we estimated. For this reason we allow a wide parameter range of 0% and 50%.

3.8 Proportion of HIV-undiagnosed/negative MSM eligible for PrEP

We used the guidelines for PrEP eligibility in England\textsuperscript{14}. We then compared this to the data from EMIS as closely as possible. The PrEP eligibility criteria for the UK are as follows:

1. MSM, trans women or trans men who are currently HIV-negative and who are clinically assessed to be at high-risk of HIV acquisition through fulfilling the following criteria:
   a) Have a documented confirmed HIV-negative test during an earlier episode of care in the preceding year (i.e. 42-365 days ago ); and
   b) Report condomless intercourse in the previous 3 months and this is documented in the clinical notes; and
   c) Affirm their likelihood of repeated condomless intercourse in the next 3 months and this is documented in the clinical notes.

OR

2. The HIV-negative partner (confirmed by a current documented negative HIV test) of a diagnosed person with HIV who is not known to be virally suppressed and with whom condomless intercourse is anticipated and so is clinically assessed and considered to be at high-risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors treatment as part of an active risk reduction intervention including health education, safer sex promotion, and exploration of treatment as prevention for the HIV-positive partner;

OR

3. HIV-negative heterosexual men and women clinically assessed and known to have had condomless sex with a person with HIV (who is not known to be virally suppressed) within the past 3 months and for whom it is anticipated that this will occur again, either with the same person or another person with similar status, and so is clinically assessed and considered to be at high-risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors as part of an active risk reduction intervention including health education and safer sex promotion.

AND

a) Where the treating clinician recommends and monitors PrEP as part of an active risk reduction intervention including health education and safer sex

b) Where the patient is and remains actively involved in the risk reduction intervention and is able to affirm their appropriate adherence to PrEP; AND

c) The use and outcomes of the intervention is recorded via the agreed prior approval and monitoring systems.

Exclusions

a) Individuals in monogamous relationships with a partner who is known to be diagnosed with HIV and whose viral load is undetectable.

b) Individuals without a current confirmed negative HIV test result (to minimise the risk of patients with undiagnosed HIV starting PrEP and developing drug resistant virus)

c) Individuals who do not or no longer meet the criteria for high-risk of HIV acquisition

d) Individuals whose only risk of HIV acquisition is due to injecting drug use (as the current HIV incidence in the UK is too low for PrEP to be cost effective)

e) People known to be diagnosed with HIV

f) Individuals under 16 years of age

g) Treatment outside of Level 3 GUM services

The way in which we processed this was to only look at the criteria applicable to MSM and approximate the proportion of MSM eligible as closely as possible with our data.
• For criteria 1a (HIV test in the last 12 months), we considered any MSM who had indicated an HIV test which had resulted in a HIV-negative status (EMIS Q71) which was taken in the last year (EMIS Q104). This criteria was met by 41.3% of HIV-negative/undiagnosed MSM.

• For criteria 1b (unprotected anal sex in previous 90 days) we did not have the data to know if an individual did not use a condom in the last 3 months. We did however know if the individual had not used a condom during a sexual encounter in the past 4 weeks or 6 months (EMIS Q150, Q152, Q153 and Q154). We also excluded any MSM who indicated that this condom less sex was only with steady partners (EMIS Q166). At 4 weeks and 6 months, this criterion was met by 16.6% and 26.6% of HIV-negative/undiagnosed MSM respectively.

• Criteria 1c (high likelihood of unprotected sex in the next 90 days) was beyond the scope of the data, so we assumed that if criteria 1b was met, so was criteria 1c.

• For criteria 2 (HIV-negative person who is in a sexual relationship with a HIV-diagnosed man who is not virally supressed and condomless anal intercourse is anticipated), we included anyone who had indicated one or more current steady partners (EMIS Q40 and Q41) who they knew to be serodiscordant to themselves (EMIS Q47). We had no data on the state of their partner’s viral suppression however, so the criteria of being virally unsuppressed was assumed to be met in all cases of serodiscordance. This criteria was met by 2.2% of HIV-negative/undiagnosed MSM.

• Criteria 3 was not relevant to our population demographic.

• We also excluded any MSM under 16 and people known to be diagnosed with HIV by filtering the data. Other exclusion criteria were outside the scope of our data or were included within the synthesis of the previous criteria naturally.

The results for this analysis meant that overall (after application of all criteria) for the case of (i) forgoing condom use at some point in the past 4 weeks, 13.2% (6.1% low-risk and 16.6% high-risk) of HIV-negative/undiagnosed MSM were eligible for PrEP and (ii) for the case of forgoing condom use at some point in the past 6 months, 18.1% (9.6% low-risk and 23.0% high-risk) of HIV-negative/undiagnosed MSM were eligible for PrEP. In actuality, our estimate for the proportion of MSM eligible for PrEP will be somewhere in the middle of these values. This is as the criteria specify that eligible MSM will have forgone condom use at some point in the last 90 days; which lies between 4 weeks and 6 months.

These estimates may over-estimate the real eligibility of PrEP among MSM in England as we could not ascertain the proportion of MSM who are likely to forgo condom use in the next 90 days and we had no data on the viral load of HIV-positive MSM in steady but sero-discordant partnerships. We also note that as EMIS is likely to attract a higher risk population of respondents, this will also mean we may be over-estimating overall PrEP eligibility.

Given too that not all MSM eligible for PrEP would take it up, then we use a cautious lower bound of PrEP uptake of 12.5% (near to our lower estimated value - based on MSM having forgone condom use in the last 4 weeks) and an upper bound of 25.0% (which we examine in our sensitivity analysis) to cover the uncertainty in our estimates. This could even extend to scenarios which include greater uptake of PrEP in the UK than expected by and limited to the NHS England criteria.

3.9 PrEP Uptake and drop-off and modified HIV testing Rate

The rate at which people stop using PrEP is 8.2 (6.6-9.8) months in our model, as parametrised by a real-world study.\textsuperscript{15} We fit the rate of PrEP uptake to match the proportion of individuals we want on PrEP at a given point in the future.

The efficacy of PrEP is highly linked to the adherence and consistency of use within those prescribed it\textsuperscript{16-18}. Although adherence was quite low within initial trials, more recent open label trials have shown a much higher level of adherence\textsuperscript{19,20}, with more recent studies set in more real-world settings similar finding an even higher efficacy than clinical trials.\textsuperscript{20} We use an uncertainty range with a lower bound of 86% as the given efficacy as found in the PROUD study from the UK\textsuperscript{12} and the 97.0% efficacy cited from real-world data in a similar setting to the UK.\textsuperscript{20}
3.10 HCV testing and treatment rates

Testing and treatment rates for HCV vary, with HIV-diagnosed MSM currently advised to be tested at least yearly. UK CHIC data from 2011 found that HCV diagnosis was followed by an estimated 2.2 year delay before treatment\textsuperscript{21} and 12.0\% of HIV-diagnosed MSM declined HCV screening\textsuperscript{21}. In HIV-negative MSM and HIV-positive but undiagnosed MSM, the duration of time between initial HCV infection and treatment is largely unknown, and so we assume a long time period due to the slow onset of symptoms. We therefore assume this is on average 10 years (assuming a wide parameter range from 5-15 years) from initial infection and that time to treatment is similar to HIV-diagnosed MSM at 2.2 years, but with no rejection of treatment due to experiencing symptoms. In all cases of treatment uptake, diagnosis is followed by treatment with direct acting antivirals which we assume to have a treatment duration of 8-12 weeks.\textsuperscript{22}

With the introduction of PrEP, MSM on PrEP may be screened more often for HCV, but exactly how often in the UK remains undecided at present. We explore the possibilities of yearly, six monthly and three-monthly screening in different scenarios. We also consider the impact of a shorter time duration to treatment in some or all groups, with treatment courses completed in six months from diagnosis of HCV infection in these simulations.
3.11 List of parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Prior Range</th>
<th>Posterior Range</th>
<th>Source</th>
<th>Symbol(s)</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflow and Outflow for the model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of initiation of sexual activity</td>
<td>15</td>
<td>-</td>
<td>EMIS</td>
<td>-</td>
<td>EMIS indicates that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>Exit age for the model due to sexual cessation</td>
<td>65</td>
<td>-</td>
<td>EMIS</td>
<td>-</td>
<td>EMIS indicates that only a very small proportion of MSM are sexually active outside of this age bracket.</td>
</tr>
<tr>
<td>The rate at which people leave the model due to ‘aging out’</td>
<td>0.02 person-years</td>
<td>-</td>
<td>EMIS</td>
<td>( \mu )</td>
<td>1/(period of sexual activity)=1/50=0.02</td>
</tr>
<tr>
<td>The amount of new individuals ‘aging in’ to the population</td>
<td>0.02 per year</td>
<td>-</td>
<td>EMIS</td>
<td>( \theta )</td>
<td>Based on a population size of 1 at model initiation. This is split proportionally between the two risk groups.</td>
</tr>
<tr>
<td>The additional death rate due to HCV mono-infection</td>
<td>0.0025 (0.0016-0.0040) person-years</td>
<td>0.0026 (0.0016-0.0039) person-years</td>
<td>23,24</td>
<td>( \mu_{HCV} )</td>
<td>20-30% of people with HCV develop cirrhosis after 15-25 years. So the rate to cirrhosis is: Lower bound = 0.2*(1/25)=0.008, Mean = 0.25*(1/20) = 0.0125, Upper bound = 0.3*(1/15)=0.02. Then five year survival rate for HCV after cirrhosis is 55.6%. Therefore overall death rate is estimated as: Lower bound = 0.008*(1/5)=0.0016, Mean = 0.0125*(1/5)=0.0025, Upper bound = 0.02*(1/5)=0.0040.</td>
</tr>
<tr>
<td>The additional death rate due to HIV infection when the individual is not on ART</td>
<td>0.089 (0.082-0.096) person-years</td>
<td>0.089 (0.082-0.096) person-years</td>
<td>25</td>
<td>( \mu_{HIV} )</td>
<td>Untreated HIV in MSM results in 11.2 (10.4-12.2) years until death. Death rate is the reciprocal. Meta-analysis of studies co-infection death rates, 10 pre-HAART, 27 post HAART suggested that pre-HAART death rate largely only affected by HIV progression. So then we defer to the death rate for when HIV is untreated.</td>
</tr>
<tr>
<td>The additional death rate due to HIV infection for individuals on ART treatment</td>
<td>0.026 (0.024-0.029) person-years</td>
<td>0.026 (0.024-0.029) person-years</td>
<td>25,26</td>
<td>( h_{ART}^{HIV} )</td>
<td>If infected with HIV but on treatment live to 73, averages 38 years of survival compared to 11.2 without HAART. So rate of death is reduced by 11.2/38 compared to not being on ART treatment.</td>
</tr>
<tr>
<td>The additional death rate due to HIV infection in those with HIV and not on ART</td>
<td>0.0063 (0.0040 – 0.0100) person-years</td>
<td>0.0063 (0.0040 – 0.0010) person-years</td>
<td>27</td>
<td>( h_{No\ ART}^{HIV} )</td>
<td>Based on the rate of fibrosis progression among individuals coinfected with HIV/HCV not on ART which is 2.5 times faster</td>
</tr>
<tr>
<td>The additional death rate due to HCV infection in those with HIV who are on ART</td>
<td>0.0043 (0.0027-0.0068) person-years</td>
<td>0.0043 (0.0027-0.0068) person-years</td>
<td>27</td>
<td>( h_{ART}^{HCV} )</td>
<td>Based on the rate of fibrosis progression among individuals coinfected with HIV/HCV on ART which is 1.7 times faster</td>
</tr>
<tr>
<td><strong>HCV related parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission factor for HCV</td>
<td>Fit to Model</td>
<td>0.0048 (0.0025-0.0087)</td>
<td>-</td>
<td>( \beta_{HCV} )</td>
<td></td>
</tr>
<tr>
<td>Efficacy of HCV treatment with Pegylated interferon with ribavirin in HIV-negative MSM</td>
<td>64% (59-69%)</td>
<td>64% (59-69%)</td>
<td>28</td>
<td>( \psi_n )</td>
<td>Real world study examining the efficacy of pegylated interferon with ribavirin in HIV-negative MSM</td>
</tr>
<tr>
<td>Efficacy of HCV treatment with Pegylated interferon with ribavirin in HIV-positive MSM</td>
<td>38% (35-42%)</td>
<td>38% (35-42%)</td>
<td>29</td>
<td>( \psi_p )</td>
<td>Meta-analysis of studies examining the efficacy of pegylated interferon with ribavirin in HIV-positive MSM</td>
</tr>
<tr>
<td>Efficacy of HCV treatment with DAAs (assumed use from 2015 onwards)</td>
<td>95% (90-100%)</td>
<td>95% (90-100%)</td>
<td>36,31</td>
<td>( \psi_n^{DAA}, \psi_p^{DAA} )</td>
<td>Real world studies examining the efficacy of HCV DAAs</td>
</tr>
<tr>
<td>Spontaneous clearance probability for HCV in HIV-negative MSM</td>
<td>0.25 (0.22-0.29)</td>
<td>0.26 (0.22-0.29)</td>
<td>-</td>
<td>( \chi_n )</td>
<td>Estimated from a meta-analysis of studies in mixed populations. However looking at specifically males 36/181 cleared the virus, giving the range we show as 95% CI</td>
</tr>
</tbody>
</table>
### HIV related parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Prior Range</th>
<th>Posterior Range</th>
<th>Source</th>
<th>Symbol(s)</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous clearance probability for HCV in HIV-positive MSM</td>
<td>0.15 (0.12-0.20)</td>
<td>0.15 (0.12-0.20)</td>
<td>35</td>
<td>( x_p )</td>
<td>Estimated from a meta-analysis, which cites a specific estimate of clearance among HIV-positive MSM</td>
</tr>
<tr>
<td>The rate at which HCV infections progress from acute to chronic.</td>
<td>2 person-years</td>
<td>-</td>
<td>34</td>
<td>( \alpha^{HCV} )</td>
<td>Given by clinical guidelines on when HCV is considered to transition to a chronic infection - 6 months from initial HCV infection</td>
</tr>
<tr>
<td>The rate of HCV screening in HIV diagnosed MSM at baseline</td>
<td>1.13 person-years</td>
<td>-</td>
<td>21</td>
<td>( d_{HIV}^{20} )</td>
<td>Based on 88% of HIV-diagnosed MSM willing to take yearly HCV tests during routine HIV check-up appointments from UK-CHIC data</td>
</tr>
<tr>
<td>Delay from HCV diagnosis on average to initiation of treatment.</td>
<td>2.2 years</td>
<td>-</td>
<td>21</td>
<td>( z_{delay}^{HCV} )</td>
<td>Baseline value taken from UK-CHIC data in HIV-diagnosed MSM and assumed for the rest of MSM also</td>
</tr>
<tr>
<td>Duration of HCV treatment</td>
<td>0.19 (0.15-0.23)</td>
<td>0.19 (0.15-0.23)</td>
<td>22</td>
<td>( z_{treat}^{HCV} )</td>
<td>Most common length of treatment courses with DAAs is 8 or 12 weeks</td>
</tr>
<tr>
<td>Rate of HCV screening in all HIV-negative MSM at baseline</td>
<td>0.10 (0.07-0.20)</td>
<td>0.10 (0.07-0.19)</td>
<td>35</td>
<td>( d_{HCV}^{nl} )</td>
<td>Often MSM do not receive diagnosis of HCV until there are symptoms unless individuals are at high-risk from sources of infection. From this information we made an assumption of 10 (5-15) years until a diagnosis is likely to be made. In our model we vary this assumption</td>
</tr>
<tr>
<td>HIV related parameters</td>
<td></td>
<td></td>
<td></td>
<td>( \beta^{HIV} )</td>
<td></td>
</tr>
<tr>
<td>The transmission factor for HIV in the chronic phase of infection with no ART treatment</td>
<td>Fit to data</td>
<td>0.0064 (0.0022-0.0141)</td>
<td>-</td>
<td>( \beta^{HIV} )</td>
<td></td>
</tr>
<tr>
<td>Increased HIV infectiousness during acute HIV phase</td>
<td>26 (10-67)</td>
<td>27 (10-64)</td>
<td>36</td>
<td>( \Delta )</td>
<td>Rakai Uganda, HIV serodiscordant heterosexual couples, stage of virus estimated for passing on infection, all couples start negative.</td>
</tr>
<tr>
<td>The rate at which HIV infections progress from acute to chronic.</td>
<td>4.1 (2.0-9.8)</td>
<td>4.4 (2.1-9.3)</td>
<td>36</td>
<td>( \alpha^{HIV} )</td>
<td>Based on acute infection duration of 2.9 (1.23-6) months</td>
</tr>
<tr>
<td>Proportion of MSM on ART who are virally supressed</td>
<td>0.72 (0.69-0.76)</td>
<td>in 2012</td>
<td>37-38</td>
<td>-</td>
<td>2012 estimate from 2012 UK data, uncertainty bounds were not available for this finding, but uncertainty in the size of the UK HIV population given in this report was +/- 5%, so we have reflected this uncertainty level in our parameter range.</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.92-1.00)</td>
<td>in 2017</td>
<td></td>
<td></td>
<td>2017 estimate from 2017 UK data, uncertainty bounds were not available for this finding, but uncertainty in the size of the UK HIV population given in this report was +/- 5% for consistency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We assume that those with an undetectable viral load cannot pass on their HIV infection as found in the PARTNER-2 study among MSM.</td>
</tr>
<tr>
<td>Proportion of diagnosed MSM on ART treatment</td>
<td>0.85 (0.81-0.89)</td>
<td>in 2012</td>
<td>37-38</td>
<td>( \psi^{ART} )</td>
<td>2012 estimate from 2012 UK data, uncertainty bounds were not available for this finding, but uncertainty in the size of the UK HIV population given in this report was +/- 5%, so we have reflected this uncertainty level in our parameter range.</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.93-1.00)</td>
<td>in 2017</td>
<td></td>
<td></td>
<td>2017 estimate from 2017 UK data, uncertainty bounds were not available for this finding, but we use +/- 5% for consistency.</td>
</tr>
<tr>
<td>The rate at which individuals are diagnosed for HIV</td>
<td>0.31 (0.26-0.38)</td>
<td>person-years in 2012</td>
<td>40,41</td>
<td>( d^{HIV} )</td>
<td>2012 estimates from a back-calculation study which calculated HIV diagnosis rates at the start of 2011 in the UK, which were 3.2 (2.6-3.8) years from infection.</td>
</tr>
<tr>
<td></td>
<td>0.43 (0.29-0.83)</td>
<td>person-years in 2017</td>
<td></td>
<td></td>
<td>2017 estimates from a modelling study which calculated 2016 HIV diagnosis rates in the UK, which were 2.3 (1.2-3.5) years from infection.</td>
</tr>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>2.6 (1.5-4.4)</td>
<td>2.8 (1.6-4.4)</td>
<td>5</td>
<td>( \Lambda )</td>
<td>Estimates come from a study which considers vertical transmission between mother and child due to lack of data on sexual transmission. Value given as an adjusted odds ratio, but as the prevalence of the event is rare in HIV-negative women (our reference group) at &lt;6%, we assume rough equivalence between the OR and relative risk.</td>
</tr>
</tbody>
</table>
### Behavioural parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Prior Range</th>
<th>Posterior Range</th>
<th>Source</th>
<th>Symbol(s)</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proportion of MSM who mix like with like by HIV-status</td>
<td>0.35 (0.28-0.42)</td>
<td>0.35 (0.28-0.42)</td>
<td>EMIS</td>
<td>ζ</td>
<td>From EMIS data we see that it is more likely for those of the same HIV-status to form partnerships. The parameter is the proportion of partnerships chosen between people of the same HIV-status assuming no errors in judging each other’s HIV-status. The remainder of partnerships are assumed to be chosen randomly.</td>
</tr>
<tr>
<td>Probability of condom usage between a HIV-diagnosed MSM and a partner assumed to be HIV-positive</td>
<td>13.0% (10.4-15.6%)</td>
<td>12.9% (10.5%-15.4%)</td>
<td>EMIS</td>
<td>-</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV-status of last partner showed a lower condom usage between partners when the asked participant was HIV-diagnosed and assumed their partner was HIV-positive. We estimate a range +/- 20% either side. This is used in conjunction with the protection provided by condoms to determine the number of infections able to transmit through the protection offered by condoms in this pairing (cₚ).</td>
</tr>
<tr>
<td>Probability of condom usage between MSM pairings other than between a diagnosed MSM and a partner assumed to be HIV-positive</td>
<td>68.0% (54.4-81.6%)</td>
<td>70.5% (55.5%-80.8%)</td>
<td>EMIS</td>
<td>-</td>
<td>EMIS questions concerning condom use with your last casual partner combined with thoughts about HIV-status of last partner. We estimate a range +/- 20% either side. This is used in conjunction with the protection provided by condoms to determine the number of infections able to transmit through the protection offered by condoms in these pairings (cₛ).</td>
</tr>
<tr>
<td>Efficacy of condoms per act</td>
<td>0.91 (0.69-1.00)</td>
<td>0.86 (0.70-0.99)</td>
<td>EMIS</td>
<td>e</td>
<td>Per act protection provided by condom use during anal sex</td>
</tr>
<tr>
<td>Chance of a serosorting judgement being incorrect. An incorrect judgement leads to random mixing</td>
<td>24.9% (19.2% -30.6%)</td>
<td>24.6% (19.4-30.4%)</td>
<td>EMIS</td>
<td>L</td>
<td>From EMIS participants, the proportion of individuals who make assumptions about partner’s HIV-status for reasons which are unlikely to be effective at determining their partner’s HIV-status.</td>
</tr>
<tr>
<td>Proportion of individuals in the Low-risk group</td>
<td>0.83 (0.79-0.86)</td>
<td>0.83 (0.79-0.86)</td>
<td>EMIS</td>
<td>L</td>
<td>Proportion of MSM in the EMIS who had &lt;15 sexual partners with whom they had anal intercourse in the last year.</td>
</tr>
<tr>
<td>Proportion of individuals in the High-risk group</td>
<td>0.17 (0.21-0.14)</td>
<td>0.17 (0.14-0.21)</td>
<td>EMIS</td>
<td>H (= 1 – L)</td>
<td>Proportion of MSM in the EMIS who had ≥15 sexual partners with whom they had anal intercourse in the last year.</td>
</tr>
<tr>
<td>Number of yearly partners with which there was anal intercourse by risk group</td>
<td>2.9 (2.3-3.5) in low-risk and 29.1 (23.3-34.9) in high-risk</td>
<td>2.9 (2.9-3.5) in low-risk and 29.5 (23.7-34.6) in high-risk</td>
<td>EMIS</td>
<td>P_L, P_H</td>
<td>From EMIS data, within the low and high groups we formed the averaged the number of anal sex partners in each group which were 2.9 and 29.1 for high and low risk respectively. We add a range of uncertainty equivalent to +/- 20%.</td>
</tr>
<tr>
<td>Elevated risk of HCV and HIV acquisition in the high-risk group (based on chem-sex participation in the previous 12 months)</td>
<td>For HIV 1.3 (1.1-1.5), For HCV 1.5 (1.1-1.9)</td>
<td>For HIV 1.3 (1.1-1.5), For HCV 1.5 (1.1-1.9)</td>
<td>EMIS</td>
<td>RHV, RHCV</td>
<td>We used EMIS data to assess the prevalence of chem-sex in our population in the last year combined with estimates for the increased risk these pose to HIV and HCV acquisition in MSM from two studies. We compared the two risk groups to see the difference in relative risk they had associated with these factors. Our parameter range is calculated using 95% CIs from the ORs within the studies, which due to low prevalence of incident HIV and HCV infections could be estimated to be equivalent to the relative risk.</td>
</tr>
<tr>
<td>The proportion of MSM who mix like with like by risk status</td>
<td>0.25 (0.00-0.50)</td>
<td>0.30 (0.02-0.49)</td>
<td>EMIS</td>
<td>b</td>
<td>Using EMIS data we assessed where individuals in each risk group meet their partners, to see if it was more likely for individuals in the same risk group to mix more often. A range of higher values were assumed due to large uncertainty.</td>
</tr>
<tr>
<td><strong>PrEP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of MSM taking up PrEP by 2020</td>
<td>12.5% or 25.0%</td>
<td></td>
<td>EMIS</td>
<td></td>
<td>Calculated from EMIS data applied to the eligibility criteria from NHS England. We use two values to encompass uncertainty.</td>
</tr>
<tr>
<td>Relative factor increase in coverage of PrEP in high-risk MSM compared to low-risk MSM</td>
<td>2.6 (2.4-2.8)</td>
<td>2.6 (2.4-2.8)</td>
<td>EMIS</td>
<td></td>
<td>Calculated from EMIS data applied to the eligibility criteria from NHS England.</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value/Prior Range</td>
<td>Posterior Range</td>
<td>Source</td>
<td>Symbol(s)</td>
<td>Details/Comments</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>--------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>The rate at which those who are HIV susceptible start using PrEP (varies</td>
<td>Fitted</td>
<td>-</td>
<td></td>
<td>( \pi_j )</td>
<td>Fitted to the number desired to be taking PrEP after specified time period for each risk group</td>
</tr>
<tr>
<td>by risk group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The rate at which individuals currently on PrEP stop using PrEP</td>
<td>1.5 (1.2-1.8) person-</td>
<td>1.5 (1.2-1.8) person-</td>
<td>15</td>
<td>( \eta )</td>
<td>Multi-clinic review found median continuation time of PrEP of 8.2 months. No range was given so we assume a +/- 20% variation on this of 6.6-9.8 months.</td>
</tr>
<tr>
<td>years</td>
<td>-</td>
<td>years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy of PrEP in reducing HIV incidence</td>
<td>91.5% (86.0-97.0%)</td>
<td>91.6% (86.4-96.6%)</td>
<td>17.30</td>
<td>( \omega )</td>
<td>We take a range which uses the large UK PROUD study as a lower bound for efficacy and an upper bound from a real world setting of PrEP use among MSM.</td>
</tr>
<tr>
<td>Rate of HIV testing for PrEP users</td>
<td>0.25 person-years</td>
<td>-</td>
<td>17</td>
<td>( d_{1}^{HIV} )</td>
<td>HIV testing occurs every 3 months if on PrEP</td>
</tr>
<tr>
<td>Rate of HCV screening for PrEP users</td>
<td>Varied in model</td>
<td>-</td>
<td></td>
<td>( d_{01}^{HCV} )</td>
<td>We examine the impact of testing for HCV over different time periods in PrEP users, from symptomatic testing to quarterly testing.</td>
</tr>
</tbody>
</table>

Table S3: Parameters with ranges and details of estimation included.
4. Supplementary figures and tables

4.1 Split of MSM subpopulations by high and low-risk

**Figure S3**: Distribution of high-risk and low-risk MSM in each MSM subgroup given 12.5% coverage of PrEP from 2018 until 2030.

**Figure S4**: Pie charts showing the degree to which different MSM subgroups contribute to the overall burden of HCV among MSM in 2030 with or without the introduction of PrEP at 12.5% coverage and no risk compensation.
4.2 Reduction in new HIV infections due to PrEP

In our analysis, we found a large proportion of new HIV infections were averted (45.2%) between 2018 and 2030 with only a 12.5% coverage of PrEP split between high and low-risk MSM dependent on the proportion eligible. This large reduction is partly due to the large number of high-risk MSM on PrEP (33.7% of total MSM on PrEP being high-risk), and that HIV infections are concentrated within the high-risk MSM population, as can be seen from figure S3. Indeed, even though the high-risk population comprises only 17.3% of the total population, they harbour 76.6% of the total HIV infections in our 2018 baseline. Figure S5 shows how PrEP at 12.5% coverage when distributed in different ways between high and low-risk MSM can affect our result. The figure shows that targeting PrEP amongst high-risk MSM has a large impact on reducing forward transmissions, both rapidly in the early years, and then building gradually to 2030. Further to this, numerical analysis shows that $R_0$ becomes less than 1 when we assume our NHS criteria for PrEP distribution with 12.5% coverage. This results in much greater decreases in HIV infections than we would usually expect as HIV is on the threshold of moving to a state of extinction with our coverage of PrEP at 12.5%.

Figure S5: Percentage of HIV infections averted per year compared to a baseline of no PrEP. PrEP is distributed at 12.5% coverage within HIV-negative MSM, either entirely (1) within low-risk MSM, (2) weighted evenly between the two groups, (3) at NHS criteria (which is skewed towards high-risk MSM being on PrEP) and (4) entirely within high-risk MSM.
4.3 Impact of screening PrEP users on prevalence and incidence of HCV in different MSM subgroups

**Figure S6:** Change in HCV (A and B) prevalence and (C and D) incidence by 2030 with the introduction of PrEP and enhanced HCV screening in PrEP users compared to 2030 values without the introduction of PrEP, for different MSM subgroups. In the scenarios presented, PrEP users are screened for HCV every 3, 6 or 12 months. MSM on PrEP also receive and complete HCV treatment within 6 months of diagnosis. Projections are given with (B and D) and without (A and C) risk compensation, with the risk compensation scenario assuming condom use among PrEP users reduces from 68% to 34%. Point estimates are the median of our model projections with the error bars representing the 2.5 to 97.5 percentiles from our 500 model fits. *This is compared to the prevalence of HCV in MSM who are eligible for PrEP in the scenario where PrEP is not introduced.
### 4.4 Central range of the main results

<table>
<thead>
<tr>
<th>Screening population and frequency</th>
<th>Scenario</th>
<th>Change in HCV Incidence by 2030 compared to 2018 baseline HCV incidence</th>
<th>Average duration between HCV screening required in HIV-negative population not using PrEP to reach 90% HCV incidence reduction by 2030.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.5% Percentile</td>
<td>Median</td>
</tr>
<tr>
<td>No Screening</td>
<td>S0</td>
<td>-16.8%</td>
<td>-45.1%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>60.4%</td>
<td>-5.9%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (12 months)</td>
<td>S0</td>
<td>-24.6%</td>
<td>-55.1%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>42.0%</td>
<td>-21.4%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (6 months)</td>
<td>S0</td>
<td>-26.3%</td>
<td>-56.5%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>38.8%</td>
<td>-23.7%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM (3 months)</td>
<td>S0</td>
<td>-27.0%</td>
<td>-57.1%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>37.2%</td>
<td>-24.8%</td>
</tr>
<tr>
<td>PrEP users (12 Months)</td>
<td>S0</td>
<td>-52.7%</td>
<td>-67.3%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-29.4%</td>
<td>-54.2%</td>
</tr>
<tr>
<td>PrEP users (6 Months)</td>
<td>S0</td>
<td>-57.1%</td>
<td>-70.2%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-40.3%</td>
<td>-60.4%</td>
</tr>
<tr>
<td>PrEP users (3 Months)</td>
<td>S0</td>
<td>-59.5%</td>
<td>-71.8%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-46.1%</td>
<td>-63.5%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (12 Months)</td>
<td>S0</td>
<td>-59.0%</td>
<td>-75.4%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-38.3%</td>
<td>-65.0%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (6 Months)</td>
<td>S0</td>
<td>-63.9%</td>
<td>-78.8%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-49.7%</td>
<td>-71.4%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (3 Months)</td>
<td>S0</td>
<td>-66.6%</td>
<td>-80.4%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-55.4%</td>
<td>-74.3%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (12 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>-64.6%</td>
<td>-79.6%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-47.2%</td>
<td>-70.9%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (6 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>-69.0%</td>
<td>-82.5%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-57.4%</td>
<td>-76.4%</td>
</tr>
<tr>
<td>HIV Diagnosed MSM and PrEP users (3 Months), plus all MSM treated within 6 months</td>
<td>S0</td>
<td>-71.3%</td>
<td>-83.9%</td>
</tr>
<tr>
<td></td>
<td>S1</td>
<td>-61.7%</td>
<td>-79.0%</td>
</tr>
</tbody>
</table>

Table S4: 2.5% and 97.5% percentiles and mean values for each main scenario at 12.5% PrEP coverage over 500 randomised runs. Showing (1) the overall change in HCV incidence by 2030 and (2) the HCV screening frequency required in HIV-negative non-PrEP users to reach 90% HCV incidence reduction by 2030.
4.5 ANCOVA analysis of model parameters

<table>
<thead>
<tr>
<th>Change in HCV incidence by 2030</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>71.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probability of condom usage between another other partnership pairing than a diagnosed MSM and a partner assumed to be HIV-positive</td>
<td>9.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>7.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of individuals in the Low-risk group</td>
<td>6.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The proportion of MSM who mix like with like by HIV-status</td>
<td>1.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table S5:** ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the change in HCV incidence observed by 2030 when screening HIV-diagnosed MSM and PrEP users 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.

<table>
<thead>
<tr>
<th>Screening frequency in HIV-negative MSM not on PrEP to reach 90% HCV incidence reduction by 2030</th>
<th>var (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased HCV infectiousness due to HIV infection</td>
<td>65.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probability of condom usage between another other partnership pairing than a diagnosed MSM and a partner assumed to be HIV-positive</td>
<td>12.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Efficacy of condoms per sex act</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of individuals in the Low-risk group</td>
<td>4.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The proportion of MSM who mix like with like by HIV-status</td>
<td>2.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table S6:** ANCOVA results, limited to the first five parameters which contributed most to the sum of squares for the frequency of screening needed in HIV-negative MSM not using PrEP in order to reduce HCV incidence by 90% by 2030 given HIV-diagnosed MSM and PrEP users are screened 6-monthly for HCV and treating all HCV diagnosed MSM within 6 months. This result is based on all parameters varied in the model over 500 runs.
4.6 Model runs compared to observational data

Within this model our fitting is performed using a non-linear least-squares fitting algorithm. This algorithm fits a set of $m$ observations with a model that is non-linear in $n$ unknown parameters. The basis of the method is to approximate the model by a linear one and to refine the parameters by successive iterations. In each iteration we calculate the differences between (1) the desired value of each outcome and (2) the actual value of each outcome. These differences are then squared and summed together to give an error value. The algorithm minimises this error by intelligently selecting values from the ranges of the $n$ unknown parameters, until an acceptable tolerance of error is reached. A full description of this algorithm and alternatives can be found here.

In agreement with UK data, our model projects much higher HCV incidence among HIV-diagnosed MSM than among other HIV-negative MSM, due to these groups having higher risk behaviour. Indeed, despite not being fit to this data, our modelled HCV incidence estimates for 2012 are comparable to published sub-national UK estimates from 2008-2012 for HIV-diagnosed MSM (2.0 (95%CR 1.6-2.7) per 100pyrs by our model versus 0.5-1.9 per 100pyrs in different UK studies) and HIV-negative MSM not on PrEP (0.10 (95%CR 0.04-0.17) per 100pyrs in model versus 0.15 (95%CI 0.05-0.35) per 100pyrs in one UK study). Unfortunately, there is no available HCV incidence data for the UK after 2012 and so we cannot compare our model to more recent data.

Our model also compares well with HIV incidence data in projecting a median fall in HIV incidence of 60.2% (95%CR 43.8-79.6%) between 2012 and 2018, in-line with data suggesting a 55.5% (95% CI 34-4-72.7%) decrease in the annual rate of new HIV infections among MSM in the UK over this period.

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**Figure S7:** HIV prevalence as projected in our model runs from 2012-2030 from our 500 model fits, given the baseline scenario where no PrEP is introduced, versus HCV screening scenarios included from 2018 which include the introduction of PrEP. *Observational data sourced from the 2013 Public Health England Report utilising data from 2012.*
Figure S8: HCV prevalence as projected in our model runs from 2012-2030 from our 500 model fits, given the baseline scenario where no PrEP is introduced, versus HCV screening scenarios included from 2018 which include the introduction of PrEP. *Observational data sourced from a London based survey which collected samples from MSM at community venues in 2011.48
Figure S9: HIV incidence as projected in our model runs from 2012-2030 from our 500 model fits, given the baseline scenario where no PrEP is introduced, versus HCV screening scenarios included from 2018 which include the introduction of PrEP.
Figure S10: HCV incidence as projected in our model runs from 2012-2030 from our 500 model fits, given the baseline scenario where no PrEP is introduced, versus HCV screening scenarios included from 2018 which include the introduction of PrEP. *Observational data sourced from data from a sexual health clinic in Brighton in 2008, the overall incidence range was calculated a weighted average of the reported incidence in HIV-negative and HIV-positive MSM in this study combined with the prevalence of HIV in our model runs.46
Figure S11: HCV incidence in HIV-positive MSM as projected in our model runs from 2012-2030 from our 500 model fits, given the baseline scenario where no PrEP is introduced, versus HCV screening scenarios included from 2018 which include the introduction of PrEP. *Observational data sourced from data from a sexual health clinic in Brighton in 2008.
**Figure S12:** HCV incidence in PrEP users as projected in our model runs from 2012-2030 from our 500 model fits, showing HCV screening scenarios included from 2018 which include the introduction of PrEP.
References:

35. BHIVA Guidelines for the treatment of management of coinfection with HIV-1 and hepatitis viruses 2013.
37. Brown AE, Nardone A, Delpech VC. WHO 'Treatment as Prevention' guidelines are unlikely to decrease HIV transmission in the UK unless undiagnosed HIV infections are reduced. *AIDS* 2014; **28**(2): 281-3.


