The scale-up of PrEP for HIV prevention in high-risk women in sub-Saharan Africa: use of mathematical modelling to inform policy making

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Abstract

Background: Women in sub-Saharan Africa carry a disproportionate burden and risk of HIV. In this context, women at high HIV risk are not a discrete group, rather on a spectrum of risk caused by a multitude of behavioural, economic, structural, cultural and geographic factors. Pre-exposure prophylaxis (PrEP) is a promising new HIV prevention method, effective at reducing HIV risk when adhered to. However, the results of PrEP trials and implementation studies to date reveal challenges in women's programme retention and drug adherence. There are also concerns that behavioural disinhibition (reductions in condom use) following the introduction of PrEP may further limit its ability to avert infections. In the context of HIV resource limitations and decreasing donor budgets, this thesis seeks to use mathematical modelling to assess strategies for PrEP scale-up for women across a spectrum of risk in sub-Saharan Africa, accounting for heterogeneities in HIV risk factors and PrEP programme outcomes. Considering the challenges faced by policy makers in using mathematical models to guide decision making, often considered to be complex 'black boxes', this thesis also sets out to assess the contexts in which simple models are sufficient to guide policy making around the introduction of a new HIV prevention intervention.

Methods: This thesis adopts mathematical modelling approaches to inform HIV policy making. First, a simple static model of HIV risk to female sex workers is developed and used to assess the impact of behavioural disinhibition on PrEP's ability to avert HIV infections. The static model formulation is then evolved to incorporate dynamic effects to account for the downstream effects of population interactions. The models account for heterogeneities in women's HIV risk factors and PrEP programme outcomes, and the low levels of PrEP programme retention and adherence reported in studies. The outcomes of the static and dynamic model formulation are compared over different time horizons and epidemic contexts, to contribute to understanding around the importance of modelling complexity to inform HIV policy. Finally, the static model is refined to represent women across a more broadly defined spectrum of risk: women 15-24 years, 25-34 years, 35-49 years and female sex workers. The models are parameterised to case study countries spanning a range of high HIV burden contexts in sub-Saharan Africa: South Africa, Zimbabwe and Kenya, and used to assess strategies for PrEP scale-up in each country, considering cost-effectiveness and population-level impact.

Conclusions: PrEP is likely to be of benefit in reducing HIV risk in women across a spectrum of HIV-risk in sub-Saharan Africa, even if reductions in condom use occur. PrEP will be most cost-effective for individuals at great HIV risk, such as female sex workers. However, PrEP has potential to significantly reduce the number of new infections at population-level if made widely available

beyond those at highest individual risk, including to women in the general population. Strategies for PrEP scale-up will need to weigh the potential cost-effectiveness and population-level impact of PrEP with the potential for PrEP integration into a wide range of national services and at community level, in order to significantly bring down the costs and improve cost-effectiveness in resource-constrained environments.

Static models can be sufficiently robust to inform policy making around the introduction of new HIV prevention interventions in high HIV-burden settings over short-medium time horizon of up to 5 years, where underlying HIV epidemics have reached equilibrium. Over longer timeframes, and in contexts where the underlying HIV epidemics are still evolving (other than over short time horizons of less than a year), static models may under-emphasize situations of programmatic importance and dynamic models will be more appropriate to guide decision making.

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Preface: Motivation for PhD

Observed challenges in use of modelling to inform policy making in global public health

For the last 12 years I have worked in policy making at national and international levels in public health and development, with a particular focus on HIV. Having come originally from an educational background in mathematical modelling, I have always taken a particular interest in how policy makers perceive, use and trust mathematical models.

I have witnessed or been part of processes to adopt mathematical models to inform resource allocation at national and international levels, to inform the global advocacy and resource mobilization agenda, national and global target setting, to set global-level key performance indicators, and to inform normative guidance around the adoption of policy directions and technical norms. Throughout these processes, a number of mathematical models have had tremendous influence on decision making, the allocation of resources and ultimately public health outcomes across the world. It has been my experience that the policy makers who are relying on the outcomes of these models are rarely able to fully engage with or interrogate the models to determine the extent to which they are appropriate to inform their decision making. I have often heard models typified as 'black box' processes, with policy makers challenged to assess the appropriateness of the model, its inputs, and uncertainty around communicated results or implications.

In undertaking a PhD, it was therefore a keen interest of mine to explore the use of mathematical modelling to inform policy making; in particular, elements of model complexity and their importance in informing decision making in HIV.

Motivations for focus on HIV prevention in high-risk women in sub-Saharan Africa

With the highest burden of HIV in the world, sub-Saharan Africa is central to the global HIV response. In this region, women face the highest burden of HIV, driven by a complex combination of biological, epidemiological, cultural and structural factors. These cultural, epidemiological and structural drivers of HIV differ tremendously by locality and cultural context. It is impossible not to be touched by the challenges faced by women across the region, including in many cases, not having full agency to control their HIV status. Focusing on ways to prevent HIV for women across a spectrum of risk in sub-Saharan Africa was a driving factor in my decision to undertake a PhD.

Thesis Structure

This thesis is divided into six chapters: Background, Methods, Research Papers 1, 2 and 3, and Discussion.

The Background chapter consists of four parts: 1) epidemiological and policy background on HIV in women in sub-Saharan Africa; 2) an overview of PrEP, including open policy questions in relation to PrEP for high-risk women in sub-Saharan Africa; 3) an overview of the use of mathematical modelling to inform HIV policy making, including outstanding challenges; and 4) PhD aim and objectives. The aim and objectives of this PhD are:

Aim: to use mathematical modelling to inform policy making around the scale-up of PrEP for women across a spectrum of high HIV risk in sub-Saharan Africa, accounting for heterogeneities in HIV risk factors and potential PrEP programme outcomes

Objectives:

1. To assess the potential effectiveness of PrEP in reducing HIV infections among high-risk women in sub-Saharan Africa
2. To explore the extent to which behavioural disinhibition may outweigh the potential benefits of PrEP
3. To assess the robustness of conclusions made on the basis of static modelling techniques to incorporation of dynamic effects, to contribute to understanding around the importance of modelling complexity to inform HIV policy making
4. To explore strategies for the scale-up of PrEP across high-risk women at population-level, weighing considerations around HIV infection reduction and cost-effectiveness
5. To evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa, to explore how the approach to PrEP scale-up may differ by epidemic and implementation context

The Methods chapter gives an overview of the methodological approaches used in the three research chapters, describing how they build upon each other. Each research chapter is proceeded by a brief introduction, noting the PhD objectives that the research seeks to address, and followed by a short summary of the implications of the research.

Research Paper 1 explores the extent to which behavioural disinhibition may outweigh the potential HIV risk reduction benefits of PrEP for high-risk women, considering a spectrum of baseline condom

consistencies and levels of HIV risk reduction achieved on PrEP. It is applied to the high HIV risk population of female sex workers, in the high HIV risk setting of inner-city Johannesburg, South Africa. The analysis is undertaken using a simple static Bernoulli formulation of HIV risk.

Research Paper 2 assesses the extent to which the conclusions of Research Paper 1 hold, when the dynamics of population interactions are accounted for through the incorporation of dynamic modelling effects. The outcomes of the two models are compared over different time horizons of 3 months to 20 years, and applied to different epidemic contexts.

Research Paper 3 explores strategies for PrEP scale-up among groups of women at high HIV risk, weighing cost-effectiveness on an individual basis with potential population-level impact. The analysis is applied to three settings, spanning a range high HIV burden sub-Saharan African contexts: Kenya, Zimbabwe and South Africa, and to four broadly-defined female population groups at risk of HIV in these settings: female sex workers, adolescent girls and young women aged 15-24 years; women aged 25-34 years; and women aged 35-49 years.

The Discussion chapter is divided into six parts: 1) main findings; 2) contributions of the thesis; 3) limitations; 4) key area not addressed through research; 5) areas for further research; and 6) conclusions.

There are five appendices to the thesis. Appendix 1 is a table of ongoing, planned and completed PrEP open-label extension, demonstration and implementation projects among women in sub-Saharan Africa. Appendices 2-4 are the Supplementary Materials to Research Papers 1-3, and Appendix 5 is recent commentary on risk compensation, to which I contributed.

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List of Abbreviations

AGYW	Adolescent girls and young women
AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral drugs
ART	Antiretroviral treatment
Fast Track	UNAIDS Fast Track Strategy: Ending the AIDS Epidemic by 2030
FSW	Female sex worker
GAP	Global Action Plan for Healthy Lives and Well-being for All
GBV	Gender-based violence
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	Human immunodeficiency virus
HSV2	Herpes simplex virus type 2
LHS	Latin Hypercube Sampling
MC	Monte Carlo
MCMC	Markov Chain Monte Carlo
MSM	Men who have sex with men
OLE	Open label extension (of a randomized controlled trial)
PEP	Post-exposure prophylaxis
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PHIA	Population-based HIV impact assessment (surveys)
PLHIV	People living with HIV
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
RCT	Randomized controlled trial
SDG	Sustainable Development Goals
SSA	Sub-Saharan Africa
STI	Sexually transmitted infections
TGW	Transgender women
UHC	Universal health coverage
UNAIDS	Joint United Nations Programme on HIV/AIDS

VMMC	Voluntary medical male circumcision
WHO	World Health Organization

Chapter 1

1. Background

This chapter sets out background to the use of mathematical modelling to inform policy making around the scale-up of PrEP for HIV prevention in high-risk women in sub-Saharan Africa in four sections:

Section 1.1 gives background on the HIV epidemic in sub-Saharan Africa, the particular HIV prevention needs among women, and relevant aspects of the policy and development landscape;

Section 1.2 sets out an introduction to PrEP as an emerging HIV prevention tool, and the open policy questions in relation to its use by women across a spectrum of HIV risk in sub-Saharan Africa;

Section 1.3 describes the use of mathematical modelling in HIV policy making, key considerations around model choice, and the outstanding challenges with the use of models for policy making;

Section 1.4 gives a summary of the open policy questions around PrEP for high-risk women in sub-Saharan Africa and around the use of modelling to inform HIV policy making, followed by the aims and objectives of the PhD.

1.1 Epidemiologic and Policy background: HIV in women in sub-Saharan Africa

1.1.1 Overview of the HIV epidemic in sub-Saharan Africa

Since the introduction of the human immunodeficiency virus (HIV) to humans most likely in 1920s Kinshasa, Democratic Republic of Congo[1], the virus has spread differentially across regions of the world, influenced by dominant modes of transmission, biological, virological, cultural, political and structural factors[2,3]. Sub-Saharan Africa (SSA) has been the region hardest hit, with more 65% new infections and almost 70% of all people living with HIV[4]. Eastern and southern Africa is the sub-region most affected, with 20.4 million people living with HIV compared to 5.0 million in west and central Africa, and 800,000 compared to 280,000 new infections in 2018[4]. In SSA 59% all new adult infections (aged 15 years and older) are among women[5]. The distribution of new HIV infections by population group in 2018 in west and central Africa and eastern and southern Africa is set out below in Figure 1.

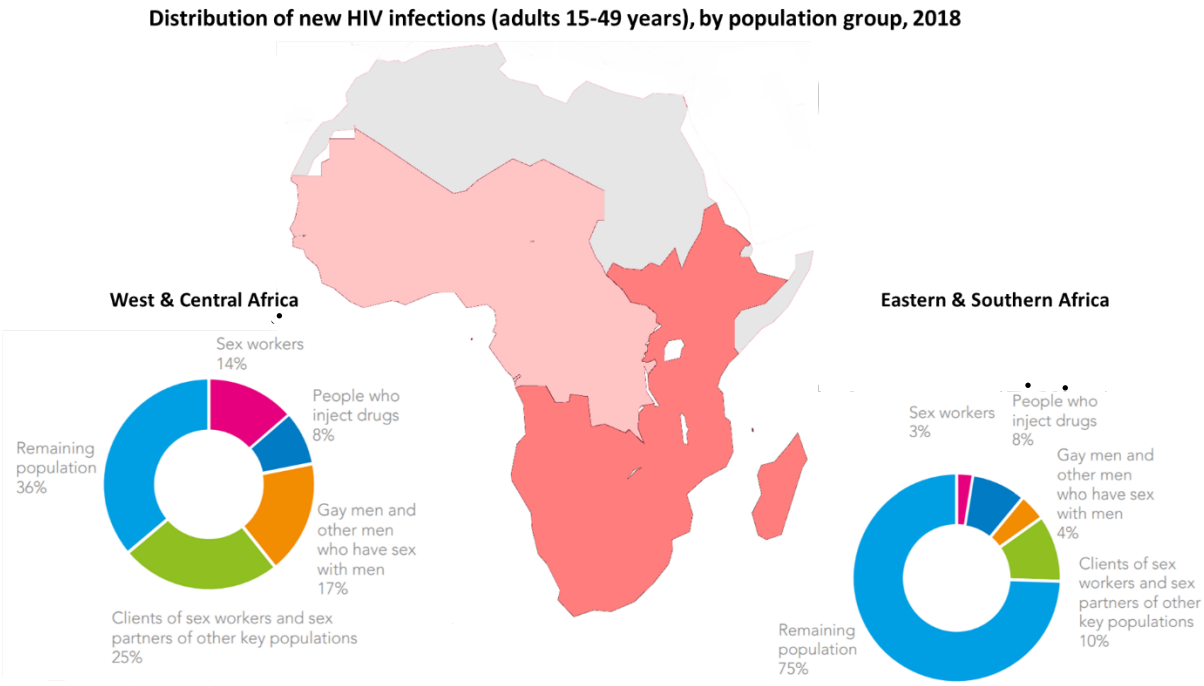

Figure 1: Distribution of new HIV infections by population group.

Reproduced from UNAIDS, 2019[4].

1.1.2 Higher HIV risk among women in sub-Saharan Africa

Women in sub-Saharan Africa are at greater HIV risk than men for a number reasons spanning physiological, structural, behavioural, economic and cultural factors[5]. HIV risk, as estimated through mathematical models, depends on a number of factors, including the basic risk of HIV transmission (e.g. from a male to a female through penile-vaginal intercourse); the likelihood that sexual partners are HIV positive; the infectiousness of HIV positive partners (determined by stage of infection and whether they are taking antiretroviral treatment); the presence of sexually transmitted infections in partnerships; the number of partners, sex acts and frequency of partner change; and the effective use of HIV prevention measures such as condoms or male circumcision[6,7]. This section focuses on the factors that give rise to comparatively higher HIV risk among women in sub-Saharan Africa.

In regions, such as sub-Saharan Africa, where heterosexual sex is the main route of HIV transmission, women are at higher physiological HIV risk than men per sex act, for reasons including differences in the mucosal immunology of women's and men's genitalia[8,9] and that women have a greater mucosal surface area at risk of injury during sexual intercourse[10]. The basic risk of HIV transmission per penile-vaginal sex act is estimated to be approximately twice that for women (8 per 10,000 exposures, 95% confidence interval (CI) 6-11 per 10,000) than men (4 per 10,000 exposures, 95% CI 1-14 per 10,000)[11], although there remains uncertainty in these estimates[11,9].

In sub-Saharan Africa, younger women are more likely than younger men to be in age-disparate relationships, with, for example, 17% and 14% of women 15-19 years reporting relationships with men at least 10 years older in Zimbabwe[12] and Kenya[13] respectively, and 36% South African women 15-19 years reporting relationships with men at least 5 years older.[14] Given that HIV prevalence peaks later in men than women across the region[15], older men are more likely to be HIV positive than younger men, increasing the likelihood of HIV transmission to younger women through age-disparate relationships. Indeed, across sub-Saharan Africa, adolescent girls and young women aged 15-24 years are at 2.4 times the risk of HIV than males the same age[4]. Graphs demonstrating the earlier adult (15-49 years) HIV prevalence peak in women and later peak in men in two countries in sub-Saharan Africa, eSwatini and Malawi, are shown in Figure 2.

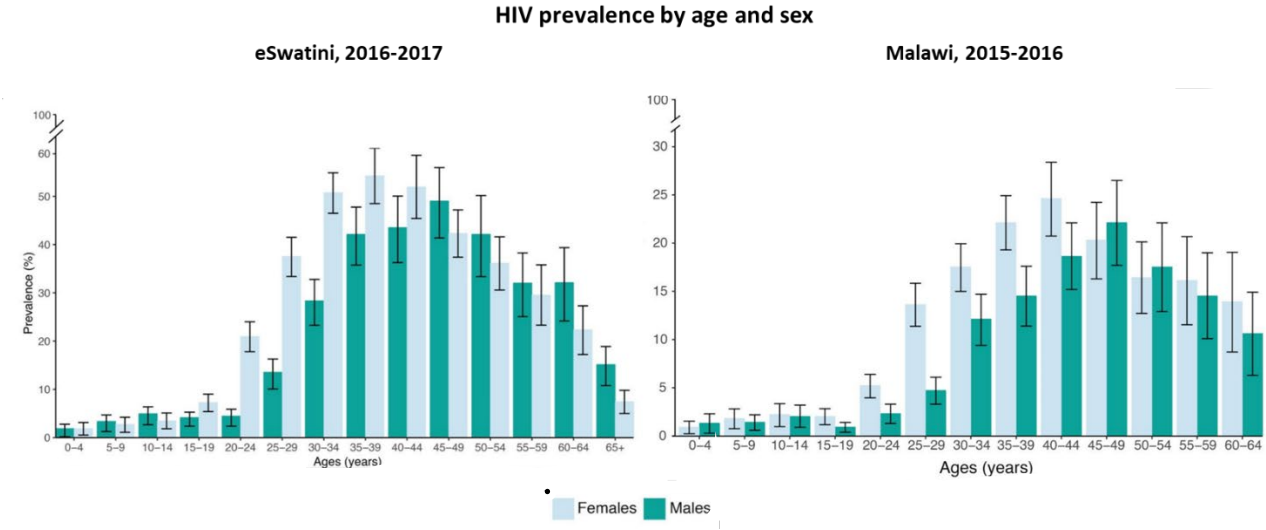

Figure 2: HIV prevalence for adults 15-49 years by 5-year age group and sex, for eSwatini 2016-2017 (left) and Malawi 2015-2016 (right).

Source: PHIA final reports, eSwatini 2019[16] and Malawi 2018[17]. Error bars represent 95% confidence intervals.

Whilst sexually transmitted infection (STI) levels are heterogenous across sub-Saharan Africa (and much of the available data dated), STI levels remain high among many populations[18]. For example, prevalence of herpes simplex virus type 2 (HSV2) among 15-24 years olds is estimated to be between 33.7% and 78.6% across southern and eastern Africa clinic and community settings[19], and syphilis levels of 23% have been reported among sex workers in Zambia[20]. STIs, especially those that are ulcerative, may increase HIV transmission[9,21] by a cofactor of up to 6 (depending on the STI)[22], exacerbating underlying risks.

Sub-Saharan Africa is vast heterogenous region made up of a multitude of cultural contexts and norms[23]. Nonetheless, patriarchy remains the dominant force in a number of cultures across the

region[10]. This affects women's ability to choose their sexual partners, and when they have sex, their ability to protect themselves during intercourse, as well as acceptability around multiple concurrent sexual partners for men[10]. Where concurrency results in networks of sexual partners, HIV infection, especially in early highly viraemic stages, can be readily transmitted throughout the network of sexual partners[24].

Cultural norms that negatively affect women's agency over sex vary by culture and context. These range from wife inheritance among certain communities in Zimbabwe, Malawi, Zambia, Namibia and Uganda, to widow cleansing (through unprotected sex with a man chosen by community elders) among certain communities in Kenya, Malawi, Zambia and Bostwana[25]. Female economic disempowerment is a major structural driver of increased HIV risk for women, arising for reasons including lack of ability to complete education and obtain gainful employment[26] and land disinheritance laws[25]. Economic disempowerment is associated with earlier sexual debut, having multiple sexual partners, forced, violent or transactional sex (intercourse in exchange for money, goods or other material benefit), all of which have been shown to increase HIV transmission[10,27–29].

Gender-based violence (GBV), reported by more than half of women in many sub-Saharan African contexts[30,31], is both a driver and consequence of HIV[32]. GBV increases HIV transmission by affecting women's ability to negotiate safe sex, women's agency in health-seeking behaviours[33] and the risk of physiological trauma through intercourse[32]. A recent Ugandan study found an increase in the risk of HIV transmission by up to 55% as a result of GBV[34].

1.1.3 Spectrum of HIV risk among women in sub-Saharan Africa

This section focuses on the changing, heterogenous HIV risk factors that mean that women at 'high HIV risk' in sub-Saharan Africa are far from a discrete group, rather on a spectrum of risk defined by a multitude of factors, spanning behavioural, economic, structural, cultural, age and geography.

To start, HIV incidence among the 'general population' (a heterogenous group in itself) reveals significant differences in HIV risk by age group and sex alone. For example, as shown in in Figure 3 from the recent PHIA studies from eSwatini[16] and Malawi[17], women 15-24 years and 35-49 years in eSwatini and women 15-24 years and 25-34 years in Malawi are at considerably higher HIV risk than their male counterparts of the same age group, as well as compared to the adults 15-49 years overall.

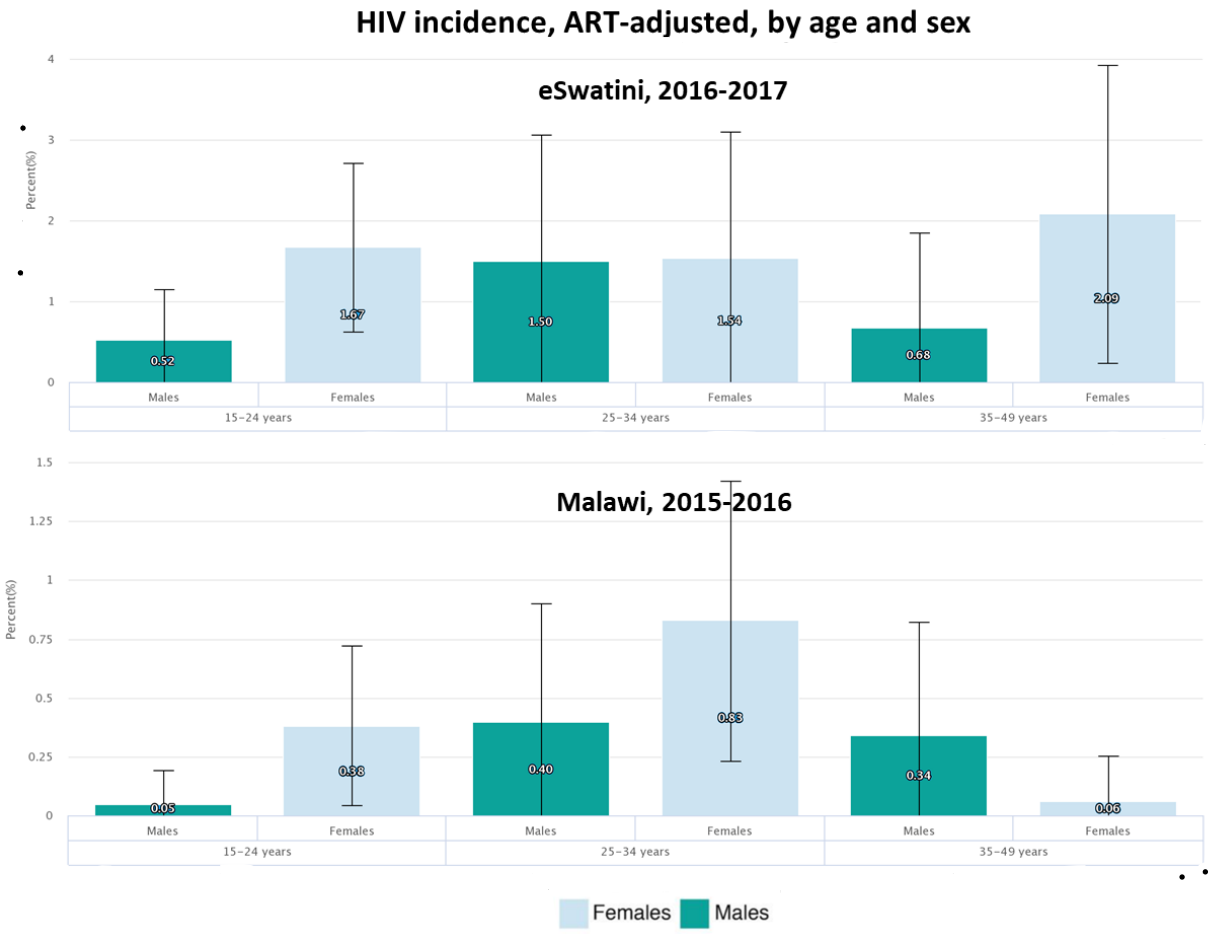

Figure 3: Adult HIV incidence, ART-adjusted, by 10-year age group and sex, for eSwatini 2016-2017 (left) and Malawi 2015-2016 (right).

Source: PHIA final reports, eSwatini 2019[16] and Malawi 2018[17]. Error bars represent 95% confidence intervals.

Since partner HIV prevalence is a predominant driver of HIV, a woman's HIV risk is likely to be greater in regions with higher male HIV prevalence (assuming the majority of sexual intercourse is heterosexual)[6,7]. At sub-national level, male HIV prevalence is incredibly diverse, as evidenced through the PHIA studies recently undertaken in the region[35]. Viral suppression, reducing the infectiousness of HIV positive males on anti-retroviral treatment to zero[36], also varies significantly at sub-national level and by age-group[35,37,38]. By way of example, the heterogenous adult (15-49 years) HIV prevalence at sub-national level for Kenya and South Africa are shown in Figure 4.

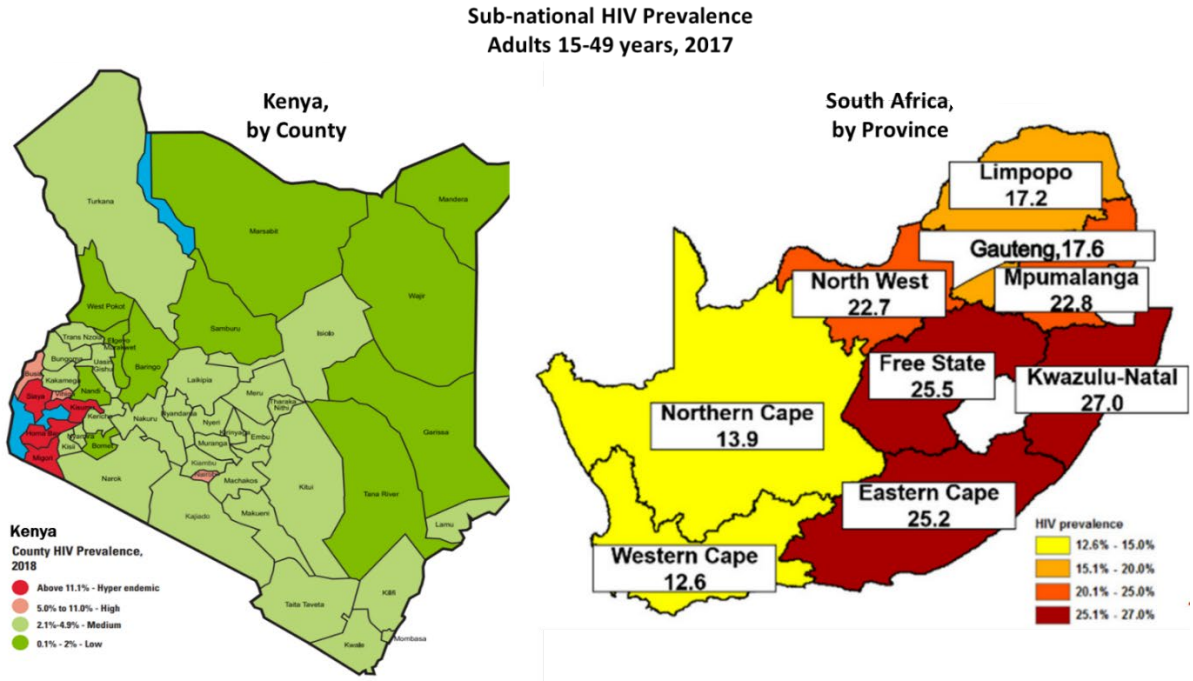

Figure 4: Sub-national HIV prevalence for adults 15-49 years, 2017 for Kenya (left hand side) by county, and South Africa (right hand side) by province.

Sources: Kenya AIDS Response Progress Report 2018[39] and Fifth South African National HIV Prevalence, Incidence and Behaviour and Communication Survey, 2018[14].

Migration is widespread across parts of the sub-continent. Higher-prevalence male populations may be resident in or often pass through communities with lower levels of HIV prevalence. This is the case, for example, on the major highways through sub-Saharan Africa[40–42], where truck drivers with often higher levels of HIV than the communities through which they pass engage in transactional sex or sex worker on their journeys. Truck drivers passing through depots across the southern corridor of the Trans-Africa highway were found to have 3 times the national HIV prevalence of men of the same age group in the domestic population[42]. Similarly, the risk of HIV transmission to women is often higher in communities hosting male migrant workers. In the South African communities hosting Mozambican migrant mine workers, more than 50% miners reported two or more partners in the last 12 months, 18.5% used a condom at last sexual intercourse, and nearly three quarters of HIV-positive mine workers were unaware of their HIV status[43].

HIV risk is higher among women who engage in transactional sex[44,15] (transactional sex describing the continuum of sexual relationships where there is an implicit or overt exchange of goods, money or benefits in social status[45,29]). Transactional sex in the region spans women exchanging sex-for-fish among fishing communities spanning Namibia to Lake Victoria[27], to sex in exchange for school fees or transport in Soweto, South Africa[28]. A recent systematic review found prevalence of transactional

sex of up to 14% among adolescent girls and young women, aged 15-24 years (AGYW), in sub-Saharan Africa, and up to 30% among women across all age groups, with women who practice transactional sex between 1.5 and 2 times more likely to be HIV-infected than those who do not[29]. Transactional sex has been shown to be associated with gender-based violence, a risk factor for HIV[46].

Female sex workers (FSW) are among women at highest risk of HIV infection in society, at up to 13-times the risk of women in the general population across lower- and middle-income countries, and with vastly elevated levels of STIs[47]. HIV prevalence among FSW varies by context, ranging from less than 1% in Comoros[48] to 72% in Hillbrow, inner-city Johannesburg[49]. FSW face risk of HIV acquisition from each of their partner groups: regular partners (e.g. boyfriends or husbands), to regular and occasional clients, with often blurred distinctions in between[50].

FSW clients often come from groups who have multiple sexual partners and elevated levels of HIV prevalence compared to men in the general population, such as seasonal agricultural workers, truck drivers, sailors and men in the military[50]. FSW may face challenges in negotiating consistent use of condoms with clients due to power imbalances[50] or threat of reduced income, with FSW in some contexts receiving a quarter of the price for sexual intercourse where condoms are insisted upon[51]. FSW may face also pressure from pimps to engage in condomless sex, as documented in Ethiopia[52], as well as barriers to access to condoms, STI treatment and post-rape care (including post-exposure prophylaxis)[50]. Police are well-document perpetrators of violence against FSW, rape, extortion (including demands for sexual intercourse)[53,54], especially affecting non-brothel based FSW, without intermediaries to negotiate for them[50].

The regular partners of sex workers may themselves have higher than average prevalence of HIV and engage in high HIV-risk behaviours[50,55,56]. Condom use with regular partners, as with regular clients, is typically very low, as a sign of trust[57,58]. In one study of boyfriends of FSW in Benin and Guinea, 70% of boyfriends reported having been clients of at least one other FSW[59]. Several studies postulate greater likelihood of HIV transmission from regular partners than clients, due to low levels of condom use with the former[50,55].

Sex work is thought to account for greater onwards transmission of HIV in contexts where HIV epidemics are increasing and the basic reproductive number (number of secondary cases caused by a primary case) of HIV is high, but less so in stable generalised epidemics when HIV is endemic in high-burden contexts and some risk factors (such as lack of condom use in transactional and age discordant relationships) may be higher in the general population[60–62].

In conclusion, HIV risk is neither constant nor homogenous in any one group at any time. The large number of risk factors contributing to an individual's HIV risk means that the continuum of risk does not always place self-identifying sex workers at the highest end and women who consider themselves to be in the general population at the other. Rather, HIV risk evolves over time according changes in risk behaviours, population movement, vulnerabilities and structural norms[50].

1.1.4 Global health and development landscape for scaling up HIV prevention efforts

Scaling-up HIV prevention for high-risk women in sub-Saharan Africa is recognised as a global priority, with particular attention given to the needs of adolescent girls and young women[63–65]. However, there is limited fiscal space for scaling up resources for HIV prevention among programmes in sub-Saharan Africa. In spite of the successful 2020-2022 replenishment of the Global Fund to Fight AIDS, TB and Malaria (the second biggest external funder of HIV programmes in sub-Saharan Africa)[66], external resources for HIV have overall been flatlining over the past years, and increases in domestic spending on health have not taken place across countries in the region at a pace needed to meet the needs[63,64,67,68]. In 2018, for the first time since the year 2000, the total resources available globally for the HIV response have started to decline[4], with the $1.9 billion available in 2018 less than half the annual amount estimated to be needed to achieve UNAIDS's 2020 global Fast Track targets (see below for an explanation of these targets)[4,69].

Increasing domestic resources for HIV prevention is also challenging in the context of the global drive for countries to ensure universal health coverage (UHC) - ensuring that all people and communities have equal access to health services (promotive, preventive, curative, rehabilitative and palliative), of sufficient quality to improve the health of those receiving the services, and with the people accessing them protected from financial risk whilst doing so[70]. Achieving UHC by 2030 is one of the ten targets under the health-focused sustainable development goal (SGD) 3[71]: *Ensure healthy lives and promote well-being for all at all ages*; specifically SDG 3.8: *Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.*

Unlike the under the 2015 Millennium Development Goals (MDGs), where one of eight goals was specifically HIV-focused (MDG 6: *Combat HIV/AIDS, Malaria and Other Diseases*)[72], under the SDGs, HIV takes comparatively less priority, falling under a different SDG 3 target, SDG 3.3: *By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.* Commitment to the SDGs has been pledged

by all UN Member States (including all Sovereign States in Sub-Saharan Africa)[71], with support for SDG 3 underpinned by commitment of the 12 leading global health and development organizations (including those with an HIV-focus: the Global Fund to Fight AIDS, TB and Malaria (Global Fund), UNAIDS, Unitaid, as well as the World Health Organization (WHO)) through the *Global Action Plan for healthy lives and well-being for all* (Global Action Plan)[73].

HIV prevention is a constituent component of a comprehensive universal health care system, just as a strong health system is critical in the successful delivery and achievement of the HIV response[4,70,74,75]. This interdependence plays out at country level, with an underlying tension between the need to continue to support and scale up the HIV response and the need for country Treasuries to prioritise investments in health systems and UHC[75–78]. Among donors, the biggest external financers of HIV programmes, PEPFAR (the U.S. President's Emergency Plan for AIDS Relief) and the Global Fund, remain committed to the HIV response[68,79]. However, this tension between prioritizing investments 'vertically' in HIV versus 'horizontally' UHC is ubiquitous, with the Global Fund also focusing investments on building resilient and sustainable systems for health (as well as the Malaria and TB responses)[74], and other bilateral donors, including those who have been former bilateral supporters of the HIV response (such as Germany, Sweden and Japan)[80–83] now prioritizing the use of their development assistance for health to incentivize health systems strengthening and UHC delivery in the SDG landscape[83,84].

Available budget space for HIV programming is also squeezed in the context of the global drive to scale up antiretroviral treatment (ART) for all people living with HIV. Since 2016, ART has been recommended for all people living with HIV, regardless of their stage of HIV infection[85]. Having previously been prioritised for people with more advanced stages of HIV infection (CD4 count less than or equal to 500 cell/mm^3 per 2013 guidance), this updated guidance was based on the results of randomized control trials and observational studies, which suggested that earlier initiation of treatment reduces mortality and the chance of HIV-associated coinfections[85]. It was also based on the results of a randomized control trial, which showed that earlier ART reduced the risk of HIV transmission to HIV-negative partners (supported by others since published[86]), and the results of modelling and ecological studies, which suggested that high uptake and retention of ART at population level would reduce HIV incidence at population level[87–91]; termed 'treatment as prevention'[85].

Based on the emerging evidence, in 2014, UNAIDS concurrently published their strategy Fast Track: Ending the AIDS Epidemic by 2030 (Fast Track)[69]. The Fast Track strategy encourages all countries globally to achieve "90-90-90" targets by 2020 (90% of people living with HIV (PLHIV) knowing their

status (i.e. receiving an HIV test), 90% of PLHIV who know their status receiving ART, and 90% of people on ART having viral suppression so their immune system remains strong and they are no longer infectious) and 95-95-95 targets by 2030[69]. These ambitious targets have been spearheaded in particular by UNAIDS[69,92] and PEPFAR[79,93], as well as using Global Fund resources in many eastern and southern African countries[94].

Whilst more recent randomized-control trials and observational studies have since highlighted that the anticipated benefits of treatment as prevention are unlikely to materialise[95–98], treatment for all remains a global strategy[4], with many national and donor budgets prioritised for treatment, leaving more limited space for HIV prevention activities[94]. The drive for treatment scale-up has also resulted in high 'treatment mortgages', since once individuals have been started on ART, they should be continued on treatment for life, meaning funds for prevention need to be additional and resources cannot be reprioritised away from ART budgets. A lesser-recognized paradox of this situation is that the modelling underpinning the treatment as prevention aspect of the global 90-90-90 and 95-95-95 targets assumed full access to prevention activities[69,88,95]. So whilst this strategy has been immensely successful in reducing mortality among people living with HIV[4,99], the current budget imbalances in many countries may be self-limiting from a prevention point of view[95,100]. As a consequence, the need for innovative and effective HIV prevention approaches, especially to address the drivers of HIV risk among high-risk women in sub-Saharan Africa, must be met by cost-efficient interventions to be feasible and be prioritizable in a resource constrained environment.

1.2 PrEP as a potential tool to reduce HIV incidence

1.2.1 Overview of combination prevention prior to PrEP introduction

Prior to PrEP introduction, normative guidance on HIV prevention in high-prevalence settings consisted of a 'combination approach' based on saturated coverage of condoms, targeted prevention interventions for adolescent girls and young women, voluntary medical male circumcision (VMMC), behavioural and structural interventions, focused communication and demand creation using new and digital media, as well as secondary prevention using post-exposure prophylaxis (PEP) after possible HIV exposure[69]. A comprehensive package of interventions for key populations (MSM, transgender people, sex workers, PWID, incarcerated people[101]) included comprehensive condom and lubricant programming, harm reduction programmes for people who inject drugs, behavioural and structural interventions, VMMC, PEP, prevention of HIV in healthcare settings[102]. In 2015, HIV prevention guidance was updated to include HIV testing and HIV treatment for people living with HIV, regardless of CD4 count, for reasons including the anticipated benefits of HIV treatment as prevention[103]. However, as set out at the beginning of this chapter, the implementation of these HIV prevention interventions has been insufficient to address the global HIV prevention needs, including for high-risk women in sub-Saharan Africa, and new approaches were called for[104].

1.2.2 Overview of PrEP

This section gives an overview of evidence to date on PrEP use-effectiveness and introduces the PrEP programme cascade.

Oral PrEP is the use of tablet-form antiretroviral drugs among HIV negative persons to prevent HIV acquisition. The six early oral PrEP randomized controlled trials (RCTs) took place globally between 2007 and 2011, using oral PrEP formulations of either tenofovir (TDF) or tenofovir and emtricitabine (TDF/FTC, known commercially as Truvada). The study population, location, study name, PrEP formulation, number of participants, adherence and HIV risk reduction effectiveness corresponding to each of the trials is set out in Table 1 below.

Population/ Location/ Study	Oral PrEP Formulation	Number of Participants	Adherence	HIV Risk Reduction Effectiveness
MSM and TGW (multiple geographic regions)				
iPrEx[105]	TDF/FTC vs placebo	2,499	51% by drug detection	44% (95% CI: 15%, 63%; p=0.005)
People who inject drugs, Thailand				
Bangkok Tenofovir Study[106]	TDF vs placebo	2,413	83% based on study drug diaries	48·9 (95% CI: 9·6%, 72·2%; p=0.01)
Women in Africa				
FEM-PrEP[107] (women 18-35 years)	TDF/FTC vs placebo	2,120	37% by drug detection	6% (95% CI: -52%, 41%; p=0.81)
VOICE[108] (women 18-45 years, oral arms only)	TDF/FTC and FTC vs placebo	3,019	28–29% by drug detection	TDF: −49% (95% CI: −129%, 3%; p=0.07); TDF/FTC: −4% (95% CI: −49%, 27%; p=0.81)
Serodiscordant couples in Africa				
Partners PrEP[109]	TDF/FTC and FTC vs placebo	4,758	82% by drug detection	TDF: 67% (95% CI: 44%, 81%; p<0.001); FTC/TDF: 75% (95% CI: 55%, 87%; p<0.001)
Heterosexual men and women in Africa				
TDF2[110]	TDF/FTC vs placebo	1,219	84% by clinic pill count	62% (95% CI: 22%, 83%; p=0.03)

Table 1: Results of the six early oral PrEP randomized controlled trials.

The table set out the population, location, study name, oral PrEP drug formulation, number of participants, adherence and effectiveness levels for each of the six studies. TDF is short for tenofovir and FTC is short for emtricitabine. The table builds on that from Haberer[111].

Of the six RCTs, four found oral PrEP to be effective in reducing HIV incidence, with effectiveness directly associated with drug adherence[111]. The two trials, FEM-PrEP[107] and VOICE[108], that were

stopped early for futility were undertaken in women in Africa, with both citing lack of adherence as the cause for no effectiveness. None of the early RCTs were undertaken in other high-risk women populations, such as female sex workers and adolescent females.

Based on the results of the RCTs, in July 2012, the WHO called for demonstration projects to be carried out to better understand the acceptability, patterns of use, and sustainability of PrEP[112]. At the same time, they introduced oral PrEP into normative guidance, recommended for serodiscordant couples (couples, where one partner is HIV positive and the other is HIV negative), men who have sex with men (MSM) and transgender women (TGW) as part of demonstration projects[113].

Early demonstration projects, including open label extensions (OLE) of original RCTs, helped to set the direction of PrEP implementation research[111]. Priority areas of investigation included exploring approaches to strengthen drug adherence and program uptake and retention; behavioural disinhibition (in this case, reductions in condom use on PrEP); drug safety and resistance; priority populations for PrEP scale-up; and cost-effectiveness; as well as exploring PrEP effectiveness for populations not addressed in the RCTs[111,114].

Importantly, the OLE projects of two of the RCTs, iPrEx and Partners PrEP, were able to establish that the drug adherence levels need to achieve the same levels of protection against HIV are different between women and men. The iPrEx OLE[115] undertaken in MSM and TGW, established that only 4 out of the 7 weekly doses of PrEP are required to achieve almost full protection against HIV. The study was also able to link levels of drug adherence, through blood drug concentration, to levels of HIV risk reduction, as set out in Table 2.

% of iPrEx OLE[115] trial participants	Estimated drug dosing (adherence)	TFV-DP in DBS (fmol/punch)	Estimated HIV incidence	Estimated HIV relative risk reduction compared to no adherence
26%	None	<2.5	4.7/100 PY (95% CI: 2.8 to 7.2)	
27%	<2 tablets/week	2.5 to < 350	2.2/100 PY (95% CI: 1.1 to 4.1)	53%
12%	2 to 3 tablets/week	>=350 to < 700	0.6/100 PY (95% CI: 0.0 to 2.5)	87%
22%	4 to 6 tablets/week	>=700 to 1249	0 /100 PY (95% CI: 0.0 to 0.6)	100%
5%	Daily	>=1250	0 /100 PY (95% CI: 0.0 to 1.1)	100%

Table 2: Detailed adherence-effectiveness outcomes estimated from the iPrEx OLE trial[115].

The iPrEx OLE demonstration project was carried out among MSM and TGW in multiple geographic locations. The table links the estimated daily dosing of PrEP (adherence) in trial participants with estimated levels of HIV risk reduction achieved. The table shows the proportion of trial participants exhibiting different adherence behaviours (estimated number of daily pills taken a week), measured by drug concentrations found in participants' dried blood spots. For each adherence group an estimated HIV incidence is given and corresponding relative HIV risk reduction compared with no PrEP adherence. TFV-DP in DBS = Tenofovir-diphosphate in dried blood spots. PY = person years. The data in the table are reproduced from Grant et al[115].

The Partners PrEP OLE (called Partners Demonstration Project)[116] carried out in serodiscordant couples, using PrEP as a bridge to viral suppression in the HIV positive partner using ART, was able to relate levels of drug adherence to levels of HIV risk reduction through multi-variate regression (rather than blood drug concentration levels). The estimates for women in the trial are set out in Table 3.

% of Partners Demonstration Project[116] female trial participants	Estimated drug dosing (adherence)	Estimated HIV relative risk reduction in HIV incidence compared to no adherence
82%	≥4 Doses/week	89% (95% CI: 79%–99%), p=0.03
71%	≥6 Doses/week	88% (95% CI: 73%–106%), p=0.17 (not statistically significant)

Table 3: Estimated HIV risk reduction associated with PrEP adherence levels of ≥4 and ≥6 doses a week for females in the Partners Demonstration Project[116].

The table shows the estimated daily dosing of PrEP (adherence) associated with estimated levels of HIV risk reduction achieved in the project, calculated through multivariate analysis. The Partners Demonstration Project was undertaken in sero-discordant couples in Kenya and Uganda.

Unlike in men, for whom 4 out of 7 weekly doses are estimated to achieve full protection against HIV, for women, the results of the Partners Demonstration Project[116], along with more recent pharmacokinetic[117] and modelling studies[118] suggest that at least 6 out of 7 weekly, if not 7, doses of PrEP are needed to achieve full protection against HIV. It is postulated that this relates to differences in between-tissue drug transport systems between the lower female genital tract in women and colorectal tissue in men, resulting in stronger PrEP drug concentrations in colorectal tissue than the lower female genital tract[118,119].

In 2014, normative guidance was revised to recommend PrEP for MSM[102], based primarily on the results of the iPrEx Study among MSM and TGW[105], and later in 2015 to include all people at substantial risk of HIV infection, defined as incidence of greater than 3 per 100 person years, as part of a combination approach to HIV prevention[103]. This guidance was updated with the latest clinical and drug formulation recommendations in 2016[85]. To date, more than 100 PrEP demonstration projects are underway or have been carried out across populations and countries globally to address the priority areas for implementation research[120] and many countries, including in sub-Saharan Africa, have started rolling out PrEP 'implementation programmes' for highest-risk populations[121–123].

Drug safety and resistance

Oral PrEP, using either TDF or TDF/FTC, is considered to be safe across populations and geographies, including during pregnancy and whilst using hormonal contraceptives[85,124]. Mild adverse events, such as gastrointestinal symptoms, are reported on PrEP, and though usually disappear after the first month, have caused limited PrEP interruption in demonstration projects[124]. Subclinical decreases in

renal function are reported on PrEP, usually disappearing with drug continuation, as well as subclinical decreases in liver function and bone density[124]. Quarterly renal testing for the first 12 months is recommended as standard on PrEP, as well as annually thereafter[85].

Antiretroviral drug resistance, which may be acquired through HIV acquisition in persons with sub-optimal drug adherence, has, despite early fears and challenging levels of drug adherence in demonstration programs, been rare on PrEP[85,124]. Whilst seroconversion and resistance is closely monitored in PrEP programmes, the potential for drug resistant infections (against drugs that are included as first line ART) is not generally considered prohibitive to wide PrEP program scale up[85,125,126].

PrEP program cascade

An illustrative conception of the PrEP program cascade[127–129] is set out below in Figure 5. The cascade depicts the programme stages from recruitment to programme retention at a defined end point. It should be noted that the stages of the cascade and their definitions are not standardised across OLE, demonstration and implementation projects[120]. As such there is no single reference cascade meaning that direct comparisons between cascade stages across studies can be challenging. Furthermore, as PrEP is intended to cover seasons of risk, rather than for long term use[85], it does not always make sense to compare retention after lengthy time horizons across studies (as it does with ART retention), as periods of risk may be shorter depending on the population in question. This lens should be taken when considering PrEP program uptake, retention and adherence (key stages of the cascade to help ascertain the effectiveness of a PrEP programme[85]) throughout this manuscript.

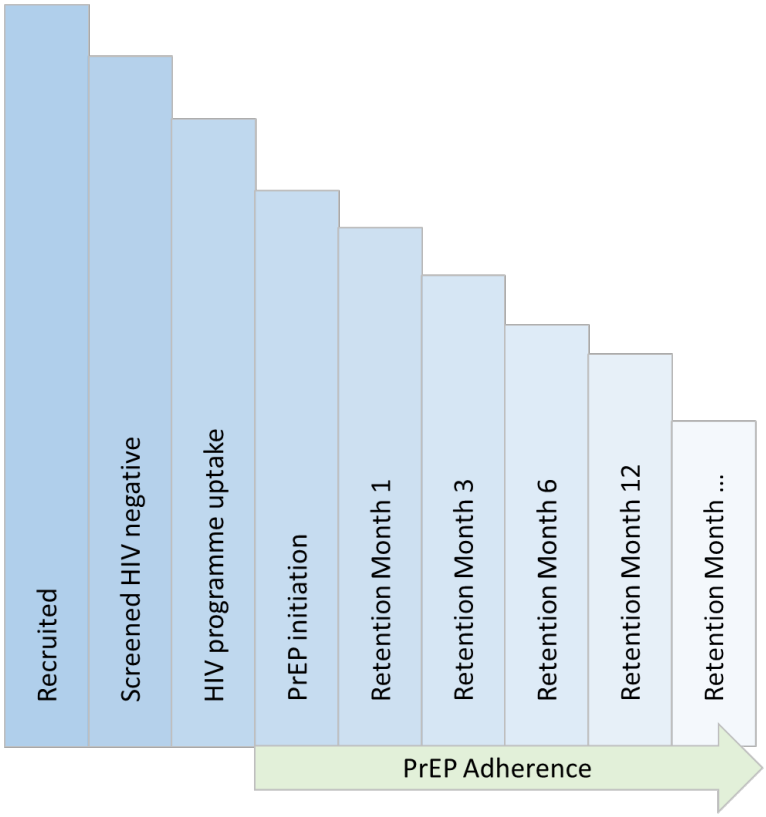

Figure 5: Illustrative PrEP program cascade from recruitment to program retention at a given time end point

1.2.3 PrEP programme uptake and retention, and drug adherence by population in SSA

Whilst only a subset of the more than 100 PrEP demonstration projects underway have published results, perhaps the biggest challenge observed globally to date in PrEP demonstration as well as implementation programs is in ensuring high levels of programme uptake and retention, and drug adherence[85,111,124,130]. This section gives an overview of PrEP uptake, retention and adherence by population in sub-Saharan Africa.

Serodiscordant couples

Programme uptake, retention and adherence have, in general, been reported to be higher among serodiscordant couples observed in studies globally[131,132]. The Partners Demonstration Project (OLE of Partners PrEP RCT) among serodiscordant couples in Kenya and Uganda reported 97% HIV-negative partners initiating PrEP, 51% retained in the program to the end point of 6 months following partner initiation on ART, and 71% participants reporting at least 80% PrEP drug adherence.

MSM and TGW

Uptake, retention and adherence have been mixed among studies for MSM and TGW, with program indicators generally lower in contexts where there is widespread stigma against these populations[133]. The iPrEx OLE study[133] for MSM and TGW across regions globally (USA, Peru, Ecuador, Thailand, South Africa, USA) had levels of uptake ranging between 67% (Peru) and 95% (Ecuador), with average 93% retention and 70% clinically significant adherence measured through TDF blood concentration at 12-weeks (retention and adherence not reported disaggregated by country). This is contrasted with the IPCP-Kenya demonstration project, which reported only 22% 12 week and 15% 6-month PrEP programme retention among MSM[134].

People who inject drugs

Few demonstration projects have been completed for people who inject drugs (PWID), though the OLE[135] of the Bangkok Tenofovir Study for PWID in Thailand has so far reported 35% uptake (among the original study's participants who remained HIV negative), that only 30% of participants were retained at 12 months and 26% participants are regularly adhering to PrEP according to participant diaries.

High-risk women

Given the challenges of the PrEP RCTs in achieving levels of HIV-protective PrEP adherence in women, as well as that none took place in defined high-risk groups such as FSW or AGYW, a large number of the PrEP demonstration projects and implementation studies are taking place for women across the spectrum of HIV risk[120]. The currently ongoing, planned and completed PrEP OLE, demonstration and implementation projects for women in sub-Saharan Africa are set out in Appendix 1, including a description of the studies' specific research questions.

Female sex workers: Emerging results from demonstration projects among FSW in sub-Saharan Africa reveal challenges in programme retention, consistent with the challenges faced by FSW in adhering to ART and wider health services related to stigma, unstable routines, criminalization of their work, disempowerment and disenfranchisement and discrimination by healthcare providers[4,136]. The TaPS demonstration project[137] for FSW in Johannesburg, South Africa, reported PrEP uptake of 98%, and self-reported adherence of 70-85% among those retained in the programme, but only 22% 12-month retention levels. The SAPPH-IRe trial[138] among FSW in

Zimbabwe reported 38% uptake, and an average of 4 months' programme retention and did not report on adherence (as is the case for the following studies where adherence is not mentioned). In Kenya, the IPCP trial[134] reported 66% uptake and 14% 6-month retention among FSW. PrEP retention in trials among FSW in West Africa has been slightly more encouraging, with 83% uptake and 67% retention at 12 months in Senegal[139] and 88% uptake and at 12 months 47% retention, with 57% participants self-reporting 100% adherence in Benin[140].

AGYW: Similar retention challenges have been observed in studies among AGYW. For young women 15-29 years in Kenya, IPCP[141] reported 86% uptake and 10% 6-month retention. The EMPOWER Study[142] in South Africa and Tanzania for AGYW aged 15-24 years reported 97% PrEP uptake and 34% retention at 6 months. The challenging retention levels seen in AGYW are consistent with the increased challenges that young people have in adhering to treatment compared to adults, as seen in the case of ART[136].

Other high-risk women: The HPTN 067/ADAPT trial[143] in South African women aged 18 years and older reported 93% uptake, and compared daily, time-driven (twice per week and a post-sex dose), and event-driven (one tablet before and after sex), and reported 75%, 56% and 52% of sex events respectively covered by PrEP after 6 months, and adherence to the prescribed regimen of 75%, 65% and 53% respectively. Use of PrEP as a 6-week short course for the female partners of Mozambican miners returning home[144], was successful in obtaining 97% uptake, 91% retention at week 6 and 42% of those women retained at week 6 having drug concentration levels consistent with at least 4 out of 7 pills a week. Early results from the SEARCH study[145] among adults 15 years and older in rural Uganda so far report 43% uptake among women and 47%, with clinic distance reported as a barrier to uptake and retention. Early results from the PrIYA study[146] of PrEP for women 15-45 years delivered through maternal child health and family planning clinics in Kisumu, Kenya has so far reported 38%, 21%, and 10% retention at 1, 3 and 6 months respectively. Although many other studies are underway across high-risk female populations, they are yet to release their results[120].

A table of the ongoing, planned and completed PrEP OLE, demonstration and implementation projects among women in Sub-Saharan Africa is set out in Appendix 1.

1.2.4 Open policy questions regarding PrEP for high-risk women in SSA

This section gives an overview of the open policy questions relating to PrEP programmes for women at high risk of HIV in sub-Saharan Africa. The section concludes by categorizing the open questions as

those that can be assessed through standalone modelling studies, and those that need to be evaluated in conjunction with RCTs, OLE, demonstration and implementation trials.

Strategies to improve PrEP uptake, retention and adherence

Given the challenges observed in the original PrEP RCTs, a focus of OLE, demonstration and implementation studies for high-risk women in SSA is evaluation of strategies to improve PrEP program uptake, retention and drug adherence. On the supply side, this includes evaluating peer-based as well as more general information campaigns; community outreach; exploring platforms for scaling up PrEP availability (including schools, sexual and reproductive health clinics, antenatal clinics); tailored services to the needs of different high-risk women populations including differentiated care models and mobile services to meet the needs of mobile populations such as sex workers; ensuring PrEP is affordable and freely available; and addressing structural barriers such as policies that preclude discussion of sexuality education and HIV prevention in education settings, stigma or legal barriers to provision of PrEP to young people[111,120,136,147–150].

On the demand side, this includes evaluating approaches to strengthen risk awareness; empowerment of women and their communities with correct information about PrEP and HIV prevention; working to ensure PrEP providers have supportive attitudes; integration of PrEP provision with other sexual and reproductive health and social services; integration with empowerment and gender-based violence reduction programmes (strengthening demand for PrEP as well as HIV prevention in general); and offering PrEP through approaches that are sensitive to local cultural and religious norms[111,120,136,147–150]. Specific approaches being explored to strengthen retention and adherence include adherence counselling; approaches (such as text messaging and smart phone applications) to remind participants to take medication; structural interventions to address social determinants of non-retentive and non-adherent behaviour (e.g. cash transfers, working with police to support FSW programmes, building self-empowerment, efficacy and social cohesion); the use of 'adherence buddies'; direct follow up with defaulters; and medication refill groups that alternate drug collection among group members[111,120,136,147–150].

Alternative PrEP dosing strategies and formulations are also being explored, with the aim of improving programme uptake, retention, adherence and thereby effectiveness (as set out in the next section).

Different PrEP dosing strategies

Once PrEP had been proven effective with drug adherence, OLE, demonstration and implementation projects have been exploring different dosing strategies to assess the effectiveness of non-daily PrEP HIV prevention, to see if this helps improve adherence to the intended drug regimen. Such alternative dosing strategies include on demand (before and after sex) and time-driven (usually few doses a week plus a dose after sex)[120]. Given the different PrEP dosing strategies being explored among OLE, demonstration and implementation projects, comparison of drug adherence between studies should be according to regimen rather than directly comparable.

To date, the results of different dosing strategies have been mixed, according to population. The HPTN/067 – ADAPT trial[143] of different dosing strategies in South African women aged 18 years and older found that daily dosing resulted in a higher coverage of sex events, strengthened adherence to the dosing regimen and blood drug concentrations. The IPERGAY study for Canadian and French MSM on the other hand found that event-driven dosing (in this case 2 tablets 2-24 hours before sex, 1 tablet 24 hours later and 1 tablet 48 hours later) found 43% correct use of PrEP according to adherence regimen and 86% relative HIV risk reduction after 2 years[151]. These differences in effectiveness of non-daily dosing of PrEP may relate to the differences in drug levels needed to achieve similar levels of protection against HIV between women and men, as well as different risk awareness, behavioural, structural and contextual considerations between populations[152]. It was also noted that the frequency of sex acts in the IPERGAY study were sufficiently high such that many participants had drug levels consistent with the at least 4 doses a week needed to achieve full protection noted through the iPrEx OLE study[152]. Throughout this thesis, it has been specifically noted where referenced studies involve non-daily dosing strategies.

Different PrEP formulations

To date, PrEP formulated for daily oral consumption through tablet form, 'oral PrEP', is the only formulation with regulatory approval for use outside of trial settings (although the most recent US Food and Drug Administration approval of the tenofovir alafenamide/emtricitabine oral PrEP option is not yet indicated for women having receptive vaginal sex)[153]. Long-acting PrEP microbicide formulations are under investigation through randomized controlled trials and OLEs, with the Dapivirine ring the most progressed[153]. Longer-acting formulations intend to strengthen PrEP program outcomes by avoiding the need to take pills on a daily basis, which has proven a barrier in many studies[107,108,124]. The latest results of the DREAM[154] OLE study in South African and Ugandan

women aged 20 years and older showed 90% retention at 12 months, 90% of women using the Dapivirine ring at least some of the time and 63% HIV risk reduction estimated through modelling, an improvement on the 30% risk reduction through the original clinical trial form of the study, the RING Study[155]. As of August 2019, regulatory approval is being sought for the Dapivirine ring[153].

Other long-acting formulations of PrEP are also under investigation, the most advanced of which are injectable formulations being explored through the HPTN 083[156] and HPTN 084[157] clinical trials. These trials are taking place respectively for MSM and TGW in the Americas, Asia and South Africa, and young women in SSA, using the antiretroviral cabotegravir in comparison to daily oral PrEP (using TDF/FTC), with results expected 2021-2022. Given that for the duration of this PhD PrEP implementation has predominantly focused on the roll out of oral PrEP[120], the focus of the PhD is on the oral formulation. However, much of the work contained herein can be easily adapted to assess other formulations if they are approved.

Behavioural disinhibition

Since the commencement of PrEP RCTs, there has been concern around behavioural disinhibition or risk compensation – in particular, reductions in condom use (also termed condom migration) – following the introduction of PrEP, and its impact on the ability for PrEP to reduce HIV risk[114,124,149,150,158–160]. These concerns remained as the results of the early RCTs showed poor adherence in some groups, which led to worries that the levels of protection against HIV would be insufficient to counterbalance reduced levels of protection against HIV through reductions in condom use, as well as increase exposure to STIs, some of which increase the likelihood of HIV acquisition[22,150,158–160]. These concerns regarding behavioural disinhibition mirror those surrounding the introduction of previous innovative HIV prevention measures, including the introduction of STI-efficacious microbicides[161,162] from almost two decades ago, voluntary medical male circumcision[163,164] a decade ago, and treatment as prevention in recent years[165,166].

Concerns around behavioural disinhibition relate especially to women across the spectrum of HIV risk in SSA, as well as others, who have limited agency over condom use[10,25,167], with worries that they would readily reduce condom use once PrEP is offered, further exposing themselves to STIs, without achieving protective levels of PrEP efficacy. This is also particularly relevant to FSW, who in many situations may receive increased payment for condomless sex[50,52,55,57,58] (up to four times the amount in some settings[168]), or women engaging in transactional sex, who may receive greater benefits where condoms are not used[29,43,45,169].

None of the early RCTs reported reductions in condom use[170], neither did the early OLE projects and demonstration projects[124]. Qualitative surveys among young women in South Africa, however, reported appetite to reduce condom use on PrEP[149,171], and more recent PrEP demonstration and implementation programmes in developed country contexts for MSM are starting to report decreased condom use and increases in STIs[172–175]. In particular, community-level behavioural disinhibition (reductions in condom use in individuals not taking PrEP, but in the same community as those who are) have recently been reported among MSM, TGM and bisexual male communities in Sydney and Melbourne, Australia, associated with rapid PrEP scale for MSM, TGW and bisexual men[176]. Given that few of the demonstration and implementation projects underway in high-risk women in SSA have published results[120], it is too early to rule out behavioural disinhibition as a reality for high-risk women taking PrEP in SSA. There are also more limited concerns about increases in other risky behaviours on PrEP, such as increased numbers of sexual partners, however concerns surrounding reductions in condom use have predominated, potentially in relation to the more direct motivations for condomless sex, as well as results of PrEP studies to date[85,177].

In response, many mathematical modelling studies of PrEP over the past decade have assessed the impact of reduced condom use following PrEP commencement, and concluded that this would lead to lower levels of HIV risk reduction, as well lower PrEP cost-effectiveness[126,137,178–182]. Concerns around behavioural disinhibition in relation to the introduction of other new HIV prevention interventions, such as the STI-efficacious microbicide, had previously been assessed through mathematical modelling studies, quantifying the extent to which the intervention may be of benefit, even with sub-optimal product adherence[161,183]. However, at the time of commencing this PhD (and to date, other than the study that arose through this PhD), no mathematical modelling study had been undertaken to understand the extent to which reductions in condom consistency on PrEP could take place without increasing HIV risk, including for high-risk women in SSA, should it become an implementation reality.

Scale-up of PrEP for individuals beyond those at highest HIV risk

With PrEP proven an effective HIV prevention intervention for those achieving defined levels adherence[115, 116], policy makers in many countries in SSA (such as South Africa[121], Zimbabwe[181] and Kenya[182]) are now considering how best roll out PrEP among at-risk populations, considering impact and cost-effectiveness in resource constrained environments[4,85,150,186]. Among high-risk women in countries in SSA, FSW are being prioritised due to their elevated risk, and in some cases AGYW[121,181,182,187,188]. However, women in SSA are on a spectrum of risk, with heterogeneous risk

factors, including in numbers of partners, HIV and STI prevalence in partner populations, condom use, ART and VMMC coverage among partners of different types, periods of risk, making it difficult to target PrEP appropriately[4,12,189–191]. Additionally, female population groups with lower HIV incidence rates are larger in number than higher risk groups such as FSW, meaning that the greatest number of new infections in absolute terms are occurring in comparatively lower-risk groups[16,17,191,192]. The limited information available on the PrEP program cascade outcomes (including uptake, retention and adherence) also varies by female population and context, as with the number of secondary infections resulting from each infection in a high-risk woman group, altogether making it challenging to know how to most effectively scale-up PrEP beyond highest-risk groups[120,150,186].

Many of the PrEP demonstration and implementation projects have used screening tools to identify those at significant risk[85], though have received criticism for having better sensitivity than specificity, and not being sufficiently focused to identify those that would most benefit from PrEP[193,194]. There is also now growing momentum from community groups to move from targeted programs for key population groups towards universal access to PrEP as part of a rights-based approach to health[195,196].

Many mathematical modelling studies have assessed the impact and cost-effectiveness of PrEP for high-risk populations in sub-Saharan Africa[182,197–200], between population groups (between key populations or key populations and men/ women in the general population)[200–202], as well as relative to other HIV prevention interventions[203–205]. The studies conclude PrEP to be less cost-effective than other prevention interventions such as condoms, but cost-effective as part of a combination prevention approach for those at greatest risk[182,197–205]. Modelling studies have not systematically accounted for the low levels of PrEP program adherence and retention reported across different high-risk women groups in SSA[182,197–205]. None of the studies to date have addressed the scale-up of PrEP across high-risk women population groups in SSA, considering heterogeneities in risk factors, PrEP program outcomes, population size, and their effect on population-level impact and cost-effectiveness considerations to guide local strategies for PrEP roll-out.

1.2.5 Summary of open policy questions around PrEP implementation for high-risk women in SSA

As this review illustrates, there are many outstanding policy questions surrounding PrEP implementation for high-risk women in sub-Saharan Africa. These include:

1. Which strategies can be undertaken to improve PrEP uptake, retention and adherence?

2. How effective are alternative PrEP dosing strategies and formulations in strengthening programme outcomes?
3. The extent to which behavioural disinhibition may outweigh the potential HIV-protective benefits of PrEP, should it become an implementation reality?
4. How to prioritise PrEP scale-up across high-risk women, weighing considerations of impact and cost-effectiveness in resource constrained environments?

Open questions 1 and 2 will be predominantly answered through RCTs, OLE, demonstration and implementation trials, with the aid of mathematical modelling studies to help assess outcomes, especially when undertaken alongside the trials.

Open questions 3 and 4 can be explored independently of trials using mathematical modelling methods. As this PhD is not attached to an intervention trial, it will focus on open questions 3 and 4 using modelling approaches.

1.3 Modelling for HIV policy making

Mathematical models play an important role in public health by providing policy makers with evidence to inform decision making [206–208]. They are quantitative frameworks that draw upon data, evidence and processes from a number of different disciplines (for example, demography, biology, economics, epidemiology, anthropology, behavioural sociology) to generate evidence of past or projected impact and cost-effectiveness of programmes or interventions. They can be evaluated over very short (hours, days, weeks) to very long (multiple decades) time horizons.

Mathematical models allow policymakers to assess the impact of policy options under consideration, which may be impractical or unethical to test in implementation settings or over longer time horizons[206,209]. Undertaken alongside implementation studies, they can be used to evaluate the impact and, when combined with costing data, the cost-effectiveness of interventions or program approaches[207,210]. Mathematical models allow policy makers to explore the role of heterogeneity in risk, program or implementation factors on a study's outcome; or the effect of factors within or external to a study[207,211]. They also provide evidence to assess non-linearities between HIV risk factors or HIV infection and programme outcomes, to weigh the effects of circular interactions (for example, behavioural disinhibition following introduction of PrEP), and to explore how different time horizons of evaluation affect decision making[212].

This section gives an overview of the use of mathematical modelling in HIV policy making in five areas. It presents an overview of different model types used in HIV policy making; how models account for uncertainty; how models are fit to observed data; how they have been used to date in HIV policy making; and the challenges around their use.

1.3.1 Overview of different model types for use in HIV policy making

Mathematical models are simplified representations of complex realities and situations[209]. There are many possible (not necessarily mutually exclusive) forms that a model can take to address policy questions in relation to an infectious disease such as HIV.

This sub-section gives an overview of the different forms that models can take in addressing questions of relevance to HIV policy making. It is split into two parts. First, an overview of the key considerations of more direct relevance to policy makers[213]. Second, an overview of other model considerations faced by modellers in ensuring the model is appropriate to addresses the policy question at hand[209,213].

Overview of key model considerations of direct relevance to policy makers

Static vs dynamic models

Static models do not account for feedback loops affecting the force of infection (rate at which susceptible individuals are infected) over time[209]. Instead, the force of infection takes a predetermined value and does not capture the downstream effects of population interaction. For example, if modelling the risk of HIV infection to a FSW through sexual intercourse with male clients, the likelihood that the client population is HIV infected (i.e. the HIV prevalence) does not change over time. If the model shows the FSW's risk of infection going up over time, static models do not capture the downstream effects on clients' HIV prevalence, and in turn, this onward effect on FSWs' future risk of infection.

Static models of HIV risk are typically employed when the time horizon for evaluation of the policy question is short, and assumes the probability of exposure to the infectious diseases is constant for the time period under examination and therefore unaffected by programme, policy or other epidemiological or social changes[214]. They are generally structurally more straightforward, less data- and time-intensive to develop[209,215] and often form the basic building blocks for more complex models[209].

An example of a static model is the Bernouilli formulation of HIV risk[216–218], where the probability of the HIV virus being transmitted through each sexual contact is treated as an independent risk event. This formulation of HIV risk is a Bayesian statistical approach, which assumes that model parameters are based on prior distributions which are used to make statistical inferences about that chance of an event happening[219]. The other main statistical approach for calculating risk is the frequentist approach, which defines the likelihood of an event based on the limit of its relative frequency over a large number of trials[219]. A simple formulation of the Bernouilli model of risk is as follows:

$$\pi = 1 - (p(\,1 - \beta) + (1 - p))^{C} \qquad (1.1)$$

Where, using the same example of a FSW's risk from her clients, π is the HIV risk to a FSW per unit of time, p is the prevalence of HIV in the client population, β is the average probably of HIV transmission during a sex act with an HIV-infected client, and C is the total number of sex acts per unit of time.

From this formulation, we can explore a simplified, intuitive version of the fundamental concept in infectious disease modelling, R_0, the basic reproduction number, which represents the average

number of secondary infections arising from a single infectious person when introduced to a fully susceptible population[220].

$$R_0 = \beta CD,$$

(1.2)

Where D is the average duration of infectiousness in an individual. In HIV, the average duration of infectiousness is affected by whether or not an individual becomes virally supressed on ART, and indeed β, the risk of transmission per sex act with an HIV-infected partner, would change according to the stage of infection, which affects the level of infectiousness. This is a simplified version of the basic reproduction in the context of a homogeneous population, with more sophisticated, real world-like derivations calculable according model type and its complexity[220,221].

R_0 is important in the analysis of infectious diseases as it represents the threshold for stability of a disease-free equilibrium. In a fully susceptible population, if $R_0 > 1$, then an infectious disease will persist in a population, and if $R_0 < 1$, it dies out. Although inevitably a simplification of complex realities, R_0 is an important measure at the start of an epidemic, to help predict the rate of infection invasion in a population, the potential magnitude of the outbreak and the impact of disease prevention and control interventions. R_0 takes comparatively less prominence when infectious diseases are at endemic equilibrium, such as in the HIV contexts in sub-Saharan Africa[4] that will be explored through this thesis, but rather is used to help quantify the efforts needed to bring $R_0 < 1$ for the disease to be on a trajectory to elimination[222].

Unlike static models, dynamic models, on the other hand, account for feedback loops affecting the force of infection and therefore can account for changes over time owing to population interactions and evolving contextual factors[209]. They are therefore able to more fully gauge the extent of an intervention's impact across populations[223]. Continuing with the example of a FSW and male client population, the likelihood that the client population is HIV infected (i.e. the HIV prevalence) will change over time as a result of the interactions between (in this simple case) the FSW and her clients.

Dynamic models are typically represented by a system of differential or difference equations, evaluated numerically using programming tools with increased data requirements[214,215]. They are usually more time-intensive and expensive to devise, calibrate and solve, and often require critical assumptions to be made about current and future trends[215,224].

A simple dynamic model of static equation (1.1) can be approximated using the Kermack-McKendrick SIR system of differential equations[209,225,226,227], where $S(t)$ is the number of susceptible individuals in a population at time t, $I(t)$ the number of infected, and $R(t)$, the number removed from the population.

For FSW we have:

$$\frac{dS_f(t)}{dt} = a_f N_{f0} - \lambda_m(t) S_f(t) - m_f S_f(t)$$

$$\frac{dI_f(t)}{dt} = \lambda_m(t) S_f(t) - (r + m_f) I_f(t)$$

$$\frac{dR_f(t)}{dt} = m_f S_f(t) + (r + m_f) I_f(t)$$

And for the client population:

$$\frac{dS_m(t)}{dt} = a_m N_{m0} - \lambda_f(t) S_m(t) - m_m S_m(t)$$

$$\frac{dI_m(t)}{dt} = \lambda_f(t) S_m(t) - (r + m_m) I_m(t)$$

$$\frac{dR_m(t)}{dt} = m_m S_m(t) + (r + m_m) I_m(t)$$

With per capita forces of infection:

$$\lambda_m(t) = \beta_f c_f \frac{I_m(t)}{N_m(t)} \quad \text{and } \lambda_f(t) = \beta_m c_m \frac{I_f(t)}{N_f(t)}.$$

With total population sizes:

$$N_f(t) = S_f(t) + I_f(t) \text{ and } N_m(t) = S_m(t) + I_m(t).$$

And the equations balanced using

$$c_f = c_m N_f / N_m$$

(1.3)

Where a is the rate of recruitment into the population, c is the per capital rate of partner change, t_0 is at time zero, m the non-AIDS related mortality rate, β is the average probably of HIV transmission per sex act and r the AIDS-related mortality rate. The subscript f denotes females, and m denotes males, and N_{f0} and N_{m0} are the initial population sizes of FSW and males respectively.

For deterministic compartmental models (see later section for description) of infectious diseases, R_0 can be calculated using a Next Generation Matrix approach, as set out by Diekmann[228], van den Driessche and Watmough[229], Jones[230], Mukandavire[231] and others, using the linearized matrices. Following van den Driessche and Watmough[229] approach, we have:

$$F = \left[\frac{\partial F_I(x_0)}{\partial x_j}\right] \text{ and } V = \left[\frac{\partial V_I(x_0)}{\partial x_j}\right],$$

(1.4)

Where F_I is the rate at which newly infected individuals enter the infected compartment, I; V_I is the transfer of individuals out of and into the infected compartment by individuals j in classes R and S respectively; and x_0 is the disease-free equilibrium state. Then, for FSW:

$$F_f = \beta_f c_f S_f(t) \frac{I_m(t)}{N_m(t)} \text{ and } V_f = \begin{pmatrix} m_f S_f(t) - a_f N_{f0} \\ (r + m_f) I_f(t) \end{pmatrix}.$$

(1.5)

With disease free equilibrium when $S_{f0} = \frac{a_f N_{f0}}{m_f}$.

The Next Generation Matrix FV^{-1}gives the expected number of secondary cases in compartment I by an individual in compartment j. $R_{0\mathrm{f}}$, the number of new female infections produced by a typical infected male at disease free equilibrium is determined by the spectral radius (i.e. dominant eigenvalue) of the system, as follows (noting, here $N_{f0} = S_{f0}$):

$$R_{0\mathrm{f}} = \frac{\beta_f c_f S_{f0}}{S_{m0}(r + m_f)}$$

(1.6)

Similarly, for males:

$$F_m = \beta_m c_m S_m(t) \frac{I_f(t)}{N_f(t)} \text{ and } V = \begin{pmatrix} m_m S_m(t) - a_m N_{m0} \\ (r + m_m) I_m(t) \end{pmatrix}.$$

(1.7)

With disease-free equilibrium when $S_{m0} = \frac{a_m N_{m0}}{m_m}$, and

$$R_{0\mathrm{m}} = \frac{\beta_m c_m S_{m0}}{S_{f0}(r + m_m)}$$

(1.8)

Then, for the system, R_0, the expected number of secondary infections by an infected individual is:

$$R_0 = \sqrt{R_{0\mathrm{f}} R_{0\mathrm{m}}} = \sqrt{\frac{\beta_f c_f \beta_m c_m}{(r+m_f)(r+m_m)}},$$

(1.9)

Which is the average number of secondary infections arising from a primary infection. When $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable, and when $R_0 > 1$ the disease will persist in the population.

Comparisons of static and dynamic models are explored through the 2nd research chapter of this thesis.

Stochastic vs deterministic

Stochastic models capture uncertainty in transition between the different states represented by the model. They are formulated using probabilistic random variables, such that for the same set of initial conditions, a stochastic model's outcome will vary[209]. They can be modelled as individual-based models, tracking the path of an individual through a model, with chance affecting whether they get infected, or compartmental models (see later section for description), where the individual are treated as a group or compartment, with chance determining what happens to the group in total[209,232]. Stochastic models should be repeated a large number of times to build up a picture for the decision maker to assess, overall, the likely outcomes of an approach of interest[209]. Monte Carlo models are example stochastic models, which use parameter values randomly drawn according to set distributions, and with repeated runs can be used to ascertain the likelihood of an outcome happening[210]. Such models are often used in accounting for data uncertainty in models but tend to be difficult to simulate without the use of computing resources[209].

Deterministic models have a set pathway, such that with the same parameter values and initial conditions, the results of a model's simulation will always be the same[232]. They tend to be more straightforward to calculate, and, in general, to describe to and be understood by policy makers, but are a more simplified version of real-world dynamics[209,213]. Stochastic models are particularly appropriate for use with small population sizes, where chance may play an importance role in a population's behaviour through an intervention or in population interactions, and therefore parameter and initial condition specification[209]. Deterministic models may be more appropriate with

larger population sizes where the effects of chance over a large number of interactions become much less significant, and the system conditions can be appropriately reflected by a set of states determined upfront based on parameter averages [233].

Overview of key model considerations in determining appropriate model structure

Capturing population heterogeneity

Accounting for the appropriate level of model heterogeneity is a key concern of modellers in developing models to assess policy questions[213]. It is important that models appropriately represent a policy problem at hand by accounting for the key underlying heterogeneities that affect model outcomes[221]. This includes heterogeneities in epidemiological, risk and behavioural characteristics, in the dynamics of interaction between populations, progression through programme stages (e.g. intervention uptake, retention and adherence) and in relation to the policy question at hand (e.g. different scenarios under consideration)[234,235]. This level of model detail has to be balanced with the availability of data of reasonable quality, to ensure that model parameterization reasonably reflects the underlying population and programme under consideration, and does not inadvertently introduce inaccuracies in model outcomes[209,210].

Many of the choices faced by modellers in in determining the appropriate model structure to assess a policy question come about explicitly due to heterogeneity. For example, modellers must consider whether it is important that heterogeneity in transition between model states be represented stochastically rather than deterministically; or heterogeneity in partner mixing represented through individual-based network models rather than approximated using population averages (further description of these approaches are laid out later in this section). Heterogeneity adds complexity to models[213]. However, if models fail to capture important heterogeneities, their conclusions risk misleading policy makers[209,213].

Compartmental vs distributional

Compartmental models divide a pathway into a set of states with parameters attached to govern individuals' or populations' transition between these set of states[210]. They are most appropriate when a policy problem or disease states can be broken down into distinct stages, and parameters (determined through stochastic or deterministic approaches) assigned to them[209,210]. An illustration of a compartmental model is set out in Figure 6. It sets out the pathway of HIV negative individuals

through a PrEP programme, and if they become HIV infected, their pathway through stages of disease progression (denoted by CD4 count) in the absence of ART, on ART, and following ART drop out. In compartmental models, each arrow between the compartments in Figure 6 would be parameterised to describe the chance of progression between model compartments.

Distributional models, on the other hand, represent progression through disease states or a policy pathways using pre-determined distributions. Gradations of disease severity or pathway stages are used to assess the progression of individuals through these distributed states[210].

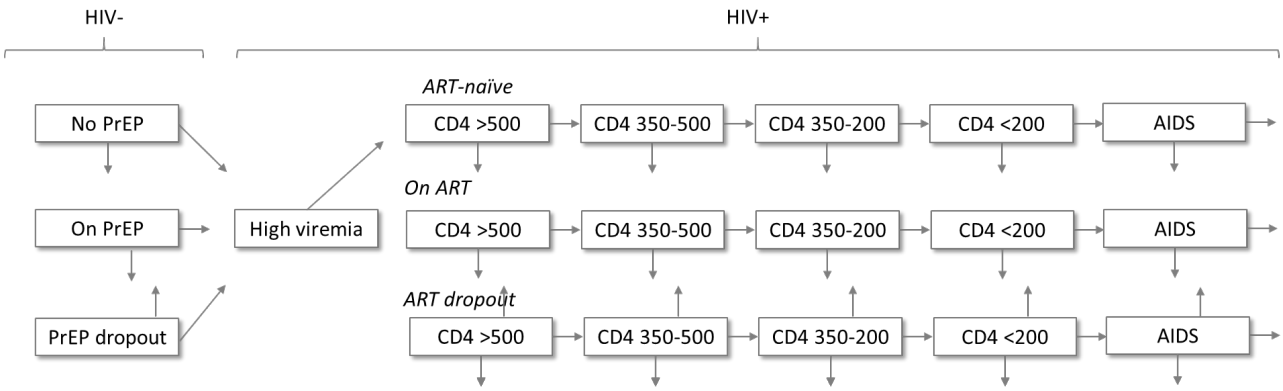

Figure 6: Illustrative compartmental model showing the pathway of HIV negative individuals through a PrEP programme, and when HIV infected, their pathway through stages of disease progression (denoted by CD4 count) in the absence of ART, on ART, and following ART drop out.

Discrete or continuous time

The transition of individuals or populations through model states can be assessed either through discrete timesteps or continuously. When modelled through discrete time, progress through model states can only happen after defined time steps (e.g. 1 day, 3 months or 12 months). As such, model progression can be abrupt, rather than happening on an ongoing basis[210]. Discrete models allow model policy makers to understand the numbers of individuals in a given model state based on the number in that state at the previous point in time[209]. Discrete models are suited where transition through disease states or the policy pathway happen only after defined periods, and data is available to parameterise the model corresponding to larger discrete timesteps[210]. Discrete models can be evaluated in simple computing tools such as Microsoft Excel[161].

Modelling using continuous time on the other hand allows for transition between states to be continuous and happen on an ongoing basis through infinitely small timesteps[221]. These models can be evaluated at any point in time and are better suited where process happen in an ongoing manner[221]. Unlike with discrete models, it may not always be possible to describe the numbers of

individuals in a given model state based on the number in that state at the previous point in time[209]. Continuous models usually need to be evaluated using computing tools, as they are evaluated using differential calculus[210]. However, in practice, many models such as the SIR models set out in equation (1.3) can equally be evaluated using discrete and continuous time using the same computing tools[236].

For example, the differential SIR model in equation (1.3) can be written in discrete form[237], using difference equation formulation, as follows:

For FSW:

$$S_{f_{t+1}} = a_f N_{f0} - \lambda_{m_t} S_{f_t} - m_f S_{f_t}$$

$$I_{f_{t+1}} = \lambda_{m_t} S_{f_t} - (r + m_f) I_{f_t}$$

$$R_{f_{t+1}} = m_f S_{f_t} + (r + m_f) I_{f_t}$$

And for the client population:

$$S_{m_{t+1}} = a_m N_{m0} - \lambda_{f_t} S_{m_t} - m_m S_{m_t}$$

$$I_{m_{t+1}} = \lambda_{f_t} S_{m_t} - (r + m_m) I_{m_t}$$

$$R_{m_{t+1}} = m_m S_{m_t} + (r + m_m) I_{m_t}$$

With per capita forces of infection:

$$\lambda_{m_t} = \beta_f c_f \frac{I_{m_t}}{N_{m_t}} \quad \text{and } \lambda_{f_t} = \beta_m c_m \frac{I_{f_t}}{N_{f_t}}.$$

With total population sizes:

$$N_{f_t} = S_{f_t} + I_{f_t} \text{ and } N_{m_t} = S_{m_t} + I_{m_t}.$$

And the equations balanced using

$$c_f = c_m N_{f_t} / N_{m_t}$$

(1.10)

Here, t is time. As the time steps in discrete models become infinitesimally small, they tend towards continuous-time models[209,238]. That is, where the size of the timestep, δt becomes infinitesimally small:

$$\lim_{\delta t \to 0} \frac{S_{t+\delta t} - S_t}{\delta t} \to \frac{dS(t)}{dt}, \lim_{\delta t \to 0} \frac{I_{t+\delta t} - I_t}{\delta t} \to \frac{dI(t)}{dt} \text{ and } \lim_{\delta t \to 0} \frac{R_{t+\delta t} - R_t}{\delta t} \to \frac{dR(t)}{dt}$$

(1.11)

In other words, the system of equations in (1.10) tends towards the system of equations in (1.3).

Individual-based network vs population averages

Network models can be used to describe the system or network of contacts between individuals with sexual partnerships, with the risk of infection dependent on the individuals with whom a person is connected[209]. Such models can be a powerful tool for understanding the role of specific networks in disease spread. However, they require very detailed, individual-level parameterization, which is often not feasible to collect in practice, and the results of network models often not broadly generalisable at population level[210]. Models otherwise, and more often, use population averages to describe to parameterise and describe transition through model stages, capturing heterogeneity through model stratification according to key heterogenous characteristics or transition parameters[210].

1.3.2 Accounting for uncertainty

There are two main types of uncertainty to be accounted for in modelling infectious diseases – parametric (about the model parameters) and structural (about the model's structure).

Parametric uncertainty

Uncertainty in the underlying data used to parameterise a model can be estimated through Frequentist or Bayesian approaches. Both aim to give policy and decision makers a level of understanding around the uncertainty in model outcomes due to uncertainty in model inputs.

Frequentist inference approaches assume that parameters have fixed (unknown) values and cannot be ascribed underlying distributions with associated probabilities[239]. They involve deriving parameter estimates using approaches such as maximum likelihood functions, to obtain the best fit model to observed data (e.g. HIV prevalence), then generating multiple samples from the best fit model using methods such as bootstrapping, to re-estimate parameters and then quantify uncertainty in underlying data sets[240,241]. They are used to produce (e.g. 95%) confidence intervals, indicating that over large number of samples, (e.g. 95%) of confidence intervals calculated would contain this range of values[239].

Bayesian inference approaches are used to assess uncertainty around model parameter inputs as well as outputs[242,243]. They assume prior distributions for parameters, and combine them with likelihoods derived through methods such as Monte Carlo simulations to build up parameter sets[242,244]. These simulated parameter sets are run through the model and typically fitted to observed data ranges (e.g. HIV prevalence)[245,240]. Uncertainty in model outcomes is then described by calculating (e.g. 95%) credible intervals based on this data, which signifies that there is (e.g. 95%) certainty that the true value lies within this range[246,247]. Bayesian inference approaches are nowadays more typically used in estimating parameter uncertainty and fitting models to data where prior distributions can reasonably estimated for parameters[248,244], and since 2006 have been used in UNAIDS's core modelling approaches for estimating uncertainty in national HIV estimates (Estimation and Projection Package, EPP, using Bayesian Melding and Spectrum using Monte Carlo methods)[249,250].

Two common Bayesian methods for accounting for model uncertainty and fitting to data using different approaches for deriving likelihoods are illustrated in Figure 7 and Figure 8. First, the Markov Chain Monte Carlo (MCMC) approach, where a chain is constructed through a 'walk' over a defined parameter space, constantly checking the closeness of the model outcome for each new parameter explored with a target outcome, and adjusting its path so that it converges towards the target outcome[251,252]. The example uses equation (1.3), and for illustrative purposes, simulates MCMC chains only on the parameters β_f and β_m (the probably of HIV transmission during a sex act with an HIV infected partner to women and men respectively), and uses the following model parameters: [$N_{f0} = 1000$, $C_m = 37$, $C_f = 4$, $\frac{I_{m0}}{N_{m0}} = 0.24$, $m_f = 0.0005$, $m_f = 0.0006$, $r = 0.0002$, $\beta_f, \beta_m \epsilon [0,0.01]$, with starting values for the chain of 0.0001] over 1000 iterations. Figure 7 below sets of the MCMC chains simulated for β_f and β_m, and Figure 8 the histograms of the posterior distributions generated.

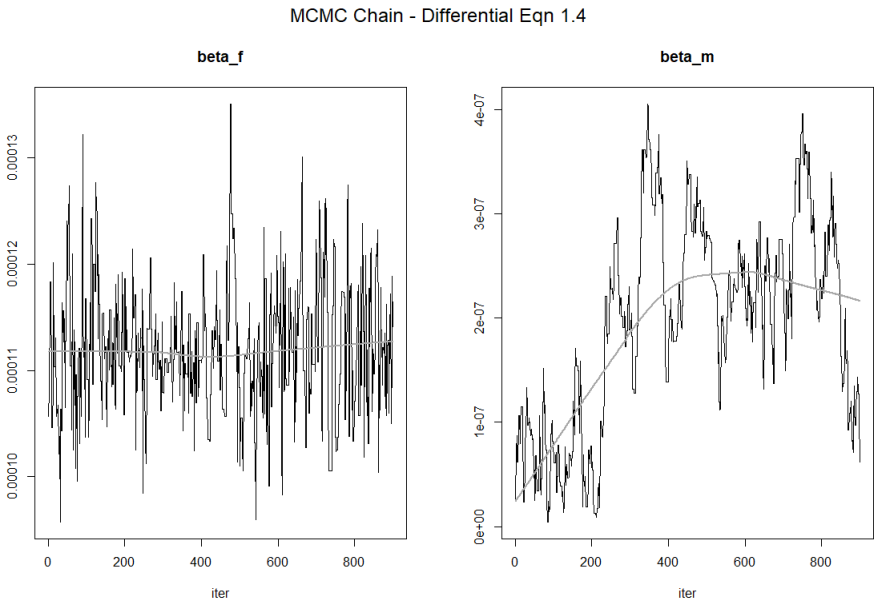

Figure 7: MCMC chain for equation (1.3), for parameters β_f and β_m.

The x-axis shows the number of iterations and y-axis the parameter values explored. The MCMC chains were simulated using the following parameter values: [$N_{f0} = 1000, C_m = 37$, $C_f = 4, \frac{I_{m0}}{N_{m0}} = 0.24$, $m_f = 0.0005, m_f = 0.0006$, $r = 0.0002$, $\beta_f, \beta_m \epsilon [0,0.1]$ with starting values for the chain of 0.0001] over 1000 iterations.

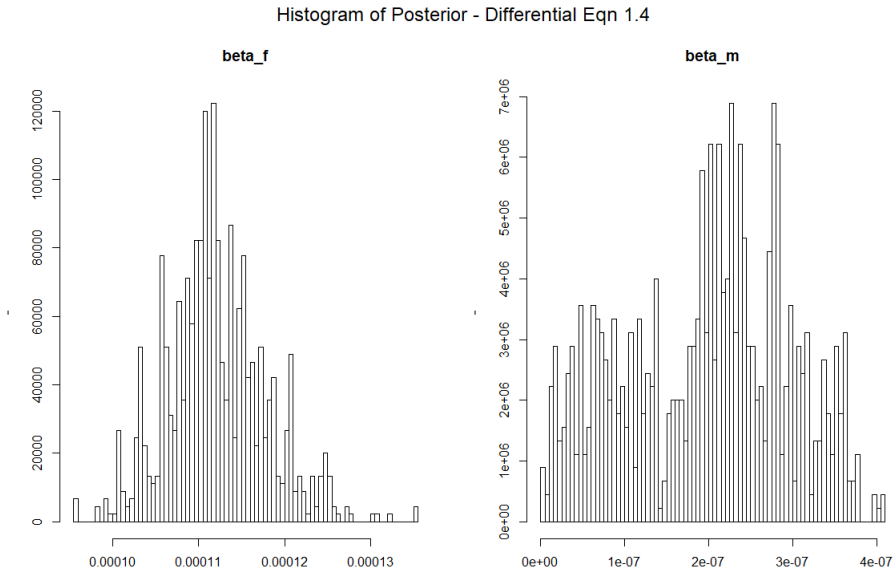

Figure 8: Histograms of the posterior distributions derived for parameters β_f and β_m from equation (1.3) using MCMC.

The x-axis shows the parameter values and y-axis the frequency. The MCMC chains were simulated using the following parameter values: [$N_{f0} = 1000, C_m = 37$, $C_f = 4, \frac{I_{m0}}{N_{m0}} = 0.24$, $m_f = 0.0005, m_f = 0.0006$, $r = 0.0002$, $\beta_f, \beta_m \epsilon [0,0.01]$ with starting values for the chain of 0.0001], over 1000 iterations.

The Latin Hypercube Sampling (LHS) is a type of Monte Carlo simulation that works by dividing the cumulative density function of each parameter into equal spaces, and sampling randomly from each of the spaces[253,254,255]. These sampled parameter values are run through the model and those sets of sampled parameters within a range of observed data are taken as fits and used to build up uncertainty intervals around model outcomes[253,254,255]. Compared to other Monte Carlo-based approaches, LHS is considered to be particular efficient computationally[254,255]. As an illustration, Figure 9 sets out the resulting distribution (range, standard deviation and range) of model outcomes (HIV prevalence in females (left) and males (right)) through LHS performed on parameters β_f and β_m using equation (1.3) and the parameter sets as described above for the MCMC simulation.

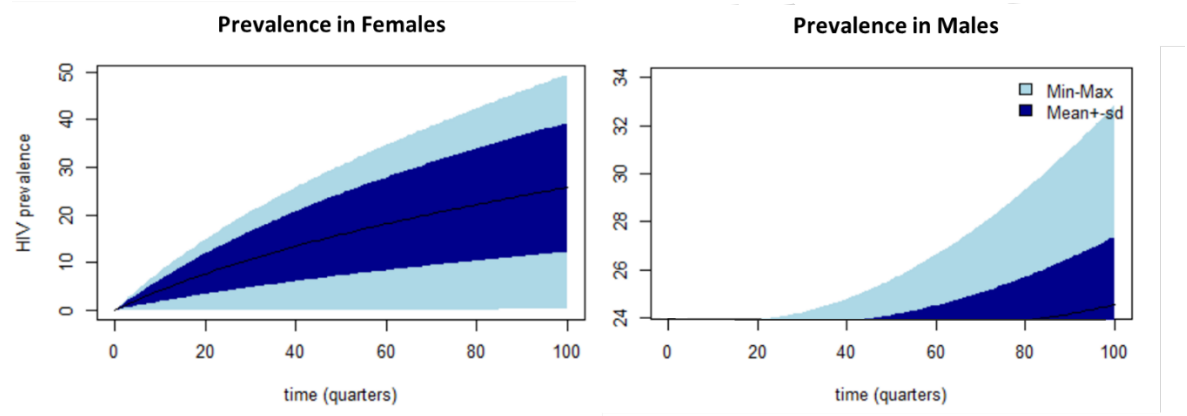

Figure 9: Graphs showing the range (min, max), median and standard deviation using all sampled parameters for β_f and β_m from equation (1.3) using LHS.

The range is shown in light blue, the standard deviation in dark blue and the median in black. The x-axis is the time steps and the y- axis HIV prevalence (%) for females (left had side) and males (right hand side). The LHS were run using the following parameter values: [$N_{f0} = 1000, C_m = 37$, $C_f = 4, \frac{I_{m0}}{N_{m0}} = 0.24$, $m_f = 0.0005, m_f = 0.0006$, $r = 0.0002$, $\beta_f, \beta_m \epsilon [0,0.01]$ with starting values for the chain of 0.0001], over 1000 iterations.

Structural uncertainty

As noted above, a model's structure should be driven by its intended use, and ideally represent the key policy or programme states under evaluation, as well as important heterogeneities in relation to populations, their interactions and underlying epidemiology, as well as data availability[235]. Uncertainty in model structure is usually assessed through introducing greater, and also lesser, complexity in the structure of the model, and then comparing outcomes[256–259]. For example, modellers can start with simpler structural versions of a model and progressively add more structural heterogeneity, to gain understanding into how model structural complexity affects a model's outcome[235,258].

In practice, however, it is difficult to separately address model structural uncertainty in the absence of assessing parametric uncertainty. For example, introducing greater model structural heterogeneity also necessitates greater heterogeneity in parameterization[256]. One technique called Bayesian Model Averaging, an extension of Bayesian inference methods[260], has been developed to concurrently address structural and parametric uncertainty in stochastic modelling [261]. The technique averages over a set of models that are supported by the underlying data, requires specification of prior distributions of competing models and then averages over the class of models deemed to be most appropriate[261]. However, in practice, the requirements for performing such analyses are too vast and require too many assumptions to be practicable[260,261].

1.3.3 Fitting models to data

Fitting models to observed data aims to improve the accuracy of model predictions[209]. Model fitting is undertaken by ensuring that the sets of parameters used by the model to describe the as-is situation give rise to observed basic model outcomes (e.g. populations' prevalence or incidence)[262]. Where models are evaluated over time horizons, their accuracy can be strengthened if they can be fit to observed data at several point in the past, thereby appropriately depicting the past epidemic course. This is undertaken with the hope that when the model with fitted parameter sets is then used to evaluate a policy question (e.g. introduction of an intervention, or a counterfactual), its outcomes will be more likely to be grounded in implementation realities[262].

There are a wide range of approaches for fitting models to data, usually based on minimizing the distance between model predictions and observed data using goodness of fit statistics[263]. Examples of fitting approaches include least square approaches where parameter sets are adopted that lead to the least sum of squares between predicted and observed outcome data; or maximum likelihood approaches where parameter sets are adopted that maximise the likelihood of observing the outcome data[209].

Where approaches are concurrently being used to estimate uncertainty in model outcomes, credible intervals around model parameters can be obtained at the same time as the best fitting parameter values[209]. This can be done through a variety of approaches, including the Bayesian MCMC and Latin Hypercube Sampling approaches previously described, using algorithms to generate parameter sets and select those as 'fits' that lead to model outcomes within observed data ranges[244,255].

1.3.4 Use of models in HIV policy making

Mathematical models have been used to inform HIV policy making since the early days of the HIV epidemic response[85,264–269]. Their key uses in HIV policy making include informing normative guidance setting[85,113,270]; informing resource allocation across populations, interventions and geographies at global, regional, national and sub-national levels based on consideration of impact and cost-effectiveness[201,271–273]; supporting assessment of the results of intervention trials[197,274,275]; and informing strategy development, target setting and resource mobilization investment cases[68,69,74,276,277]. These models range from those which can be applied across multiple countries or tailored to multiple different implementation contexts[93,202,272], to those built specifically to address particular policy questions at hand[161,256,278]. Whist very far from an exhaustive list, Table 4 illustrates a number of the mathematical models that have been used in informing policy and decision making at global, regional, national and subnational levels in recent years. For each model, the table sets out its key usages in policy and decision making, the model type, the approach that was used in accounting for data uncertainty and fitting to data, and the computing tool that the model was programmed in.

Model name	Key usage in policy and decision making	Model type	Approach for assessing uncertainty and fitting to data	Programme/ Package
EPP[279,280]	Used by UNAIDS and countries in estimating and projecting national HIV prevalence in countries with generalised epidemics	Dynamic, compartmental SI (susceptible, infected) model	Bayesian, MC Melding	Java, R Studio
Spectrum[281] (suite of models including AIDS Impact Model (AIM) and Goals)	Used by UNAIDS and countries, in conjunction with EPP, to estimate national HIV prevalence, as well as to assess the consequences (impact, cost) of the HIV epidemic and assess intervention choices. Used to inform the Global Fund 2017-2022 Strategy targets and 5th and 6th replenishment investment cases[276,269,68] and UNAIDS Fast Track Strategy[69].	AIM is discrete, compartmental model[282] Goals is compartmental, based on Bayesian risk formulation[273]	Bayesian, MC methods	Java, Delphi
Imperial College Model[201,202] for sub-Saharan Africa	Used by researchers and countries to evaluate the consequences (impact, cost) of intervention choices on countries' HIV epidemics, by population and sub-national location. Used to inform the Global Fund 2017-2022 Strategy targets and 5th and 6th replenishment investment cases[276,269,68].	Dynamic compartmental model	Bayesian, LHC methods	Not specified[202,201]
EMOD (Epidemic Modelling)[283,87,284]	Used by researchers to evaluate the consequences (impact, cost) of intervention choices on countries' HIV epidemics	Discrete, stochastic, individual-based SIR model	Bayesian methods	C++
Optima[272]	Used by the World Bank to evaluate the consequences (impact, cost) of intervention choices on countries' HIV	Dynamic, differential compartmental model, with force of transmission based	Bayesian methods	MATLAB and Python

	epidemics. Used to confirm Spectrum's UNAIDS Fast Track Strategy modelling[69].	on Bayesian risk formulation.		
Modes of Transmission[285,286,287]	Used by UNAIDS and countries to evaluate the consequences (impact, cost) of HIV prevention intervention choices	Static, compartmental model based on Bayesian risk formulation.	Not calibrated. Uncertainty assessed using simple Bayesian approach involving uniform sampling from user-prescribed plausibility ranges	Excel
HIV Synthesis Model[288,289]	Used by researchers to evaluate the consequences (impact, cost) of intervention choices on countries' HIV epidemics	Individual-based, stochastic model	Approximate Bayesian Computation methods	SAS
Thembisa[290,291]	Used by researchers to evaluate the consequences (impact, cost) of intervention choices on the South African HIV epidemic. Also used as data source for UNAIDS's South African HIV estimates, and as demographic projection model for the country.	Compartmental, discrete model	Bayesian methods	C++ and Excel/ VBA versions
13 modelling studies assessed in systematic review of cost-effectiveness of PrEP[197]	Modelling evidence used in WHO's 2016 normative guidance to provide PrEP for all individuals at substantial risk of HIV[85]	Of 13 studies, 11 deterministic transmission models, 2 stochastic Markov simulations	Various	Various
Modelling studies assessed in determination of WHO's 2015 and 2016 treat all Strategy[270,85]	Modelling evidence used in WHO's 2015 and 2016 normative guidance to provide ART for all people living with HIV	Stochastic and deterministic transmission models (Granich[292]); deterministic transmission (Kato[293]); Literature review of 12 studies: 9 deterministic compartmental, 3 individual-	Various	Various

		based microsimulation (Eaton et al[87])		

Table 4: Table illustrating a number of the mathematical models that have been used to inform policy and decision making at global, regional, national and subnational levels in recent years.

The for each model, the table sets out its key usages in policy and decision making, the type of model, the approach that was used in accounting for data uncertainty and fitting to data, and the computing tool that the model was programmed in. The models listed in the table are far from exhaustive.

1.3.5 Challenges in use of models for policy making

A predominant challenge and barrier to the use of models for policy making, as well as cause of misuse, is a perception that models are too complex to understand; referred to as intimidating 'black box' processes with challenges in assessing their applicability to real-life settings[206,210,294–298]. These challenges of model complexity span the models themselves, as well as challenges on the part of both modellers and policy makers.

Model complexity can come from many sources including the level of heterogeneity captured in the model (e.g. populations and their interactions, risk factors, program and disease transition states)[206,6,299]; the model structure (e.g. simple static models may be more accessible to policy makers than simple dynamic models, which require a greater level of mathematical understanding[215]) and level of sophistication in data uncertainty and calibration tools[6,300,301]; and the accessibility of the tool in which the model computations are undertaken (e.g. Excel may be more accessible than computer programmes that require vast training)[210,215]. Models that can be more easily understood, parameterized, run, and correctly interpreted by policy makers themselves, or with the partial support of modellers, may increase the likelihood of their uptake and use to inform decision making, as well as ownership by policy makers[302,303].

Challenges on the part of the modellers include the need to clearly distil key pieces of information around model structure, parameterisation and interpretation to ensure that the model being developed is appropriate to the context and question at hand[6,301,234]; and appropriately communicate the meaning and limitations of its results (including alignment with observed data and the results of other studies) through an approach that is accessible to policy makers that may not have advanced analytical training[206,295,296,301]. On the part of policy makers, challenges include the need to engage with modellers to clearly communicate the rationale, scope and objectives of the modelling assignment[296,301]; key epidemiological, population, program and implementation characteristics that affect the policy question[206]; as well as availability and quality of data to parameterise the model, to ensure that the model can be structured appropriately[296,304].

Addressing challenges to do with modelling complexity

In recent years, to facilitate the use of models to inform policy making, several frameworks have been put forward to guide the information exchange and facilitate dialogue between modelers and policy makers to address these communication challenges[206,295–298,303–307].

Recommendations in the literature around model structural complexity suggest that to improve uptake in decision making, models should adopt only the minimum level of complexity needed to appropriately represent the policy question at hand, in view of the availability of data, important interactions between populations, heterogeneities in risk factors, program and disease transition states[210,306,308–311]. Einstein is quoted in stating: ''*Everything should be made as simple as possible, but not simpler*''[309]. In response to the lack of specificity of existing guidance around the requisite level of model structural complexity, a 2015 HIV Modelling Consortium dialogue between modellers and policy makers concluded that there is a need to better understand the minimum level of complexity to address policy questions[295].

Prudden *et al*. explored the importance of heterogeneity in population grouping according to risk factor in the context of low level, generalised epidemics, and concluded that the lack of heterogeneity in UNAIDS's simple static Modes of Transmission model may underestimate the importance of different vulnerable groups (e.g. women engaged in transactional sex, and brothel-based vs. non-brothel based FSW) in an HIV reponse[285]. Mishra *et al*. also explored the simple, static model Excel-based Modes of Transmission tool used extensively to prioritise HIV prevention interventions between groups at country-level[285–287] They concluded that because the static model does not capture the dynamic effects of partner interaction, the model underestimates the contribution of epidemic drivers to HIV transmission over time[286].

When are simple, static models appropriate to guide policy making in HIV?

Simple, static models form the basic building blocks for more complex models[209]. They can be manipulated through simple methodological approaches that may be comparatively accessible to policy makers, and used to deduce broad principles to help guide decision making[210,264]. They rely on a snap-shot of data without accounting for the downstream effects of population interaction[209,215]. They typically are more straightforward structurally, are less data- and time-intensive to develop, can often be programmed in simpler programming tools such as Excel[209,215]. Simple, static models therefore have appeal for use in policy making, making them easier tool with which to engage policy makers, and in view of data limitations in implementation contexts[302,303].

A key attribute of static models that differentiates them from structurally more complex models is their lack of ability account for time-dependent changes[209,215]. Unlike static models, dynamic models account for changes over time owing to population interactions and evolving contextual factors[215,224]. They are usually structurally more complex, have significantly increased data

requirements and need to be evaluated using more advanced programming tools[215,214]. As a result, dynamic model are more time-intensive and costly to develop, usually require assumptions to be made about relationships and parameters that are not empirically available, and may be less accessible to policy makers[215,224]. Dynamic models are extensively used across models to inform policy making at global, national and sub-national levels[87,197,201,202,272,280,281,290,292,293] including the majority of those set out in Table 4.

To date, there has been limited assessment of the conditions under which simple static models are robust enough to guide policy making in HIV[224,285,286,295]. In this vein, as previously stated, Mishra *et al.* have assessed the static Modes of Transmission model and concluded that by not capturing the dynamic effects of partner interaction, the model underestimates the contribution of epidemic drivers to HIV transmission over time[286]. Foss *et al.* have incorporated dynamic features into a static model of HIV risk when exploring the impact of an STI-efficacious microbicide, and compared the models' projections at an end timepoint[161,183]. They concluded that the static model may over- or under-state the magnitude of microbicide efficacy depending on the product's HIV-risk reduction characteristics and behavioural disinhibition[161,183].

To the best of my knowledge, no study has yet examined the extent to which the conclusions of static models remain robust to the incorporation of dynamic effects when considering the introduction of a new HIV prevention intervention. Considering the opportunity for mathematical modelling to address some of the key outstanding questions in relation to PrEP introduction for high-risk women in sub-Saharan Africa, such studies would provide an opportune case study for exploring the conditions under which static models can provide adequate insights to inform HIV policy making.

1.4 PhD aims and objectives

1.4.1 Summary of open questions to be addressed by thesis

In view of the urgent need to address the disproportionate and vast scale of new HIV infections across the spectrum of high-risk women in sub-Saharan Africa as set out in section 1.1, this thesis aims to address the open policy questions 3 and 4 from section 1.2 that can be directly addressed through mathematical modelling approaches, and the open methodological question around the contexts in which static models can provide adequate insights to support policy making concerning the introduction of a new HIV prevention intervention.

Specifically, this PhD research will aim to use mathematical modelling to inform policy making around the scale-up of PrEP for high-risk women in sub-Saharan Africa. It will intend to do so by accounting for the heterogenous behavioural and epidemiologic risk factors and PrEP programme outcomes across women at a spectrum of risk in sub-Saharan Africa, exploring:

- The extent to which behavioural disinhibition may outweigh the potential HIV-protective benefits of PrEP
- Strategies for scale-up of PrEP across women at a spectrum of risk in sub-Saharan Africa, weighing impact and cost-effectiveness considerations in resource constrained environments
- The conditions under which static models remain robust to the incorporation of dynamic model effects when evaluating the introduction of a new HIV prevention intervention

Accordingly, the aims and objectives of this PhD are set out on the following page.

1.4.2 Aim and objectives

Aim: to use mathematical modelling to inform policy making around the scale-up of PrEP for women across a spectrum of high HIV risk in sub-Saharan Africa, accounting for heterogeneities in HIV risk factors and potential PrEP programme outcomes

Objectives:

The specific objectives are to:

1. Assess the potential effectiveness of PrEP in reducing HIV infections among high-risk women in sub-Saharan Africa
2. Explore the extent to which behavioural disinhibition may outweigh the potential benefits of PrEP
3. Assess the robustness of conclusions made on the basis of static modelling techniques to incorporation of dynamic effects, to contribute to understanding around the importance of modelling complexity to inform HIV policy making
4. Explore strategies for the scale-up of PrEP across high-risk women at population-level, weighing considerations around HIV infection reduction and cost-effectiveness
5. Evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa, to explore how the approach to PrEP scale-up may differ by epidemic and implementation context

The next chapter sets out the methods adopted in responding to the aim and objectives of this thesis.

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Chapter 2

2. Thesis Methods

2.1 Overview of Thesis Methods

This thesis adopts mathematical modelling approaches to inform HIV policy making. First, a simple static model of HIV risk to FSW is developed using the established Bernouilli[1–4] formulation. It is used to assess the impact of behavioural disinhibition on PrEP's ability to avert HIV infections, accounting for heterogeneities in FSWs' initial condom consistency and PrEP adherence. The static model is then evolved into a more complex dynamic model formulation, using a system of difference equations, to account for the downstream effects of population interactions. The outcomes of the static and dynamic models are compared over different time horizons and epidemic contexts, to explore the conditions under which the policy conclusions based on the two models are consistent. Finally, the static model is refined to represent women across a more broadly defined spectrum of HIV risk: women 15-24 years, 25-34 years and 35-49 years, in addition to FSW. These models are used to explore the cost-effectiveness and population-level impact of PrEP scale-up from FSW to women in the general population, in order to highlight policy considerations as countries consider rolling out PrEP beyond those at highest individual risk.

The models are parameterised to case study countries spanning a range of high HIV burden contexts in sub-Saharan Africa: South Africa, Zimbabwe and Kenya, using published biological, epidemiological and sexual behavioural data. The models are solved using both analytical and numerical mathematical approaches, and using both Microsoft Excel (for Office 365) and the R programming environment[5]. The static and dynamic models are fitted to data using Bayesian Monte Carlo Filtering with Latin Hypercube Sampling assuming uniform prior distributions. The following sections present more detailed information on the methods used in each Research Paper.

2.2 Research Paper 1

2.2.1 Research Paper Objectives

Research Paper 1 aims to address PhD Objectives 1 and 2; specifically:

1. To assess the potential effectiveness of PrEP in reducing HIV infections among high-risk women in sub-Saharan Africa

2. To explore the extent to which behavioural disinhibition may outweigh the potential benefits of PrEP

2.2.2 Rationale for Research Paper Setting

The setting for Research Paper 1 is PrEP for FSW in South Africa – specifically in Hillbrow, inner-city Johannesburg. This setting and population was chosen in order to be able to explore the modelling in this first analysis applied to a particularly high HIV burden setting and population – Hillbrow has particularly high HIV-burden among sub-Saharan African settings, and FSW are a particularly high HIV risk female population within this context, with up to 72% HIV prevalence[6–8].

In addition, it is hoped that this case study will help inform policy decision making around PrEP scale-up in South Africa, in line with PrEP roll out for FSW in South Africa under the National Sex Worker HIV Plan (2016-2019)[9]. This is a pertinent case study for examining the potential impact of behavioural disinhibition considering heterogeneities in PrEP programme outcome, given the challenges FSWs face in negotiating condom use[10] and the financial incentives they may receive for condomless sex with clients[11], as well as the challenges in PrEP retention observed in TaPS[12], a 2015-2017 PrEP and early antiretroviral treatment (ART) demonstration project undertaken among the Hillbrow FSW community.

2.2.3 Overview of Methods

Research Paper 1 builds on the approach of Foss *et al.*[13] in assessing the effectiveness of and potential implications of behavioural disinhibition (reductions in condom use) following introduction of an STI-efficacious microbicide. Research Paper 1 uses the established Bernoulli model of HIV transmission[1–4] where the probability of the HIV virus being transmitted through each sexual contact is treated as an independent risk event.

To be able to explore the consequences for FSWs of behavioural disinhibition on PrEP, condoms are assumed to be used with consistency that may vary with the introduction of PrEP (γ_0 prior to PrEP introduction and γ_1 after its introduction). Condoms were assumed to have an HIV risk reduction efficacy, ε, including slippage and breakage, with the risk reduction effectiveness of condom following a linear relationship between use and efficacy ($\varepsilon\gamma$). At the time of undertaking Research Paper 1, the exact effectiveness relationship between adherence and PrEP efficacy remained under

investigation[14–16], so the model took an overall level of 'PrEP effectiveness', b_α, corresponding to a level of FSW PrEP adherence, α. No partner populations are assumed to be taking PrEP.

To start, a single partner population is considered, in which the proportion HIV infected is p. For a given time period, h, a FSW is assumed to have an average m partners, and an average of n sex acts with each partner. Parameter h is taken as 3 months, corresponding to the minimum period after which an individual on PrEP must return to the provider to perform an HIV test to check for seroconversion (amongst other indicators) [17]. For simplicity these equations assume an overall average probability of HIV transmission, β, per sexual contact with an HIV infected partner. It is assumed that all sex acts are peno-vaginal on the basis of available epidemiological data for FSWs in Hillbrow[18]. The models for all Research Papers in this thesis are parameterised using sexual behaviour, biological, epidemiological and PrEP programme data from the literature. The HIV risk from a single partner population to FSW with consistency of condom use γ_1, adhering to PrEP at level α is given by:

$$\pi(\gamma_1, \alpha) = 1 - \Big(p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m \quad (2.1)$$

In the absence of PrEP($i.e\ \alpha = 0$) the HV risk is:

$$\pi(\gamma_0, 0) = 1 - \Big(p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m \quad (2.2)$$

It is therefore beneficial to take PrEP as part of a combination HIV prevention approach, even if reductions in condom use occur, as long as $\pi(\gamma_1, \alpha) < \pi(\gamma_0, 0)$, simplifying to:

$$\Big(p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m < \Big(p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m \quad (2.3)$$

From (2.3), the condition for PrEP to be beneficial in terms reducing HIV risk is:

$$\frac{(1 - \varepsilon\gamma_1)}{(1 - \varepsilon\gamma_0)} < (1 - b_\alpha) \quad (2.4)$$

In other words, if the relative HIV risk reduction in condom use following the introduction of PrEP is less than the HIV risk reduction afforded by PrEP. Equation (2.4) can also be arranged to give:

$$b_\alpha > \frac{\varepsilon(\gamma_0 - \gamma_1)}{(1 - \varepsilon\gamma_1)}$$

(2.5)

Equation (2.5) gives the level of PrEP effectiveness that must be attained for PrEP to be of benefit in reducing HIV risk, considering any change in condom consistency. Equation (2.5) also illustrates that PrEP will be beneficial at any level of adherence $\alpha > 0$ where $\gamma_0 = \gamma_1$, that is condom consistency remains unchanged. This is independent of the number of partners, sex acts and partner HIV prevalence.

The critical level of PrEP effectiveness corresponding to adherence level α^*, which serves as the break-even point for beneficence of PrEP for HIV prevention with regard to any change in condom consistency is:

$$b_{\alpha^*} = \frac{\varepsilon(\gamma_0 - \gamma_1^*)}{(1 - \varepsilon\gamma_1^*)}$$

(2.6)

Considering the extreme scenario of 100% reduction in condom consistency on PrEP, HIV risk will not be increased as long as the achieved effectiveness of PrEP exceeds that of condoms at the consistency prior to PrEP introduction:

$$\varepsilon\gamma_0 < b_\alpha \leq 1$$

(2.7)

This is the condition under which PrEP will always be beneficial as an additional HIV prevention approach in reducing HIV risk.

Simple rearrangement of equation (2.6) gives the break-even value of condom consistency after introduction of PrEP such that HIV risk is not increased:

$$\gamma_1^* = \frac{(\varepsilon\gamma_0 - b_\alpha)}{\varepsilon(1 - b_\alpha)}$$

(2.8)

Accounting for increased STI exposure through reductions in condom use

Since reductions in condom use will result in increased exposure to STIs, a number of which are cofactors for increased HIV transmission[19], the analysis is expanded to explore the increased risk of HIV transmission resulting from any increased exposure to STIs. The probability that at least one

person in the partnership has an STI following the introduction of PrEP, s_1, is assumed to increases proportionally to the absolute change in condom consistency. Thus, $s_1 = s_0\big(1 + (\gamma_0 - \gamma_1)\big)$, where s_0 is the probability that at least one person in the partnership has an STI prior to the introduction of PrEP. Parameter δ is the multiplicative increase in per sex act probability of HIV transmission in the presence of an STI. The HIV risk equations (2.1) and (2.2) become, respectively, on PrEP:

$$\pi(\gamma_1, \alpha, s_1) = 1 - \Big(s_1 p\big(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - s_1)p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m,$$

(2.9)

and in the absence of PrEP:

$$\pi(\gamma_0, 0, s_0) = 1 - \Big(s_0 p\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s_0)p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m.$$

(2.10)

PrEP is thus beneficial in reducing HIV risk if $\pi(\gamma_1, \alpha, s_1) < \pi(\gamma_0, 0, s_0)$, which simplifies to:

$$s_0\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s_0)\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n < s_1\big(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - s_1)\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n.$$

(2.11)

Two partner populations – clients and regular partners

The HIV risk equations are extended to account for risk arising from two distinct partner populations: clients ("c") and regular partners("r"). The HIV risk equations (2.1) and (2.2) become, respectively, on PrEP:

$$\pi(\gamma_1, \alpha, s_1, c, r) = 1 - \Big(s_1 p_c\big(1 - \delta\beta(1 - \varepsilon\gamma_1^c)(1 - b_\alpha)\big)^{n_c} + (1 - s_1)p_c\big(1 - \beta(1 - \varepsilon\gamma_1^c)(1 - b_\alpha)\big)^{n_c} + (1 - p_c)\Big)^{m_c} * \Big(s_1 p_r\big(1 - \delta\beta(1 - \varepsilon\gamma_1^r)(1 - b_\alpha)\big)^{n_r} + (1 - s_1)p_r\big(1 - \beta(1 - \varepsilon\gamma_1^r)(1 - b_\alpha)\big)^{n_r} + (1 - p_r)\Big)^{m_r},$$

(2.12)

and in the absence of PrEP:

$$\pi(\gamma_0, 0, s_0, c, r) = 1 - \Big(s_0 p_c\big(1 - \delta\beta(1 - \varepsilon\gamma_0^c)\big)^{n_c} + (1 - s_0)p_c\big(1 - \beta(1 - \varepsilon\gamma_0^c)\big)^{n_c} + (1 - p_c)\Big)^{m_c} * \Big(s_0 p_r\big(1 - \delta\beta(1 - \varepsilon\gamma_0^r)\big)^{n_r} + (1 - s_0)p_r\big(1 - \beta(1 - \varepsilon\gamma_0^r)\big)^{n_r} + (1 - p_r)\Big)^{m_r}.$$

(2.13)

Thus, it is beneficial to take PrEP as part of a combination HIV prevention approach, even if reductions in condom use occur, as long as $\pi(\gamma_1, \alpha, s_1, c, r) < \pi(\gamma_0, 0, s_0, c, r)$.

In this setting, condom consistency with regular partners is low[18] and in many cases clients pay more for condom-less sex[20]. Change in condom consistency on PrEP is therefore likely to be more pronounced with clients. To explore this, Research Paper 1 assesses the percentage reduction in condom consistency *with male clients* tolerated, for HIV risk not to increase on PrEP, holding condom consistency with regular partners constant using equations (2.12) and (2.13). The Paper assesses whether the results remain the same, accounting or not for increased STI exposure through decreased condom use. In order to explore whether changes in condom use with clients or regular partners present the biggest HIV risk in such settings, the Research Paper examines whether there is a significant difference in the percentage reduction in condom consistency *with male clients* tolerated for HIV risk not to increase, if PrEP use reduces condom use to zero with regular partners.

To account for heterogeneity in PrEP programme outcomes, these equations are evaluated over a range of PrEP effectiveness levels, in increments of 10% spanning 35% to 95%. These levels were chosen as they span the range of HIV risk reduction estimated through the iPrEx OLE[21] study (53% corresponding to adherence levels of <2 tablets a week; 87% corresponding to 2-3 tablets a week, up to 100% corresponding to 4-6 tablets a week), with a lower effectiveness bound of 35% chosen, given the iPrEx OLE study was undertaken in a different study population (MSM and TGW). At the time of undertaking this study, there were no data available connecting levels of PrEP adherence in women to levels of HIV risk reduction (and even the data now available through the Partners Demonstration OLE project are less granular[22]).

Programming tool

The numerical analysis for Research Paper 1 is undertaken in Microsoft Excel, as it is in general considered a user-friendly analytical tool that is more accessible to policy makers than advanced programming tools[23]. Optimization is undertaken using Solver in Excel.

Uncertainty analysis

Simple uncertainty analyses are undertaken through basic approaches that may be more reproducible by policy makers, without requiring complex programming tools. Accordingly, the calculations are repeated across boundary cases: high risk and low risk, parameterised using high and low risk values for sexual behaviour and the transmission probability parameters.

2.3 Research Paper 2

2.3.1 Research Paper Objectives

Research Paper 2 aims to address PhD Objective 3; specifically:

3. To assess the robustness of conclusions made on the basis of static modelling techniques to incorporation of dynamic effects, to contribute to understanding around the importance of modelling complexity to inform HIV policy making

2.3.2 Rationale for Research Paper Setting

For ease of comparison with the model from Research Paper 1, the same setting and population are retained for Research Paper 2 – FSW in Hillbrow, inner city Johannesburg.

2.3.3 Overview of Methods

The static model from Research Paper 2 is first refined and then compared with a matched dynamic version of the model.

For the static model, the average number of partners that a FSW has per unit time, h, is renamed C instead of n, as it was in Research Paper 1, in line with convention[24]. Parameter C was not used in the first Research Paper to avoid confusion with the use of the subscript c to denote clients.

To facilitate ease of comparison between models, the equations consider only a single FSW partner population, male partners, denoted by subscript m and FSW are denoted by the subscript f. For clarity, β_f is the average probability of HIV transmission to a FSW, per sexual contact with an HIV infected male partner, and β_m the average probability of HIV transmission to a male, per sexual contact with an HIV infected FSW.

In refining the risk equations used in Research Paper 1, the equations for Research Paper 2 additionally account for antiretroviral (ART) and male circumcision coverage. Parameters ϑ_m and ϑ_f are the proportion of HIV+ male partners and FSW that are on ART respectively, and ϱ is the average reduction in the probability of HIV transmission due to viral suppression on ART. The proportion of male population circumcised is denoted by τ and σ_f and σ_m are the average reduction in probability HIV transmission to FSW and male partners respectively, when the male partner has been circumcised.

The static model formulation of HIV risk to FSW per time step h is:

$$\pi_{static} = 1 - \left(1 + p(\psi_f + \omega_f - 1)\right)^{C_m}$$

Where

$$\psi_f = (1-\tau)\begin{pmatrix} (1-\vartheta)s\left(1-\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +(1-\vartheta)(1-s)\left(1-\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +\vartheta s\left(1-(1-\varrho)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +\vartheta(1-s)\left(1-(1-\varrho)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \end{pmatrix}$$

and $\omega_f = \tau\begin{pmatrix} (1-\vartheta)s\left(1-(1-\sigma)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +(1-\vartheta)(1-s)\left(1-(1-\sigma)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +\vartheta s\left(1-(1-\sigma)(1-\varrho)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \\ +\vartheta(1-s)\left(1-(1-\sigma)(1-\varrho)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\right)^n \end{pmatrix}$

With $\gamma = \gamma_0$ before the introduction of PrEP, and γ_1 after the introduction of PrEP;

$s = s_0$ before the introduction of PrEP and s_1 after the introduction of PrEP; and

$s_1 = s_0(1 + (\gamma_0 - \gamma_1))$.

(2.14)

The static model is then evolved into dynamic model formulation using difference equations. The use of discrete time formulation was chosen to allow for comparison with the static model, which is evaluated in discrete time steps. The Bernoulli risk formulation (2.14) is taken as the force of infection on FSW, and an equivalent Bernoulli risk formulation of HIV risk taken as the force of infection on the male partner population. No male partners are assumed to be taking PrEP.

Under the dynamical compartmental approach using the SIR formulation, populations of size N are divided into HIV-susceptible individuals, S, and infected individuals, I. As individuals, who are removed from the system, R, cannot return to the system, their respective equations are not set out below. Instead of a static HIV prevalence, p, for each population, prevalence changes over time according to the proportion of HIV infected individuals, $\lambda = I/N$.

The dynamic model system assumes population mortality rates μ_f and μ_m in FSWs and male partners respectively, and AIDS-related death rates of ξ_f and ξ_m respectively. The rate of recruitment into both populations are θ_f and θ_m respectively.

The model is run from 1980 to 2035, with an initial prevalence of HIV at the start of the epidemic in 1980 of p_{f_0} in FSWs and p_{m_0} in male partners. Under the baseline scenario, *Epidemic Equilibrium,* PrEP is introduced for FSWs in 2015 in line with the introduction of normative guidance in 2015 recommending that PrEP be made available to all persons at substantial risk of HIV[25]. The baseline scenario is called *Epidemic Equilibrium*, as in 2015 the HIV epidemics in these populations in South Africa had stabilised[6,7,26,27].

To account for the stage of the HIV epidemic in the model comparisons, the analyses are repeated 20 years earlier, when the HIV epidemics in FSWs and their partner populations were still increasing[6,7,26,27]. Under this scenario, *Increasing Epidemic,* PrEP is hypothetically introduced in 1995.

Given that little is known about the rate of increase in condom use in these populations over time, change in condom use from the start of the HIV epidemic is approximated by a linear increase in consistency between 1980 and the year prior to the introduction of PrEP (2014 for the *Epidemic Equilibrium* analyses, and 1994 for the *Increasing Epidemic* scenarios).

To account for changes in ART coverage over time, in the dynamic model, ART coverage is taken to be zero between 1980 and 2003. Linear scale up assumed from 2003, in line with the wide-scale introduction in South Africa[28,29] in 2003, to levels in 2012 for male partners[27] and 2014 for FSW[6] (the latest data available for each population to parameterise the model up to the final point of fitting in 2014).

The model accounts for changes in male circumcision levels in the context of the 2007 WHO and UNAIDS guidance on the scale-up of VMMC for HIV prevention[30] and the 2010 South African government's introduction of their VMMC policy and programme.[27] Due to the limited data availability on circumcision levels in Hillbrow (or by proxy, Gauteng, the South African Province in which it lies), with national survey data only available for 2003[31] and 2012[27], circumcision levels are assumed to be constant at 2003 levels between 1980 and 2003, and then increase linearly to 2012 levels and are then constant thereafter (likewise as these are the latest available data to parameterise the model up to the final point of model fitting in 2014).

For the dynamic model, the force of infection from male partners to FSW is:

$$\Pi_m = 1 - \left(1 + \lambda_m(\psi_f + \omega_f - 1)\right)^{C_m}$$

Where $\lambda_m = \frac{I_m}{N_m}$

(2.15)

The force of infection from FSW to male partners is:

$$\Pi_f = 1 - \left(1 + \lambda_f(\psi_m + \omega_m - 1)\right)^{C_f}$$

Where $\lambda_f = \frac{I_f}{N_f}$ and:

$$\psi_m = (1-\tau)\begin{pmatrix} (1-\vartheta_f)s\left(1-\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +(1-\vartheta_f)(1-s)\left(1-\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f s\left(1-(1-\varrho)\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f(1-s)\left(1-(1-\varrho)\beta_m(1-\varepsilon\gamma)\right)^{n_f} \end{pmatrix}$$

and

$$\omega_m = \tau\begin{pmatrix} (1-\vartheta_f)s\left(1-(1-\sigma_m)\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +(1-\vartheta_f)(1-s)\left(1-(1-\sigma_m)\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f s\left(1-(1-\sigma_m)(1-\varrho)\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f(1-s)\left(1-(1-\sigma_m)(1-\varrho)\beta_m(1-\varepsilon\gamma)\right)^{n_f} \end{pmatrix}$$

(2.16)

With population sizes:

$N_m = S_m + I_m$, and $N_f = S_f + I_f$

(2.17)

Balancing equation:

$$C_f = C_m N_f / N_m$$

(2.18)

Difference equations:

$$S_{f_{t+1}} = \theta_f N_{f_0} + S_{f_t} - \Pi_m S_{f_t} - \mu_f S_{f_t}$$

$$I_{f_{t+1}} = I_{f_t} + \Pi_m S_{f_t} - (\mu_f + \xi_f) I_{f_t}$$

$$S_{m_{t+1}} = \theta_m N_{m_0} + S_{m_t} - \Pi_f S_{m_t} - \mu_m S_{m_t}$$

$$I_{m_{t+1}} = I_{m_t} + \Pi_f S_{m_t} - (\mu_m + \xi_m) I_{m_t}$$

(2.19)

The dynamic model is fitted to HIV prevalence data for both FSW and male partner populations between 1980 and 2014, which are then used to parameterise both the static and dynamic models. Numerical optimizations are run to determine the lowest level in condom consistency tolerated following the introduction of PrEP without HIV risk increasing. See following sections *'Programming tool'* and '*Uncertainty analysis and model fitting'* for more methodological details.

To account for heterogeneity in risk factors, FSWs' initial condom consistencies[32,13] the parameter sets are fitted individually for initial condom consistencies (prior to introduction of PrEP) of 10%, 40% and 70%, spanning the range reported by this population.[32]

At the time of undertaking this study, available data relating levels of PrEP adherence to HIV risk reduction in women were limited to recognition that up to 100% risk reduction on PrEP necessitates higher levels of adherence in women (6/7 tablets a week) than in men (4/5 in MSM and TGW)[33]. As such, the analysis spans a spectrum of potential levels of PrEP use-effectiveness (HIV risk reduction corresponding to a level of adherence): 25%, 55% and 85%. PrEP use-effectiveness of 85% was simulated as the highest level, as it equates to the threshold at which PrEP will always increase the level of HIV protection irrespective of the level of condom use, using equation 2.6 from the static model analysis in Research Paper 1 and the risk reduction efficacy of condoms as 85%[34,35].

The percentage reduction in condom consistency that can be tolerated was calculated across these levels of initial condom consistency and PrEP use-effectiveness.

Programming tool

The equations were evaluated in R[5], a more flexible programming platform that is a facilitates the evaluation of more complex model formulations, such as dynamical systems. Optimisations algorithms are run using R FME package[36] for the dynamic model and R rootSolve package[37] for the static model.

Uncertainty analysis and model fitting

The dynamic model is fitted to HIV prevalence data for both FSW and male partner populations between 1980 and 2014 using Bayesian Monte Carlo methods with Latin Hypercube Sampling (R FME package[36]), run on 50,000 parameter sets, yielding at least 200 fits for each scenario explored. Both the static and dynamic models are parameterised and evaluated using the same set of fitted

parameters, allowing for the evaluation of uncertainty ranges in both models. Monte Carlo filtering with Latin Hypercube Sampling assuming uniform prior distributions was chosen as the Bayesian method for accounting for parametric uncertainty and model fitting, as it feels to me a discernible and intuitive approach, which may be easier to explain to policy makers, and where each stage of the calculations can be easily extracted and communicated. Other methods for calculating the likelihood function in Bayesian approaches such as, for example, the Markov Chain random walk in MCMC, may be seen as a more 'black box' and less accessible by policy makers.

To explore a level of model structural sensitivity, the Research Paper explores the model's sensitivity to heterogeneity in the number of parameters. This is undertaken by removing all parameters related ART, circumcision and STIs, re-running the analyses and comparing the conclusions.

To further explore the sensitivity of the model to stage of the epidemic (in addition to PrEP being introduced in 1995 the *Increasing Epidemic* and 2015 in the *Epidemic Equilibrium* scenarios), a further scenario is evaluated, where PrEP is introduced when the epidemics are fully endemic in the populations, called the *Fully Endemic* scenario. The underlying epidemic curves for each of these scenarios are show in the Annex to this thesis, in Supplementary Materials to Research Paper 2.

2.4 Research Paper 3

2.4.1 Research Paper Objectives

Research Paper 3 aims to address PhD Objectives 4 and 5; specifically:

4. To explore strategies for the scale-up of PrEP across high-risk women at population-level, weighing considerations around HIV infection reduction and cost-effectiveness
5. To evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa, to explore how the approach to PrEP scale-up may differ by epidemic and implementation context

2.4.2 Rationale for Research Paper Setting

In order to evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa and assess how model outcomes change by epidemic and implementation context, Research Paper 3 applies modelling to three HIV endemic countries in SSA that span a range of HIV burden levels in the region: South Africa (20.4% adult HIV prevalence), Zimbabwe (12.7% adult HIV prevalence) and Kenya (4.7% adult HIV prevalence)[38]. These countries were chosen as, in addition to spanning a range of HIV burden levels in the region, they each have adopted a national PrEP strategy[39–41] and have been at the forefront of PrEP roll-out in sub-Saharan Africa[42].

2.4.3 Overview of Methods

The HIV epidemics in South Africa, Zimbabwe and Kenya are stable generalized high-prevalence epidemics[8,26]. Given that to date, few PrEP demonstration programs have achieved significant retention in women in this context beyond the first 12 months[43–50], as well as that PrEP is intended to cover seasons of HIV risk, the analyses of Research Paper 3 are conducted over a one-year timeframe. Based on the conclusions of Research Paper 2 that static models are sufficiently robust to model the introduction of an HIV prevention intervention over short-medium time horizons in contexts where the HIV epidemics are well established, Research Paper 3 adopts a static model of HIV risk.

Simple tools to help guide PrEP programme decision making

First, simple tools are developed to help guide policy makers and PrEP programmers make decisions around the scale-up of PrEP for high-risk women using a basic set of information that may typically be available in implementation settings[51].

In this Research Paper, we do not explore the effects of behavioural disinhibition, since this has been addressed through Research Papers 1 and 2. Accordingly, condom use is denoted γ independent of PrEP status. Additionally, the basic HIV risk equations (2.1) and (2.2) are refined to capture 12-month PrEP programme retention levels, r. HIV risk equations (2.1) and (2.2) therefore become, respectively:

On PrEP:

$$\pi(\gamma, b_\alpha) = 1 - \left(p\left(1 - \beta_f(1 - r\theta_\alpha)(1 - \varepsilon\gamma)\right)^n + (1 - p)\right)^C,$$

(2.20)

and in the absence of PrEP:

$$\pi(\gamma, 0) = 1 - \left(p\left(1 - \beta_f(1 - \varepsilon\gamma)\right)^n + (1 - p)\right)^C.$$

(2.21)

Heatmaps to estimate HIV incidence in women

Heatmaps are developed to help decision makers estimate the annual HIV incidence in women by number of monthly sex acts, average condom use and underlying epidemic setting, assuming a simple partner population and the simple risk equation set out in equation (2.21). Heterogeneity in epidemic setting is accounted for by assessing HIV prevalence in male partner populations of 5%, 10%, 20% and 40% (giving rise to one heatmap each). These prevalence levels are chosen to illustrate different epidemic settings, as across many sub-Saharan African contexts, 5% HIV prevalence may be consistent with HIV prevalence in males 15-24 years, 5-20% the HIV prevalence in males 25-49 years, and 20-40% the HIV prevalence in the clients of FSW (depending on the setting)[8,38]. Heatmaps are chosen as a user-friendly tool to represent the outcomes of multiple interacting scenarios for policy makers[52–54].

Within each heatmap, heterogeneity in number of sex acts and average condom use are accounted for by varying the average number of monthly sex acts between 0 and 40 (an upper bound for

women in this context[55–59]) and illustratively varying condom use between 0% and 100%. On the heatmaps, the threshold for a resulting annual incidence of 3 per 100 person years is marked, signifying the threshold for PrEP eligibility according to WHO guidelines[60]. To account for heterogeneity in the other risk factors in equation (2.21) within the heatmaps, parameters sets for r, β, ε and n (corresponding to levels of m) spanning the spectra reported for women in SSA were obtained from the literature, and used to simulate equation (2.21) across all permutations and combinations, giving yield to 720,000 distinct parameter sets.

Simple rule to assess relative cost-effectiveness of PrEP scale-up from a group of high- to lower-risk women

A simple rule is then developed to help policy makers estimate the relative cost at which PrEP will be equally as cost-effective between two groups of women with different HIV risk factors and behaviours. In the absence of willingness-to-pay thresholds, cost-effectiveness is assessed by comparing estimates of cost per infection averted between populations.

It is assumed that one woman comes from a comparatively higher-risk population (e.g. FSW) and the other from a comparatively lower-risk female population, with the women denoted $H$and L respectively. π_H and π_L are the respective HIV risks for each woman. Let $\$X_H$ and $\$X_L$be the 12-month unit costs of PrEP for each woman (the incremental cost of PrEP for a woman retained in a PrEP program over a 12-month period).

Then the cost of averting one HIV infection with PrEP per year for each woman is $\frac{\$X_H}{\pi_H(\gamma,0)-\pi_H(\gamma,\alpha_H)}$ and $\frac{\$X_L}{\pi_L(\gamma,0)-\pi_L(\gamma,\alpha_L)}$ respectively.

PrEP will become equally cost-effective in the lower-risk group as it is in the higher-risk group where:

$$\frac{\$X_L}{\pi_L(\gamma,0)-\pi_L(\gamma,\alpha_L)} = \frac{\$X_H}{\pi_H(\gamma,0)-\pi_H(\gamma,\alpha_H)},$$

(2.22)

or when:

$$\frac{\$X_L}{\$X_H} = \frac{\pi_L(\gamma,0)-\pi_L(\gamma,\alpha_L)}{\pi_H(\gamma,0)-\pi_H(\gamma,\alpha_H)}.$$

(2.23)

To derive a simple formulation of (2.23) that may be more intuitive for policy makers and programmers in real-world settings, equations (2.20) and (2.21) are simplified through a first order Binomial expansion[61]. Using the example of equation (2.20), provided $\beta(1-rb_\alpha)(1-\varepsilon\gamma) \ll 1$ we have:

$$\pi(\gamma, b_\alpha) \approx 1 - \Big(p\Big(1 - n\beta_f(1-r\theta_\alpha)(1-\varepsilon\gamma)\Big) + (1-p)\Big)^C$$

$$\approx 1 - \Big(1 - pn\beta_f(1-rb_\alpha)(1-\varepsilon\gamma)\Big)^C,$$

and provided $pn\beta_f(1-rb_\alpha)(1-\varepsilon\gamma) \ll 1$:

$$\pi(\gamma, b_\alpha) \approx Cpn\beta_f(1-rb_\alpha)(1-\varepsilon\gamma).$$

(2.24)

Thus the risk reduction on PrEP is approximately:

$$Cpn\beta(1-\varepsilon\gamma) - Cpn\beta(1-rb_\alpha)(1-\varepsilon\gamma)$$

Which simplifies to:

$$Cpn\beta(1-\varepsilon\gamma)rb_\alpha.$$

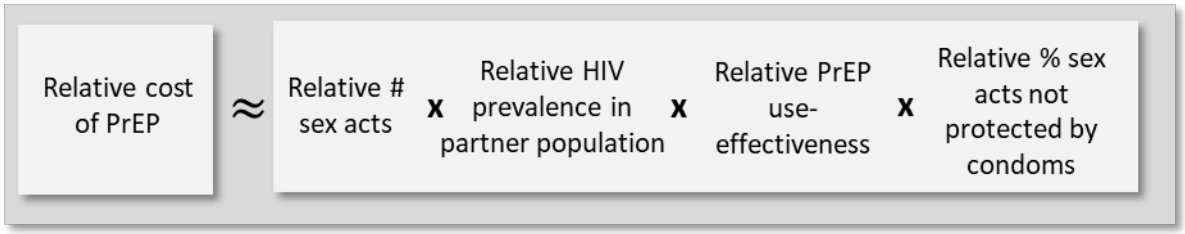
(2.25)

Therefore, when $\beta(1-rb_\alpha)(1-\varepsilon\gamma) \ll 1$ and $pn\beta(1-rb_\alpha)(1-\varepsilon\gamma) \ll 1$,the condition for equal cost-effectiveness in equation (2.23) between two female populations with different risk levels becomes:

$$\frac{\$X_L}{\$X_H} = \frac{C_L n_L p_L (1-\varepsilon\gamma_L) r_L b_{\alpha_L}}{C_H n_H p_H (1-\varepsilon\gamma_H) r_H b_{\alpha_H}}$$

(2.26)

In a simplified form for policy makers, the relative cost of PrEP at which it will be equally as cost-effective to roll out PrEP for lower-risk women compared to higher-risk women is summarised below in equation (2.27).



(2.27)

Now that the equations have been refined to account for PrEP programme retention, use-effectiveness of PrEP is defined as the HIV-risk reduction through use of PrEP at a given level of adherence, for a population with a given average program retention level.

Heatmaps to estimate the relative unit cost at which PrEP scale-up from higher- to lower-risk women is cost-effective

Heatmaps are developed to help decision makers estimate the relative unit cost at which it will be cost-effective to scale up PrEP from a comparatively higher- to comparatively lower-risk woman, using a limited set of data typically available at country level[51] and equation (2.23). Heterogeneity in epidemic setting is accounted for by accounting for HIV prevalence in the higher-risk women's partner population of 20% and 40%, and for each, simulating 4 cases for the lower-risk women's partner population at 1/4, 1/2, 3/4 and 1 times the prevalence of the higher-risk women's partner population (i.e. 5%, 10%, 15% and 20%; and 10%, 20%, 30% and 40% respectively). These levels of male partner HIV prevalences span a range of the levels seen across SSA settings[8,38]. This gives rise to two groups of four heatmaps.

Heterogeneity in condom use and number of sex acts a month are accounted for by varying the relative condom use between the lower- and higher-risk women between 0% and 150%, and the relative number of sex acts a month between the lower- and higher-risk women between 0% and 150%. In view of limited data available on PrEP retention and levels of HIV risk-reduction from PrEP demonstration and implementation projects for women, this study used the most granular available data at the time of the analysis from projects among women in SSA. Accordingly, it was assumed that the higher-risk group had 22% 12-month PrEP program retention levels and all women retained had PrEP adherence levels of 70-85% (corresponding to risk-reduction of 73-99%[62]), consistent with the South African TAPS demonstration project in FSW[43]. PrEP program retention for the lower-risk group was simulated between $\pm$25% of the 22% retention levels of the higher-risk group (i.e. 16.5%-27.5%), consistent with the difference between AGYW (the group with the largest difference in retention levels among females across available studies at the time of the analysis) and FSW retention in Kenya[44]. For lower-risk women retained in the PrEP program, it was assumed that PrEP adherence was the same as the higher-risk group (in the absence of available PrEP adherence data at the time of the study, other than from the TaPS project among FSW)[43].

Using the same approach as for the first set of heatmaps to account for heterogeneity in the other risk factors in equation (2.23) within the heatmaps, parameters sets for the remaining parameters spanning the spectra reported for women in SSA were obtained from the literature, and used to simulate equation (2.23) across all permutations and combinations, giving yield to 7,920,000 distinct parameter sets.

Assessment of strategies to guide PrEP-scale up across women on a spectrum HIV risk

To assess strategies to guide PrEP scale-up across women on a spectrum of risk, in addition to FSW, Research Paper 3 considers women at HIV risk to include the following groups: 15-24 years, women 25-34 years and women 35-49 years. These three groups of women in the general population are included in addition to FSW (who are well recognised at high risk of HIV), as HIV incidence data from all three country case study settings (South Africa[63,64], Zimbabwe[65] and Kenya[38]) reveal elevated levels of incidence among each of these groups, with the incidence patterns between the groups also varying by country. Whilst broad groupings, they have the advantage of being intuitive and easy to operationalize in country settings. The set of high-risk women groups considered in the analysis, j, is therefore $j := \{$FSW, adolescent girls and young women aged 15-24 years (AGYW), women 25-34 years and women 35-49 years$\}$.

Based on available data from the literature, AGYW are assumed to have partners drawn from their own age group and also the 25-34 years age group, given that 17% and 14% women 15-19 years report relationships with men at least 10 years older in Zimbabwe[66] and Kenya[67] respectively, and 36% South African women 15-19 years report relationships with men at least 5 years older[7]. Women 25-34 years and women 35-49 years are assumed to have partners drawn from their own age groups. FSW are assumed to have partners drawn from two populations: regular partners and clients. The set of partner populations across high-risk women groups, i, is $i := \{$men 15-24 years, men 25-34 years, men 35-49 years, men 15-49 years (regular partners of FSW), and clients of FSW$\}$.

As above, FSW are assumed to have 12-month PrEP program retention and adherence levels consistent with the South African TaPS demonstration project.[43] All other high-risk women groups were assumed to have program retention levels between $\pm$25% of FSW retention levels,[44] and the same adherence levels as FSW retained in the program. To explore the role of adherence, the analyses were repeated with 25% lower HIV risk-reduction across all groups (see section '*Uncertainty analyses'*).

To assess strategies for the scale-up of PrEP across these groups of high-risk women, risk equations (2.20) and (2.21) are modified to account for HIV risk at population-level, rather than individual-level, and to account for multi-partner populations.

The total population size of high-risk women group of type j is N_j, in which the prevalence of HIV is p_j. The coverage of PrEP in the population j is ω_j. High-risk women are assumed to have C_i number of partners from each population a year, with whom they have an average of n_i sex acts a year each. Condoms are assumed to be used with partners from each population with consistency γ_{ij}.

Parameter s_{ij} is the probability that at least one person in the partnership between high risk woman from population j and partner from population i has an STI and ϑ_i is the proportion of HIV+ partners from population i that are virally suppressed on ART. The proportion of male partners from population i that are circumcised is denoted by τ_i

Upon introduction, high-risk women from population j are assumed to adhere to PrEP at an average level α_j, which corresponds to a level of HIV risk reduction, b_{α_j}. They are assumed to have 12-month program retention levels r_j. Sex acts are assumed to be peno-vaginal, the predominant pathway of HIV transmission to heterosexual women in sub-Saharan Africa[68].

Where high-risk women from population j have partners drawn from a single male population, their HIV risk for a 12-month period, is in the absence of PrEP is given by:

$$\Pi(0) = 1 - \big(p(\psi_{(1-\tau),0} + \psi_{\tau,0}) + (1-p)\big)^C$$

Where:

$$\psi_{(1-\tau),0} = (1-\tau)\big((1-\vartheta)s(\,1-\delta\varsigma)^n + (1-\vartheta)(1-s)(\,1-\varsigma)^n + \vartheta s(\,1-(1-\varrho)\delta\varsigma)^n + \vartheta(1-s)(\,1-(1-\varrho)\varsigma)^n\big)$$

$$\psi_{\tau,0} = \tau\big((1-\vartheta)s(\,1-(1-\sigma)\delta\varsigma)^n + (1-\vartheta)(1-s)(\,1-(1-\sigma)\varsigma)^n + \vartheta s(\,1-(1-\sigma)(1-\varrho)\delta\varsigma)^n + \vartheta(1-s)(\,1-(1-\sigma)(1-\varrho)\varsigma)^n\big),$$

with $\varsigma = \beta_f(1-\varepsilon\gamma)$.

(2.28)

When women are enrolled on PrEP, their HIV risk for a 12-month period is:

$$\Pi(rb_\alpha) = 1 - \big(p(\psi_{(1-\tau),rb_\alpha} + \psi_{\tau,\ rb_\alpha}) + (1-p)\big)^C .$$

Here:

$$\psi_{(1-\tau),\,rb_\alpha} = (1-\tau)\big((1-\vartheta)s(\,1-\delta\kappa)^n + (1-\vartheta)(1-s)(\,1-\kappa)^n + \vartheta s(\,1-(1-\varrho)\delta\kappa)^n + \vartheta(1-s)(\,1-(1-\varrho)\kappa)^n\big)$$

$$\psi_{\tau,\,rb_\alpha} = \tau\big((1-\vartheta)s(\,1-(1-\sigma)\delta\kappa)^n + (1-\vartheta)(1-s)(\,1-(1-\sigma)\kappa)^n + \vartheta s(\,1-(1-\sigma)(1-\varrho)\delta\kappa)^n + \vartheta(1-s)(\,1-(1-\sigma)(1-\varrho)\kappa)^n\big),$$

with $\kappa = \beta_f(1-rb_\alpha)(1-\varepsilon\gamma)$

(2.29)

Where high-risk women from population j have partners drawn from two male populations, denoted 1 and 2, their HIV risk for a 12-month period, in the absence of PrEP is:

$$\Pi(0) = 1 - \big(p_1(\psi^1_{(1-\tau),0} + \psi^1_{\tau,0}) + (1-p_1)\big)^{C_1}\big(p_2(\psi^2_{(1-\tau),0} + \psi^2_{\tau,0}) + (1-p_2)\big)^{C_2}$$

Where

$$\psi^1_{(1-\tau),0} = (1-\tau_1)\big((1-\vartheta_1)s_1(\,1-\delta\varsigma_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-\varsigma_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\varrho)\delta\varsigma_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\varrho)\varsigma_1)^{n_1}\big)$$

$$\psi^1_{\tau,0} = \tau_1\big((1-\vartheta_1)s_1(\,1-(1-\sigma)\delta\varsigma_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-(1-\sigma)\varsigma_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\sigma)(1-\varrho)\delta\varsigma_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\sigma)(1-\varrho)\varsigma_1)^{n_1}\big)$$

With $\varsigma_1 = \beta_f(1-\varepsilon\gamma_1)$

And,

$$\psi^2_{(1-\tau),0} = (1-\tau_2)\big((1-\vartheta_2)s_2(\,1-\delta\varsigma_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-\varsigma_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\varrho)\delta\varsigma_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\varrho)\varsigma_2)^{n_2}\big)$$

$$\psi^2_{\tau,0} = \tau_2\big((1-\vartheta_2)s_2(\,1-(1-\sigma)\delta\varsigma_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-(1-\sigma)\varsigma_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\sigma)(1-\varrho)\delta\varsigma_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\sigma)(1-\varrho)\varsigma_2)^{n_2}\big)$$

With $\varsigma_2 = \beta_f(1-\varepsilon\gamma_2)$

(2.30)

Where women are enrolled on PrEP, their HIV risk for a 12-month period is:

$$\Pi(\mathrm{r_j}b_{\alpha_\mathrm{j}}) = 1 - \big(p_1(\psi^1_{(1-\tau),\,rb_\alpha} + \psi^1_{\tau,\,rb_\alpha}) + (1-p_1)\big)^{C_1}\big(p_2(\psi^2_{(1-\tau),\,rb_\alpha} + \psi^2_{\tau,\,rb_\alpha}) + (1-p_2)\big)^{C_2}$$

Where $j = 1$, with:

$$\psi^1_{(1-\tau),\,rb_\alpha} = (1-\tau_1)\big((1-\vartheta_1)s_1(\,1-\delta\kappa_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-\kappa_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\varrho)\delta\kappa_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\varrho)\kappa_1)^{n_1}\big)$$

$$\psi^1_{\tau,\,rb_\alpha} = \tau_1\big((1-\vartheta_1)s_1(\,1-(1-\sigma)\delta\kappa_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-(1-\sigma)\kappa_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\sigma)(1-\varrho)\delta\kappa_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\sigma)(1-\varrho)\kappa_1)^{n_1}\big)$$

With:

$\kappa_1 = \beta_f(1-rb_\alpha)(1-\varepsilon\gamma_1)$

And, $j = 2$, with:

$$\psi^2_{(1-\tau),\,rb_\alpha} = (1-\tau_2)\big((1-\vartheta_2)s_2(\,1-\delta\kappa_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-\kappa_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\varrho)\delta\kappa_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\varrho)\kappa_2)^{n_2}\big)$$

$$\psi^2_{\tau,\,rb_\alpha} = \tau_2\big((1-\vartheta_2)s_2(\,1-(1-\sigma)\delta\kappa_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-(1-\sigma)\kappa_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\sigma)(1-\varrho)\delta\kappa_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\sigma)(1-\varrho)\kappa_2)^{n_2}\big)$$

With $\kappa_2 = \beta_f(1-rb_\alpha)(1-\varepsilon\gamma_2)$

(2.31)

To assess the relative impact and cost-effectiveness of PrEP scale-up, FSW are taken as the benchmark against which other high-risk women groups are assessed, as they are priority groups for PrEP roll-out in the three country settings[39,40,41] in view of their very high levels of HIV risk[6,58,68,69]. The following analytical relations are derived to guide the PrEP scale-up analysis.

Let $\$Y_j$ be the unit cost per high risk woman from population $j \neq FSW$ retained in a PrEP program for population j, with 12-month retention level r_j, and $\$Y_{FSW}$ the equivalent unit cost for a FSW PrEP program per FSW retained with 12-month retention level r_{FSW}.

The program's cost to avert 1 infection per year due to PrEP in each population is $\frac{\$Y_j}{\Pi_j(0)-\Pi_j(r_j b_{\alpha_j})}$ and $\frac{\$Y_{FSW}}{\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}})}$ respectively.

Building on equation (2.23), a PrEP program for high risk population $j \neq FSW$ will then be equally as cost-effective per infection averted due to PrEP, as it is for FSW, where:

$$\frac{\$Y_j}{\$Y_{FSW}} = \frac{\Pi_j(0)-\Pi_j(r_j b_{\alpha_j})}{\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}})}$$

(2.32)

To determine the coverage, ω_j, of PrEP in high-risk woman population $j \neq FSW$ needed to achieve the same risk reduction as coverage ω_{FSW} in FSW, we have:

$$\omega_j N_j (1 - p_j)\left(\Pi_j(0) - \Pi_j(r_j b_{\alpha_j})\right) = \omega_{FSW} N_{FSW}(1 - p_{FSW})\left(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}})\right)$$

(2.33)

Which is when:

$$\omega_j = \omega_{FSW} \frac{N_{FSW}(1 - p_{FSW})\left(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}})\right)}{N_j(1 - p_j)\left(\Pi_j(0) - \Pi_j(r_j b_{\alpha_j})\right)}$$

(2.34)

These levels of coverage would be at a relative total cost of:

$$\frac{\$Y_j \omega_j N_j (1-p_j)}{\$Y_{FSW} \omega_{FSW} N_{FSW} (1-p_{FSW})}$$

(2.35)

If PrEP were to be scaled up at equal coverage in both populations, then the relative number of infections averted per year in high-risk woman population $j \neq FSW$ with respect to the FSW population would be:

$$\frac{N_j (1-p_j)(\Pi_j(0) - \Pi_j(r_j b_{\alpha_j}))}{N_{FSW}(1-p_{FSW})(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}}))}$$

(2.36)

This is equivalent to the relative total maximum number of infections averted per year if PrEP programs were scaled up to all HIV negative women in each population.

For each $\$100k$ available for PrEP programming for each population, the estimated number of infections averted a year in each population would be, in high-risk women $j \neq FSW$:

$$\frac{\$100k}{\$Y_j}(\Pi_j(0) - \Pi_j(r_j b_{\alpha_j})),$$

In FSW:

$$\frac{\$100k}{\$Y_{FSW}}(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}}))$$

(2.37)

The proportion of the potential total number of infections that could be averted a year in each population with $\$100k$, in high-risk women $j \neq FSW$, is:

$$\frac{\$100k.(\Pi_j(0)-\Pi_j(r_j b_{\alpha_j}))}{\$Y_j.N_j(1-p_j).\Pi_j(0)}$$

In FSW:

$$\frac{\$100k.(\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW} b_{\alpha_{FSW}}))}{\$Y_{FSW}.N_{FSW}(1-p_{FSW}).\Pi_{FSW}(0)}$$

(2.38)

Estimation of current PrEP unit costs per person retained after 12-months

In order to be able to compare the relative costs at which PrEP scale-up from FSW to another high-risk group is equally cost-effective to current relevant unit costs between the populations, estimates of the current cost of PrEP per person retained after 12-months for each high-risk women group were developed. These estimates of the current costs of PrEP for each group of high-risk women in each of South Africa, Zimbabwe and Kenya were developed by Dr Gabriela Gomez, a Health Economist. The following costing methodology was developed by Dr Gomez:

To estimate the cost of PrEP to each high-risk group of women, FSW were assumed to be offered PrEP through programmes with outreach and community mobilisation components. All other women were assumed to be offered PrEP through sexual and reproductive health services, with services for AGYW having larger counselling components. Cost data were reviewed from PrEP OLE, demonstration and implementation projects and previous PrEP costing publications in Kenya[70,71] and South Africa[43] (None were available from Zimbabwe).

Cost estimates were disaggregated into service delivery and drug costs. The reported drug costs were replaced by a range of $57-80 per year. The lower bound is the internationally traded value of USD3.75 with a 25% top up of freight and distribution costs in country (15% shipping and handling charges, and 10% for drug distribution costs)[72]. The high bound is the highest reported price for drugs in the demonstration projects - 30 days of TDF/FTC at $6.75. For Zimbabwe, in addition to drug costs, non-tradable components of the South African estimates were transferred using purchasing power parities[73] following standard methods[74]. All previously published costs were adjusted to $2017[75]. The amounts and detailed assumptions underpinning the estimated unit costs for each

high-risk women group by country are set out in the Annex to this thesis, in Supplementary Materials to Research Paper 3.

Analyses to inform strategies for PrEP scale-up

The following analyses were undertaken to inform strategies for PrEP scale-up across high-risk women in each country context.

First, the maximum unit costs of PrEP for non-FSW high-risk women relative to FSW is estimated, for scale-up to be equally as cost-effective as it is in FSW, for all three countries using equation (2.32). These are compared to the current estimated relative unit costs of PrEP between for non-FSW high-risk women and FSW as set out in the '*Estimation of current PrEP unit costs per person retained after 12-months'* section above.

Then, the number of infections that could be averted a year due to PrEP in each high-risk women population group are estimated, in each country, for every $100,000 available for PrEP programming using equation (2.37). The proportion of HIV infections that could be averted a year for every $100,000 allocated to each group is estimated using equation (2.38).

Finally, given the differences in relative population sizes between the high-risk women groups in each country, the relative number of HIV infections that could be averted a year with PrEP at equal coverage levels across all high-risk women groups is each country is estimated using equation (2.36).

Programming tool

The equations for Research Paper 3 were also evaluated in R^5, as flexible programming platform that facilitates fitting the model equations to incidence data and for running and storage of the results of multiple country and population simulations.

Uncertainty analysis

Parametric uncertainty: Data ranges to parameterise the models for each high-risk women group are fitted to the latest national estimates of HIV incidence by population and country using Bayesian Monte Carlo methods with Latin Hypercube Sampling assuming uniform prior distributions using the R PSE Package[76], giving yield to at least 200 sets of parameter fits for each high-risk woman population modelled and allowing for the evaluation of uncertainty ranges.

Two further parametric uncertainty analyses are undertaken, to assess the sensitivity of the model results to the PrEP adherence levels assumed for all non-FSW high-risk women groups, given the particular uncertainty around the data parameterization. At the time of undertaking the analysis, there were no PrEP adherence data available for women other than for FSW under the TaSP demonstration project in South Africa[43]. As such, for non-FSW high-risk women groups PrEP adherence was taken to be the same as in FSW. To explore the sensitivity of the results to this assumed level of PrEP adherence, the analyses were repeated with 1) 25% lower (not higher, as the existing upper bound is 99%) HIV risk-reduction across all groups; and 2) 25% lower HIV risk-reduction across AGYW, women 25-34 years and women 35-49 years (but unchanged among FSW).

Structural sensitivity: Whist the literature only provides evidence of women aged 15-25 years having male partners from an older population group in these three settings, we explored how the model outcomes change if women aged 25-34 years are also assumed to have male partners from an older population group (35-49 years) with higher HIV prevalence. This model structural sensitivity analysis was parameterised illustratively assuming 50% the number of partners a year from the male population 35-49 years as had by women 35-49 years (in addition to their partnerships with males 25-34 years).

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Chapter 3

3. Research Paper 1: When are declines in condom use while using PrEP a concern? Modelling insights from a Hillbrow, South Africa case study

3.1 Introduction to Research Paper 1

Research Paper 1 aims to respond to objectives 1 and 2 of the thesis by assessing how behavioural disinhibition may affect the potential HIV risk reduction of PrEP for high-risk women. It addresses this question considering a spectrum of different baseline condom consistencies (prior to the introduction of PrEP) and for different levels of HIV risk reduction achieved on PrEP. The study aims to assist policy makers in identifying and focusing programming efforts on women likely to be at increased risk of HIV should behavioural disinhibition occur in PrEP programs.

This study is applied to a particularly high HIV risk population and high HIV risk setting - to FSW, who typically have significantly elevated levels of HIV risk compared to women in the general population[1], and to the setting of Hillbrow, in inner Johannesburg, South Africa. Specifically, in this context, female sex workers are estimated to have extremely high HIV prevalence levels of 72%[2], with high prevalence levels of HIV among men in the general population (26% (95% confidence interval: 23-29%) among men aged 25-49) [3].

At the time this study was undertaken, PrEP had yet to be rolled out in South Africa, and was being explored through demonstration projects, such as the TaPS[4] demonstration project for female sex workers in Hillbrow, which serves as the setting for this modelling study. No studies had yet equated levels of PrEP adherence to levels of HIV risk reduction in women, nor determined whether the levels of PrEP adherence needed to be the same between men and women to achieve the same levels of HIV risk reduction. This study was the first to use mathematical models to explore the effect of different levels of PrEP adherence-associated HIV risk reduction in women on PrEP programme outcomes, with the aim of informing policy on PrEP roll-out.

Given the lack of data available at the time to equate level of PrEP adherence with levels of HIV risk reduction in women, this study refers to data from a demonstration project in MSM and TGW to indicatively link levels of HIV risk reduction to numbers of PrEP tablets taken a week by female sex workers[5]. It has since been recognised that 100% risk reduction on PrEP necessitates higher levels of adherence in women (6 out of 7 tablets a week, mode of transmission through heterosexual

intercourse) than in men (4 out if 5 in MSM and TGW, mode of transmission through anal intercourse).[6]

3.2 Cover Sheet

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Hannah Grant
Principal Supervisor	Professor Graham Medley
Thesis Title	The scale-up of PrEP for HIV prevention in high-risk women in sub-Saharan Africa: use of mathematical modelling to inform policy making

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

SECTION B – Paper already published

Where was the work published?	Journal of the International AIDS Society		
When was the work published?	20 September 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

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

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	

Student Signature: [redacted] **Date:** 14/11/19

Supervisor Signature: [redacted] **Date:** **14 November 2019**

3.3 Research Paper 1

When are declines in condom use while using PrEP a concern? Modelling insights from a Hillbrow, South Africa case study

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Abstract

Objectives: To assess whether decreased levels of condom use following introduction of oral pre-exposure prophylaxis (PrEP) might limit HIV risk reduction for female sex workers (FSWs).

Design: A static mathematical model of HIV risk.

Methods: We compared HIV risk estimates before and after the introduction of PrEP to determine the maximum tolerated reductions in condom use with regular partners and clients for HIV risk not to change. The model incorporated the effects of increased STI exposure owing to decreased condom use. Noting that condom use with regular partners is generally low, we also estimated the change in condom use tolerated with clients only, to still achieve 50% and 90% risk reduction on PrEP. The model was parameterised using data from Hillbrow, Johannesburg. Sensitivity analyses were performed to ascertain the robustness of our results.

Results: Reductions in condom use could be tolerated by FSWs with lower baseline condom use (<50%), or where PrEP effectiveness achieved is reasonably high (>65%). For scenarios where 75% PrEP effectiveness is attained, 50% HIV risk reduction on PrEP would be possible even with 100% reduction in condom use from consistent condom use as high as 70% with clients. Increased exposure to STIs through reductions in condom use had limited effect on the reductions in condom use tolerated for HIV risk not to increase on PrEP.

Conclusions: PrEP is likely to be of benefit in reducing HIV risk, even if reductions in condom use does occur. Efforts to promote consistent condom use will be critical for FSWs with high initial levels of condom use, but with challenges in adhering to PrEP.

Conflicts of Interest and Source of Funding: The authors declare no conflicts of interest.

Contributions: HG and CW designed the study. All authors input into the analyses and contributed to the writing of the paper.

Introduction

Oral pre-exposure prophylaxis (PrEP) is a promising approach to HIV prevention. It is hoped that PrEP might become an effective addition to combined HIV prevention and help to significantly reduce HIV risk for vulnerable groups. This would be especially critical for those populations with low ability to negotiate condom use due to gender and societal power imbalances, such as young women in heterosexual relationships[7] and sex workers[8]. Proof of concept has been demonstrated[9] in four out of the six randomized controlled trials conducted to date, in which higher levels of HIV risk reduction were associated with higher levels of adherence. Open label extension studies[9–12] have confirmed PrEP's importance as a prevention tool, with up to 100% risk reduction estimated in the Open Label Extension (OLE) of the iPrEx trial[13] for men and transgender women who have sex with men adhering to PrEP for at least four out of seven doses a week.

Nonetheless, the two randomised controlled trials[14,15] stopped early for futility cited lack of adherence by the study populations as the cause. Additional implementation concerns have been raised, including antiretroviral (ARV) resistance development resulting from sub-optimal drug adherence levels[16], contraindications[17], challenges in acceptability[18], barriers to access and programme retention[19], and behaviour change[20–24]. Noting both the positive trial results as well as implementation concerns, in July 2012 the World Health Organisation (WHO) [25] called for countries to undertake demonstration projects to gain insight into acceptability, patterns of use, and sustainability of PrEP.

Data since gathered has informed WHO's September 2015 PrEP guidance[26] recommending oral PrEP for all people at substantial risk of HIV (incidence >3 per 100 person years). However, concerns remain[27–31] regarding the potential limiting effects of a particular form of behaviour change - reductions in condom use ("condom migration") - on PrEP. Reductions in condom use not only increase the chance of HIV exposure, but also the exposure to and transmission of sexually transmitted infections (STIs). Increased exposure to STIs increases both the susceptibility of an HIV negative partner, as well as the infectiousness of an HIV positive partner, and thereby HIV transmission[32]. Whilst no trial to date has reported decreased condom use, the high rate of pregnancies reported in the trials[18], results of behavioural surveys[33] and qualitative research[19] indicate that efforts to tackle condom migration may need to be considered in the design of PrEP programmes.

In response to these concerns and to inform PrEP programme design, this study examines the extent to which condom migration is likely to impact PrEP effectiveness in programmes for female sex workers (FSWs). We focus on the FSW population working in Hillbrow, Johannesburg, some of whom

are participating in a PrEP demonstration programme undertaken by the Wits Reproductive Health and HIV Institute (WRHI)[34]. The FSW populations in this setting present extremely high baseline HIV prevalence (estimated to be up to 72%[2,35]), elevated levels of STIs[2,36], low levels of condom use with often high HIV risk[37] regular partners, and known challenges in condom negotiation with clients, where in such settings FSWs may receive a quarter of the average price for transactional sex if condoms are insisted upon[23].

Our study aims to inform rapidly changing policy in South Africa where in November 2015, South Africa's Medicines Control Council approved the use of the fixed-dose combination of TDF/FTC as PrEP[38]. Locally-adapted guidelines[39] were published in early 2016 and PrEP was recently included in South Africa's National Sex Worker HIV Plan (2016–2019)[40]. PrEP roll out for sex workers started in June 2016.

Methods

This work builds on that in Foss et al[41], where an adaption of an HIV risk equation was used to assess microbicides as a new HIV prevention method. This study uses the established Bernoulli model of HIV transmission[42–45] where the probability of the HIV virus being transmitted through each sexual contact is treated as an independent risk event. We employed static rather than dynamic mathematical modelling to obtain clear deductions regarding the contribution of the parameters being explored to HIV risk, and for the derivation of rules of thumb that can be broadly understood and applied to HIV prevention efforts focused on FSWs. Whilst previous studies[41,46,47] have used mathematical modelling to predict the impact of condom migration on the effectiveness of ARV-based microbicides, this is the first study to consider its impact on oral PrEP, in particular for FSWs.

The HIV risk equations for a population of HIV-negative FSWs and their partners prior to, and following introduction of, PrEP are outlined in the *Supplementary Methods*. To explore the consequences for FSWs of condom migration on PrEP, condoms are assumed to be used with consistency that may vary with the introduction of PrEP (γ_0 prior to PrEP introduction and γ_1 after its introduction). We assumed condoms to have an HIV risk reduction efficacy, ε, including slippage and breakage. Whilst the risk reduction effectiveness of condoms is generally assumed to follow a linear relationship between use and efficacy ($\varepsilon\gamma$), the exact effectiveness relationship between adherence and PrEP efficacy remains under investigation[48–50] (although one study suggested a linear relationship[51]), so we assume an overall level of 'PrEP effectiveness', b_α, corresponding to a level of FSW PrEP adherence, α. No partner populations are assumed to be taking PrEP.

Single partner population

We started the analysis by considering a single partner population, in whom the proportion HIV infected is p. For a given time period, a FSW is assumed to have *n* partners, each with whom she has an average of m sex acts. For simplicity these equations assume an overall average probability of HIV transmission, β, per sexual contact with an HIV infected partner.

We used the HIV risk equations to derive two key threshold conditions: 1) the level of PrEP effectiveness that must be attained for PrEP to be of benefit in reducing HIV risk, considering any change in condom consistency; and 2) the 'break-even' level of condom consistency after introduction of PrEP such that HIV acquisition risk is not increased.

Single partner population, accounting for increased STI exposure

We expanded our analysis to explore the increased risk of HIV transmission resulting from exposure to STIs, should condom migration occur and PrEP use be inconsistent. Parameter *s* is taken as the probability that at least one person in the partnership has an STI, and δ the multiplicative increase in per sex act probability of HIV transmission in the presence of an STI.

We derived the percentage reduction in condom consistency tolerated for HIV risk not to increase on PrEP and compared these results to those not accounting for increased STI exposure, to see whether conclusions remain robust.

Two partner populations, accounting for increased STI exposure

We then extended the HIV risk equations to account for risk arising from two distinct partner populations: clients ("c") and regular partners("r"). In this setting, condom consistency with regular partners is low[52] and clients sometimes pay more for condom-less sex[37]. As such, any change in condom consistency on PrEP is likely to be more profound with clients, and therefore its impact on HIV risk. We thus examined the percentage reduction in condom consistency *with clients* tolerated for HIV risk not to increase on PrEP, holding condom consistency with regular partners constant (using Appendix 2: Supplementary Materials equations S14 and S15). We assessed whether the results remain the same, accounting or not for increased STI exposure through decreased condom use. To gauge whether, in such settings, changes in condom use with clients or regular partners present the biggest HIV risk, we assessed whether there is a significant difference in the percentage reduction in condom consistency *with clients* tolerated for HIV risk not to increase, if PrEP use reduces condom use to zero with regular partners.

The equations were solved numerically using Solver in Microsoft Excel 2013 (set to perform 10,000 iterations per calculation) to ascertain the maximum change in condom consistency that can be tolerated for PrEP to remain of benefit, considering increased exposure to STIs, across a range of possible attained PrEP effectiveness levels.

Data and model parameterisation

The HIV risk equations were parameterised using sexual behaviour data from Hillbrow, Johannesburg collected by WRHI, as well as biological and epidemiological data from other literature (*Supplementary Methods: Table S1*). As there is uncertainty about the PrEP effectiveness corresponding to levels of

drug adherence, calculations were carried out for a range of simulated values of PrEP effectiveness for a given adherence value (b_α). The values simulated roughly span the range of risk reduction estimated through the iPrEx OLE[13] study (between 44% corresponding to fewer than 2 tablets a week and 100% corresponding to at least 4 tablets a week). We started from a slightly lower baseline of 35% to reflect, conservatively, that this study was conducted in a different study population.

It was assumed that all sex acts are peno-vaginal on the basis of available epidemiological data for FSWs in Hillbrow[52]. Three months was chosen as the period of HIV risk evaluation, as this corresponds to the period after which an HIV test must be performed on PrEP to check for seroconversion (amongst other indicators)[38,53].

Sensitivity analysis

Two categories of sensitivity analysis were performed. Firstly, the calculations were repeated for two boundary cases: high risk (HR) and low risk (LR) FSWs, parameterised using high and low risk values in the HIV risk equation for the sexual behaviour parameters (% partners HIV infected, number of partners and average number of sex acts per three months, probability at least one person in the partnership has an STI) and the transmission probability parameters (condom HIV risk reduction efficacy, probability of HIV transmission through peno-vaginal sex, multiplicative increase in per sex act probability of HIV transmission in the presence of an STI).

A second set of sensitivity analyses were undertaken to explore the case that any condom migration brings with it increases in STI prevalence, and therewith risk of HIV transmission. In spite of high levels of STI treatment in the FSW population[34], to obtain conservative results in terms of change in condom consistency tolerated following the introduction of PrEP, we assumed that STIs are present in *all* partnerships where reductions in condom consistency occur, and that these STIs are transmitted through the sex act if not already present in both partners. The probability that at least one person in the partnership has an STI following the introduction of PrEP is therefore assumed to increase at the same rate as the change in condom consistency.

Results

Single partner population

We deduced that where the level of PrEP effectiveness achieved equals or exceeds that of condoms (i.e. condom efficacy * baseline condom consistency), PrEP will be of equal or greater benefit in reducing HIV risk and therefore condom use could be reduced to zero without HIV risk increasing. Where the level of PrEP effectiveness is less than the effectiveness originally achieved with condoms, we see that greater drops in condom consistency can be tolerated for those FSW with lower baseline condom consistencies.

Figure 1 shows the break-even condom consistency after introduction of PrEP such that HIV risk is not increased. Large relative reductions in condom consistency on PrEP are anticipated to be especially well tolerated where higher levels of PrEP effectiveness achieved (>65%). For FSWs whose baseline consistencies are low (<55%), or where there is not anticipated to be a large relative drop in condom consistency on PrEP, even the achievement of low levels of PrEP effectiveness will reduce HIV risk.

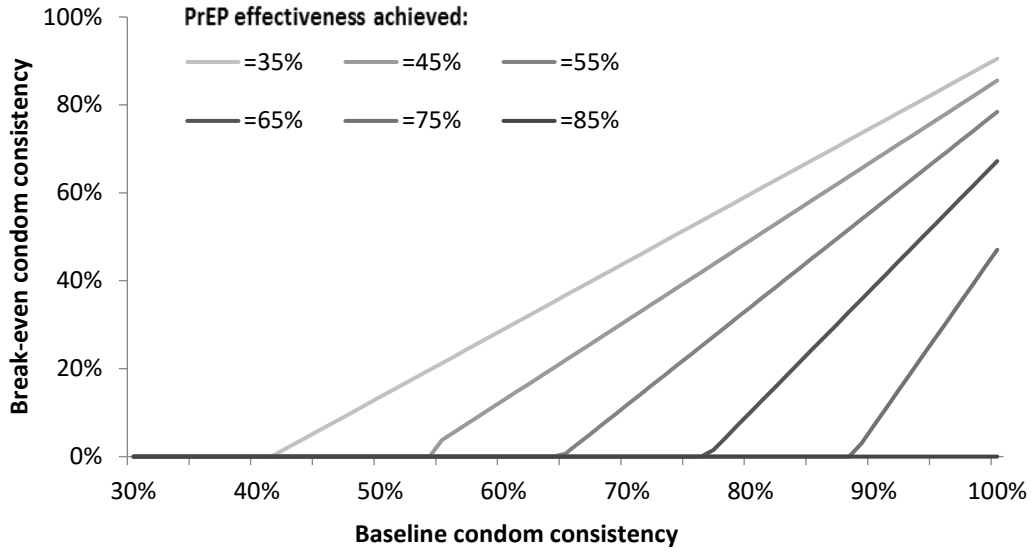

Figure 1: Break-even condom consistencies following introduction of PrEP.
In the case of a single partner population, the figure describes the break-even condom consistencies (the levels that condom use could be reduced to, following introduction of PrEP) such that HIV risk is not increased on PrEP. These break-even levels are shown for baseline condom consistencies between 30% and 100%, and corresponding to six different levels of achieved PrEP effectiveness ranging from 35% to 85% (85% corresponding to the level of condom efficacy assumed in this study).

Single partner population, accounting for increased STI exposure

The results show that reductions in condom consistency on PrEP are especially well tolerated for FSWs with lower baseline condom consistencies (<50%) and where higher levels of PrEP effectiveness are achieved (>65%). Even for the lowest level of 35% PrEP effectiveness simulated (which would correspond to adherence to fewer than two tablets a week according to iPrEx OLE[13] estimates), the percentage reduction in condom consistency tolerated steadily increases upwards from a minimum reduction of 17% (corresponding to 90% baseline condom consistency) to 100% migration (corresponding to 30% baseline condom consistency).

Where PrEP effectiveness of 85% can be achieved (which would correspond to adherence of 2-3 tablets a week according to iPrEx OLE[13] estimates; and the exact level of assumed condom protection efficacy simulated for the base case), 100% condom migration can uniformly be tolerated across all baseline condom consistencies simulated.

The percentage change in condom consistency possible is almost the same (<1% difference) whether STIs are accounted for or not in the HIV risk equations (*Supplementary Results: Table S2,* shown graphically in *Figure 2*). This is because, whilst inclusion of STI parameters in the mathematical HIV risk equations does result in increased HIV risk levels on an absolute basis, it does not significantly affect change in risk on a relative basis.

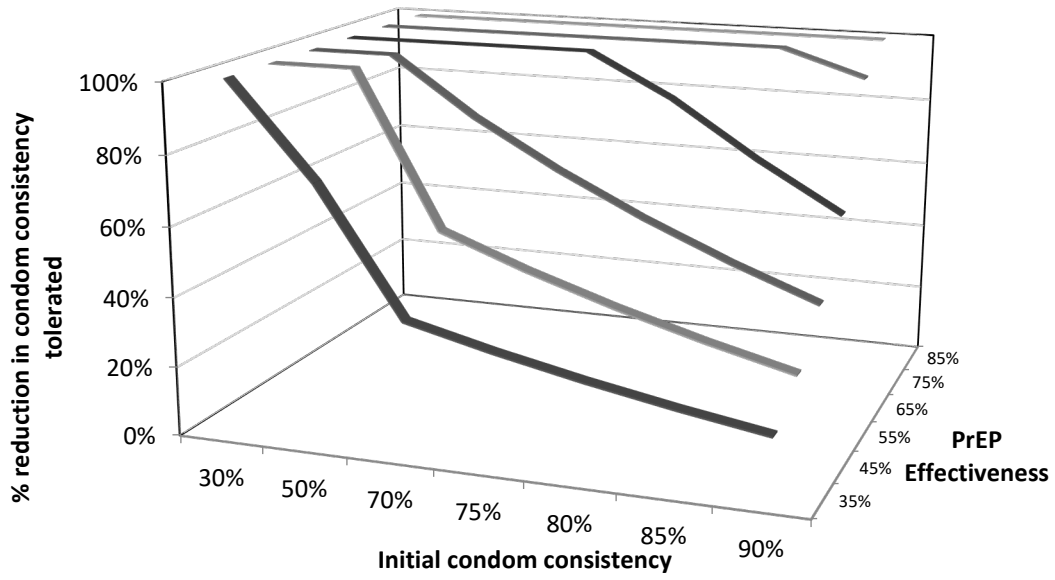

Figure 2: Percentage reduction in condom consistency tolerated with a single partner population for HIV risk not to increase on PrEP, accounting for the effect of STIs on HIV risk.
For different baseline condom consistencies between 30 and 95%, the figure describes the percentage reduction in condom consistency that could be tolerated on PrEP corresponding to six different levels of achieved PrEP effectiveness, ranging from 35% to 85% (85% corresponding to the level of condom efficacy assumed in this study).

Sensitivity analysis

Looking at the boundary cases of high and low risk FSW reveals only small variations in the percentage reduction in condom consistency tolerated (accounting for STIs or not in the equations). This is especially true at lower levels of PrEP effectiveness and higher baseline condom consistencies (4-8% reduced reduction in condom consistency tolerated), although this is slightly more pronounced at higher levels of PrEP effectiveness (up to 22% reduced reduction).

Should condom migration bring with it increases in STI prevalence in the population, there would be modest reductions in the percentage reduction in condom consistency tolerated (at most 22% reductions in relative terms compared to the base case results, or between 2% and 20% less in absolute terms), though the differences in the results are smaller especially where PrEP effectiveness achieved is lower (<65%) and initial condom consistency is high (>70%), or where PrEP effectiveness achieved is higher (≥65%) and initial condom consistency is below ~80%.

Two partner populations, accounting for increased STI exposure

Table 1 demonstrates the percentage reductions in condom consistency with clients tolerated to achieve 50% or 90% levels of reduction in HIV risk on PrEP, condom consistency with regular partners held constant (at 10%[54]).

Achievement of 50% reduction in HIV risk on PrEP is feasible across all simulated PrEP effectiveness levels (55%, 75%, 95%) and baseline condom consistencies (30-90%). As seen for single partner populations, reductions in condom consistency are best tolerated for FSWs with lower baseline levels with clients or where higher PrEP effectiveness levels are achieved.

A FSW with initial condom consistency of 30% with clients could reduce her consistency by one third and still achieve 50% reduction in HIV risk, if she were able to attain 55% PrEP effectiveness (corresponding to below 2-3 doses a week per iPrEx OLE[13]). A FSW achieving 95% PrEP effectiveness (corresponding to around 4 doses a week per iPrEx OLE[13]) could tolerate 100% condom migration to achieve HIV risk reductions in excess of 50%; and so too for those FSWs achieving 75% PrEP effectiveness for baseline condom consistencies with clients of up to 70%.

Across the parameters simulated, the higher level of 90% risk reduction on PrEP could only be achieved in the case where PrEP is 95% effective (corresponding to around 4 doses a week per iPrEx OLE[13]). In this case, an initially 90% condom consistent FSW could reduce her condom use with clients by more than half; and for FSWs with baseline condom consistencies with clients of 70% and lower, 100% condom migration on PrEP could be tolerated.

Again, there is negligible observable (<1%) difference whether or not STIs are accounted for in the HIV risk equations.

In the case that PrEP leads to full condom migration with regular partners, rather than remaining consistent at 10%, there is a small further reduction in condom consistency tolerated (between 1-8% across the scenarios simulated, see *Supplementary Results Table S4)*).

Sensitivity analysis

Looking at the boundary cases of high and low risk FSW reveals small variation in the percentage reduction in condom consistency tolerated for the lower level of PrEP effectiveness of 55%. The variation is more pronounced for higher levels of PrEP effectiveness (75% and 95%), with up to around one third change in percentage reduction in condom consistency tolerated across the parameter ranges simulated.

In the case that condom migration brings with it increases in STI prevalence in the population, there are reductions in relative terms of 14%-26% compared to the base case results, and in absolute terms the reductions are almost uniformly within the range of variation seen through examining the boundary cases of high and low risk FSW.

	55% PrEP Effectiveness								75% PrEP Effectiveness								95% PrEP Effectiveness							
	% reduction in condom consistency with clients tolerated to get overall HIV risk reduction of																							
	50%				90%				50%				90%				50%				90%			
Initial condom consistency	Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs	
	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)
90%	6%	(-3%,-3%)	6%	(-3%,3%)	-	-	-	-	57%	(-27%,26%)	57%	(-28%,39%)	-	-	-	-	100%	(*,*)	100%	(*,*)	56%	(-27%,19%)	57%	(-28%,37%)
80%	8%	(-3%,-5%)	8%	(-3%,2%)	-	-	-	-	76%	(-31%,24%)	77%	(-31%,23%)	-	-	-	-	100%	(*,*)	100%	(*,*)	75%	(-29%,20%)	76%	(-31%,24%)
70%	10%	(-3%,-6%)	11%	(-4%,2%)	-	-	-	-	100%	(*,*)	100%	(*,*)	-	-	-	-	100%	(*,*)	100%	(*,*)	100%	(*,*)	100%	(*,*)
50%	18%	(-4%,-13%)	19%	(-5%,2%)	-	-	-	-	100%	(*,*)	100%	(*,*)	-	-	-	-	100%	(*,*)	100%	(*,*)	100%	(*,*)	100%	(*,*)
30%	37%	(-6%,-29%)	38%	(-7%,0%)	-	-	-	-	100%	(*,*)	100%	(*,*)	-	-	-	-	100%	(*,*)	100%	(*,*)	100%	(*,*)	100%	(*,*)

Table 1: Maximum tolerated % reduction in condom consistency with clients (consistency with regular partners held constant) to still achieve 50% or 90% reductions in HIV risk on PrEP, for different levels of PrEP effectiveness achieved.

For each level of PrEP effectiveness demonstrated, the table shows the % reduction in condom consistency that could be tolerated, from varying levels of initial condom consistency, to achieve either 50% or 90% HIV risk reduction. The results are shown for both the case that STIs are accounted for in the HIV risk equations, as well as the case that they are not. The results are shown for the base case parameterization of the model, as well as the boundary cases explored through the first sensitivity analysis of high and low risk FSW. They assume that condom consistency with regular partners remains constant at 10% before and after introduction of PrEP. The results corresponding to the case that condom consistency with regular partners drops from 10% to 0% following the introduction of PrEP is shown in Table S4 in the Appendix 2: Supplementary Materials.

'–' indicates that achievement of the risk reduction is not possible. '' indicates full migration will still result in higher levels of risk reduction. 'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW, and the results calculated in the sensitivity analysis for the boundary parameter cases. A graphic depiction of the results corresponding to achievement of 50% HIV risk reduction on PrEP is given in Supplementary Equations, Figure S1.*

Discussion

This study provides insights into the risks associated with condom migration following the introduction of PrEP into a comprehensive HIV prevention programme for FSWs. The study demonstrates that the success of PrEP will rest upon its ability to achieve high enough PrEP adherence in FSWs such that the increased protection achieved outweighs the increased HIV risk owing to condom migration and increased STIs exposure. The added value for decision makers of our study lies upon our ability to quantify these trade-offs.

This study has demonstrated that where a FSW's adherence to PrEP achieves a level of effectiveness that exceeds that of condoms, PrEP will always reduce HIV risk. Condom migration is anticipated to be especially well tolerated where baseline levels of condom consistency are low (<50%) or where a reasonably high level of PrEP effectiveness (>65%) can be achieved. Should FSWs' condom consistency with regular partners remain low (~10%) or be reduced to zero on PrEP, reductions in condom consistency with clients could uniformly be tolerated whilst still achieving 50% HIV risk reduction (assuming achieved PrEP effectiveness of at least 55%). This is especially noteworthy having considered probabilities of up to 60% likelihood of STI exposure in a partnership if condom migration were to occur.

From a programming point of view, strategies to identify FSWs with initially higher condom-consistent behaviour but anticipated to adhere less well to PrEP will be important, and efforts to promote condom consistency and give adherence support critical. Considering that full condom migration with regular partners does not substantially increase HIV risk on PrEP (assuming initially low consistency with regular partners holds true), efforts to encourage condom consistency with clients will be critical.

The study has demonstrated that the break-even point at which PrEP is beneficial in terms of HIV risk reduction is driven primarily by the behavioural parameters of condom consistency and drug adherence, as well as by the efficacy of condoms, and much less by epidemiological parameters. This is noteworthy in programme design, as efforts to improve and sustain behaviours relating to PrEP adherence and condom consistency will have the greatest influence on programme outcomes over epidemiologic context.

There are, however, a number of caveats to the study. This work does not speak to acceptable PrEP adherence levels, given the risk of ARV resistance, noting that PrEP users in the middle adherence spectrum are anticipated to be at greatest risk[55]. This study does not account for a partner's stage of HIV infection or ARV use in partner populations. The former may increase HIV risk if partners are

likely to be recently infected and thus highly viremic, whereas the latter would likely decrease overall risk; however neither would be expected to impact comparative estimates of change in HIV risk.

Use of a static rather than dynamic model limits the study to an analysis of FSW HIV risk in isolation of the dynamics of infections between FSWs, their partners and clients and in turn to FSWs. These results, whilst suitable to indicate rules of thumb to guide HIV prevention efforts, cannot provide insight into the downstream impact of the intervention and condom migration on the HIV epidemic in South Africa. Finally, the data used to characterise the FSW population in Hillbrow is limited by being self-reported (susceptible to underreporting) and age, as little has been published since the end of the 1990s, when the HIV epidemic was less evolved[56], although studies are underway.

Most importantly, this study indicates that, assuming oral PrEP is proven effective in FSW populations through ongoing trials, in many situations oral PrEP is likely to be of benefit in reducing HIV risk even if behaviour change were to be a programme reality. It provides guidance around the characteristics of FSWs for whom condom migration may be more of an issue (those with initially high-levels of condom consistency with clients, anticipated to adhere poorly to PrEP and significantly migrate away from condoms); and those FSWs for whom PrEP is likely to be an important addition to combined HIV prevention measures (those with initially low condom consistency with clients, or anticipated to adhere reasonably well to PrEP). Importantly for the latter group, PrEP will provide additional protection against HIV transmission from regular partners, with whom there is otherwise little protection given low baseline condom levels. Finally, the analytic approach followed in this study could easily be adapted to other vulnerable populations beyond FSW.

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3.4 Implications for Thesis

The results of Research Paper 1 indicate that for high HIV risk women in a high HIV burden setting, PrEP is likely to be of benefit in reducing new infections, even if behavioural disinhibition occurs. This conclusion in made having considered a range of women's baseline condom consistencies and levels of HIV risk reduction achieved on PrEP. However, it cautions policy makers that strategies to support continued condom use will be especially critical for women who had high levels of condom use prior to PrEP introduction but anticipated to have difficulties in adhering to PrEP.

This agrees with the work by Foss et al[41] in relation to an HIV- and STI-efficacious microbicide, which also found that there are likely to be contexts in which reductions in condom use can be tolerated (depending on the efficacy and use-effectiveness of the microbicide), and that particular concern should be paid to individuals with high baseline levels of condom use anticipated to have challenges in using microbicides consistently. Research Paper 1 goes further by exploring the effect of reductions in condom consistency among two different partner populations of FSW. This Research Paper found that condom consistency with regular partners could be reduced to zero, and reductions in condom consistency with clients still be tolerated whilst achieving 50% HIV risk reduction, with levels of PrEP use-effectiveness of at least 55%. This is noteworthy given the incentives for FSW to reduce condom consistency with clients[37], and challenges with condom use between FSW and regular partners[52].

This analysis was undertaken using a simple static model, evaluated in Microsoft Excel, which has the advantage of being relatively easily replicable for application to other contexts or populations. The use of a simple static model also allowed for the deduction of simple rules of thumb to guide HIV prevention programming.

However, as the static model does not account for the dynamics of population interactions, the conclusions of this study cannot account for the downstream effects of PrEP use and behavioural disinhibition on the wider HIV epidemic over time. Accordingly, Research Paper 2, explores the extent to which the conclusions made on the basis of a static model hold when the dynamics of population interactions are accounted for using a dynamic model, evaluated over different time horizons and in epidemic contexts.

Chapter 4

4. Research paper 2: Is Modelling complexity always needed? Insights from modelling PrEP introduction in South Africa

4.1 Introduction to Research Paper 2

Research Paper 2 aims to respond to thesis objective 3 by assessing the extent to which the conclusions made in Research Paper 1 hold, when the dynamics of population interaction are accounted for through incorporation of dynamic modelling effects. To test these conclusions, the paper matches the static model used in Research Paper 1 with a dynamic model of HIV transmission between high-risk women and their partner population. It considers two epidemic scenarios: first, where the underlying HIV epidemic is at equilibrium (as it is now in many countries in sub-Saharan Africa[1]), and then, where the underlying HIV epidemic is still increasing (as it was in earlier years in many epidemics in sub-Saharan Africa[1]).

The study compares the models' predictions of the reductions in condom use that can be tolerated following the introduction of PrEP, without HIV risk increasing over a 20-year time horizon. It also assesses the extent to which the main policy conclusions made in Research Paper 1 hold when assessed through the dynamic model formulation. These policy conclusions were as follows:

1. *Condom use can be reduced to zero without increasing HIV risk, if the level of HIV risk reduction achieved through PrEP is at least high as the maximum risk reduction possible through condom use.*
2. *Reductions in condom consistency are especially well tolerated where:*
    i. *Higher levels of PrEP use-effectiveness are achieved (e.g. $\geq$65%)*
    ii. *Or where initial condom consistencies are low (e.g. $<$50%).*
3. *Even with the achievement of low levels of PrEP use-effectiveness (e.g. $\leq$45%), reductions in condom consistency are possible without increasing HIV risk.*

For consistency, the models are applied to same population and setting as in Research Paper 1, to female sex workers in Hillbrow, inner Johannesburg, South Africa.

It is hoped that the conclusions of Research Paper 2 will help contribute to the wider understanding of the conditions under which static models, which may be more user-friendly for policy makers, are sufficiently robust to inform decision making around the introduction of a new HIV prevention intervention to a population at risk.

4.2 Cover Sheet

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Hannah Grant
Principal Supervisor	Professor Graham Medley
Thesis Title	The scale-up of PrEP for HIV prevention in high-risk women in sub-Saharan Africa: use of mathematical modelling to inform policy making

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

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Public Health
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Stage of publication	**Submitted**

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4.3 Research Paper 2

Is modelling complexity always needed? Insights from modelling PrEP introduction in South Africa

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Abstract

Background: Mathematical models can be powerful policymaking tools. Simple, static models are user-friendly for policymakers. More complex, dynamic models account for time-dependent changes, but are complicated to understand and produce. Under which conditions are static models adequate? We compare static and dynamic model predictions of whether behavioural disinhibition could undermine the impact of HIV pre-exposure prophylaxis (PrEP) provision to female sex workers in South Africa.

Methods: A static model of HIV risk was developed and adapted into a dynamic model. Both models were used to estimate the possible reduction in condom use, following PrEP introduction, without increasing HIV risk. The results were compared over a 20-year time-horizon, in two contexts: at epidemic equilibrium and during an increasing epidemic.

Results: Over time-horizons of up to five years, the models are consistent. Over longer timeframes, the static model overstates the tolerated reduction in condom use where initial condom use is reasonably high (≥50%) and/or PrEP effectiveness is low (≤45%), especially during an increasing epidemic.

Conclusions: Static models can provide useful deductions to guide policymaking around the introduction of a new HIV intervention over short-medium time-horizons of up to five years. Over longer timeframes, static models may not sufficiently emphasize situations of programmatic importance, especially where underlying epidemics are still increasing.

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Background

Mathematical models play an important role in policy making for public health.[2–4] They can be used to assess the impact of different policy options, which may be impractical to test in implementation settings or over longer time horizons.[2] Nonetheless, there is often hesitation among policy makers to rely on models, perceived to be an intimidating 'black box' process of uncertain applicability to real-world settings.[5,6] This may be owing to complexity in model structure, uncertainty around model assumptions or challenges in model communication.[7] As a consequence, potentially useful models may be underemployed or in some cases inappropriately used to inform decision making.[5]

Simple models have a comparative appeal for use in policy making. They can be used to deduce broad principles to guide decision-making through an approach that is easier for policy makers to understand and critique.[8,5] For this reason, we previously used a simple, static model of HIV risk to assess the potential effect of behavioural disinhibition (in this case: reductions in the use of condoms) following the introduction of pre-exposure prophylaxis (PrEP) among female sex workers (FSW) in South Africa.[9] Simple models have been used to obtain insights into a number of other pertinent HIV policy questions – from resource prioritization across low and middle income countries[10] to the scale up of microbicides[11,12], the cost-effectiveness of male circumcision in sub-Saharan Africa[13,14], declining HIV test positivity[15] and projecting HIV diagnoses among children and adolescents in New York State[16].

To date there has been limited assessment of the conditions under which models of simple structural form are sufficient to guide policy making in HIV.[17–21] A key element of modelling complexity is the extent to which model conclusions account for time-dependent changes. Static models take a snap-shot approach and cannot capture the downstream effects of population interaction. They are typically structurally more straightforward, and less data- and time-intensive to develop.[22,23] By comparison, dynamic models account for changes over time owing to population interactions and evolving contextual factors. Dynamic models are typically represented by a system of differential or difference equations, evaluated numerically using programming tools with increased data requirements. [22,24] As a result, they are more time-intensive and expensive to devise and calibrate, and often require critical assumptions to be made about current and future trends.[21,22]

Other key considerations in the design of models to inform policy making include the extent to which models can be devised, computed and appropriately interpreted by policy makers themselves, or whether external technical support is required.[2,21,25] Simpler models, such as those calculated in Microsoft Excel, that can be developed and owned by policy makers themselves, may improve their uptake to inform decision making. However, accessibility needs to be balanced against the risk of

inaccuracies through model over-simplification, leading to misleading model outcomes or interpretation, and the derivation of incorrect policy conclusions.[3]

Modelling studies[17,21,26,27] have proposed broad frameworks to guide the development of models for policy making, noting that models should adopt only the minimum level of complexity needed to appropriately represent the policy question at hand, in view of the availability of data, the importance of accounting for interactions between population groups, the time horizon of assessment and epidemiological context. However, none have given specific guidance around the characteristics or contexts in which simpler models suffice. Given that simple, static models form the basic building blocks for more complex models,[23] it is important to determine conditions under which they can reliably provide an accessible approach to guide policy making.

In 2009 Foss et al[12] incorporated dynamic features into a static model of HIV risk[11] to explore the impact of microbicide STI-efficacy. In 2014 Mishra et al[18,28] assessed the static UNAIDS Modes of Transmission model,[10] used by many countries to prioritise HIV prevention interventions between groups at population-level. These studies[12,18,28] concluded that by not capturing dynamic effects of partner interaction, the static model underestimates the contribution of epidemic drivers to HIV transmission over time. Other studies have used static and dynamic models to explore different aspects of a policy question but have not compared model outcomes.[14,29] To the best of our knowledge, no study has examined the extent to which the conclusions of static models remain robust to the incorporation of dynamic effects over multiple time-horizons, when assessing the introduction of a new HIV intervention to a population group.

To contribute to wider understanding of the role of simple, static models in decision making, we modify our previous model of HIV risk for female sex workers (FSW) in Hillbrow, South Africa[9] to incorporate the dynamics of partner interaction over time. We assess the consistency of policy conclusions derived between the static and dynamic model formulations. We make this comparison over different time-horizons, as well as by HIV epidemic stage, to determine whether the underlying maturity of population epidemics affects the time-dependency of results. The introduction of PrEP for FSW in South Africa is a pertinent case study, in view of growing concerns around sub-optimal drug adherence[30,31] and behavioural disinhibition,[31,32] highlighting the need to understand trade-offs associated with PrEP outside of trial settings.[33]

Methods

Model structures and parameterisation

The static model was developed using the Bernoulli formulation of HIV risk,[9] where the probability of HIV being transmitted through each sexual contact is an independent risk event. The sexual partners of FSWs are assumed to come from a single population in which the proportion HIV infected is p. To assess the effect of changes in condom consistency following the introduction of PrEP, condoms were assumed to be used with consistency γ_0 prior to PrEP introduction and γ_1 after its introduction. As the relationship between PrEP adherence and effectiveness is yet to be defined for women,[34] the model assumes an achieved level of PrEP use-effectiveness, b_α, corresponding to a level of PrEP adherence, α. It was assumed that the probability that at least one person in the partnership has an STI increases proportionally to decreases in condom consistency, to account for changes in HIV risk through increased STI exposure. The static model accounts for the effects of ART and circumcision coverage (in the partner population) on FSWs' HIV risk. The term 'use-effectiveness' is used to describe the HIV risk-reduction achieved through a level of use of an efficacious HIV prevention intervention (e.g. PrEP or condoms).

A dynamic version of the static model was developed using difference equations, taking the Bernoulli risk formulation as the force of infection on FSWs per timestep, and an equivalent formulation for male partner population. Instead of a static HIV prevalence, p, the dynamic model system allows prevalence to change over time as the proportion of HIV infected individuals, I/N, where I is the number of HIV infected individuals and N the total population size. The dynamic system accounts for population recruitment and loss due to natural and AIDS-related death. The models were parameterised based on sexual behaviour, biological and epidemiological data from the literature (*Appendix 3: Supplementary Materials Table 1)* and programmed in R.

The dynamic model was fitted to HIV prevalence data for both FSW and partner populations between 1980 and 2014 using Monte Carlo methods with Latin Hypercube Sampling (R FME package[35]), run on 50,000 parameter sets. This yielded at least 200 fits for each scenario explored. Both models were then parameterised and evaluated using the same set of fitted parameters, allowing for the evaluation of uncertainty ranges in both models. PrEP was introduced in 2015 in line with its introduction to FSWs in Hillbrow under the TaPS demonstration project.[36]

Analyses

Percentage reduction in condom consistency tolerated on PrEP

For each model, optimisation algorithms were run (dynamic model: R FME package[35]; static model: R rootSolve package[37]) to ascertain the lowest level of condom consistency possible (γ_1^*) for HIV risk not to increase following the introduction of PrEP. This was used to calculate the threshold percentage reduction in condom consistency $(\gamma_0 - \gamma_1^*)/\gamma_0$ that can be tolerated. For the dynamic model, this optimisation was repeated over time horizons of 3 months to 20 years.

Accounting for behavioural heterogeneity: differences in initial condom consistencies and PrEP use-effectiveness

Given the importance of accounting for heterogeneity in FSWs' initial condom consistencies,[9,11] the parameter sets were fitted individually for initial condom consistencies (prior to introduction of PrEP) of 10%, 30%, 50% and 70%, spanning the range reported by this population.[9]

Unlike for men who have sex with men (MSM) and transgender women (TGW), where studies have been able to relate the number of weekly doses of PrEP to levels of HIV risk reduction, the same has not yet been possible for women, for whom it is only recognised that 100% risk reduction on PrEP necessitates higher levels of adherence (6/7 tablets a week in women as opposed to 4/5 in MSM and TGW).[38] As such, we chose to span a spectrum of potential levels of PrEP use-effectiveness: 25%, 45%, 65% and 85%. 85% was simulated as the highest level, as it equates to the maximum use-effectiveness of condoms as in Grant and colleagues.[9]

The percentage reduction in condom consistency that can be tolerated was calculated across these levels of initial condom consistency and PrEP use-effectiveness.

Accounting for stage of HIV epidemic

To assess whether the results change by underlying stage of HIV epidemic, the analyses were repeated 20 years earlier, when the HIV epidemics in FSWs and their partner populations were still increasing. Under this scenario, *Increasing Epidemic,* initial condom consistency was fixed in 1994 and PrEP hypothetically introduced in 1995. This is in comparison to the base case analysis, *Epidemic Equilibrium,* where initial condom consistency was fixed in 2014 and PrEP introduced in 2015 once the epidemics had started to stabilise.

Additional analyses

To assess whether the inclusion of ART, circumcision and STIs in the models affected our conclusions, we conducted a model structural sensitivity analysis, removing all related parameters from the models and rerunning the analyses. To assess whether our conclusions were sensitive to PrEP being introduced when the epidemics are fully endemic in the populations (*Fully Endemic* scenario), we repeated the analysis with PrEP introduced in 2030 (*Appendix 3: Supplementary Materials Figure 1)*.

Appendix 3: Supplementary Materials contains further information on the model structure, parameterization and calibration.

Results

The lowest levels of condom consistency that can be tolerated by FSW on PrEP (without their HIV risk increasing) at *Epidemic Equilibrium* and in the context of an *Increasing Epidemic*, are shown in Figure 1 and Figure 2 respectively.

In Figures 1 and 2, the three rows, from top to bottom, represent FSW initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70% respectively. The three columns represent, from left to right, PrEP use-effectiveness of 25%, 45% and 65% respectively. For each combination of initial condom consistency and PrEP use-effectiveness, boxplot graphs depict the lowest level of condom consistency tolerated on PrEP (vertical-axis). The far-left boxplot on the horizontal-axis of each of the graphs is the lowest level of condom consistency estimated using the static model. The boxplots to the right of it are the lowest level of condom consistencies estimated using the dynamic model, at time points of 3 months, 1 year, 2 years, 5 years, 10 years and 20 years, from left to right. The boxplots depict uncertainty in the estimated lowest level of condom consistency tolerated, with the black line representing the median value, the coloured section the interquartile range (25-75% of the values) and the whiskers the maximum and minimum values. The differences between the static and dynamic model outcomes can be understood by comparing how similar the lowest level of condom consistency estimated by the static model is to the lowest level of condom consistency estimated by the dynamic model over time.

Whilst Figures 1 and 2 depict the key trends in model differences for each scenario, more detailed plots including FSW initial condom consistency of 10% and PrEP use-effectiveness of 85% are shown in *Appendix 3: Supplementary Materials, Figures S5 and S7* for the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios respectively. The *Appendix 3: Supplementary Materials* also contain the equivalent boxplot graphs for the second model outcome: percentage reduction in condom consistency tolerated on PrEP (*Appendix 3: Supplementary Materials Figures S6 and S8*), the model fits to HIV prevalence (*Appendix 3: Supplementary Materials Figures S1-S4)*, as well as all underlying data (*Appendix 3: Supplementary Materials Tables S2-S10)*.

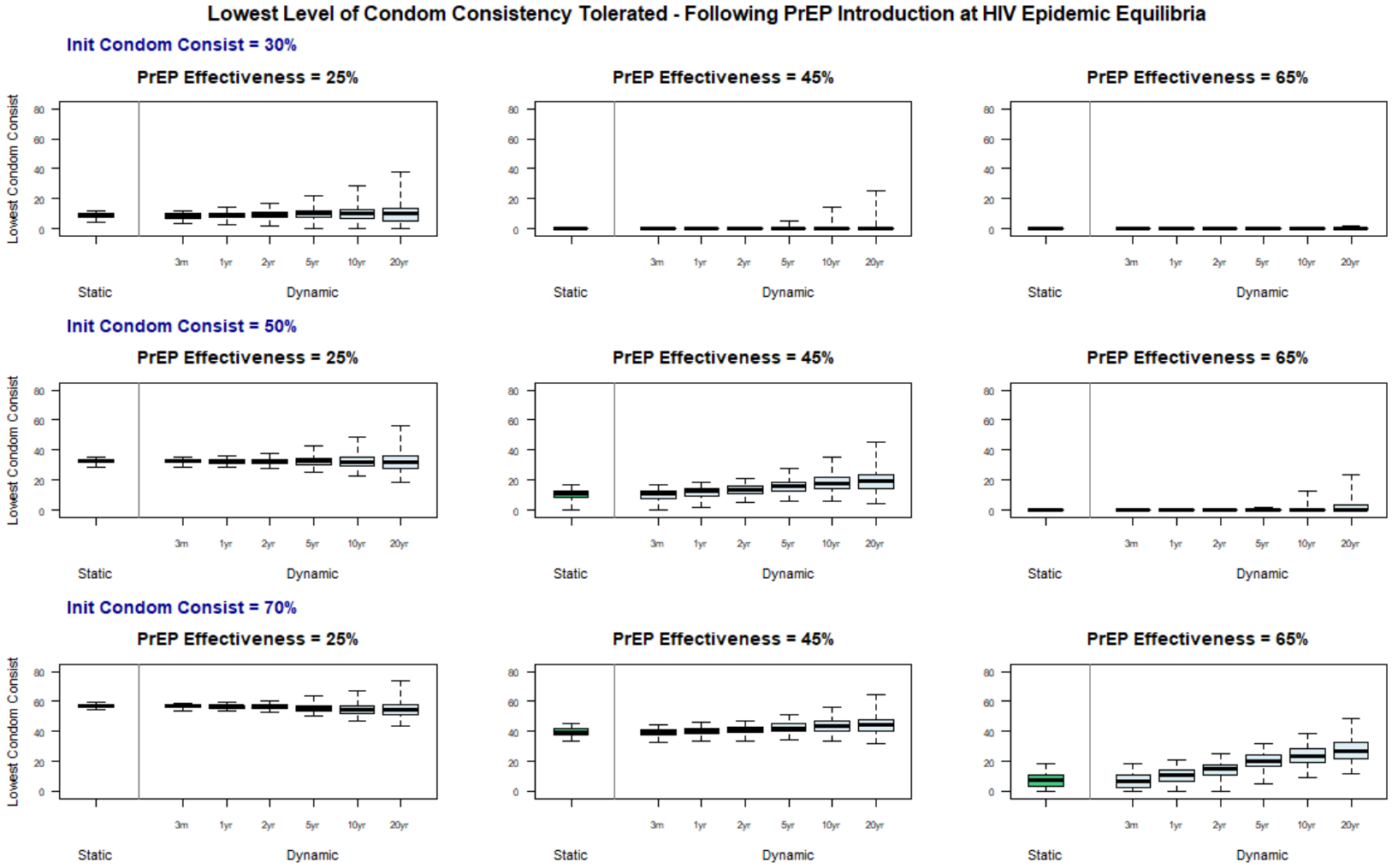

Figure 1: Boxplots showing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45% and 65%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

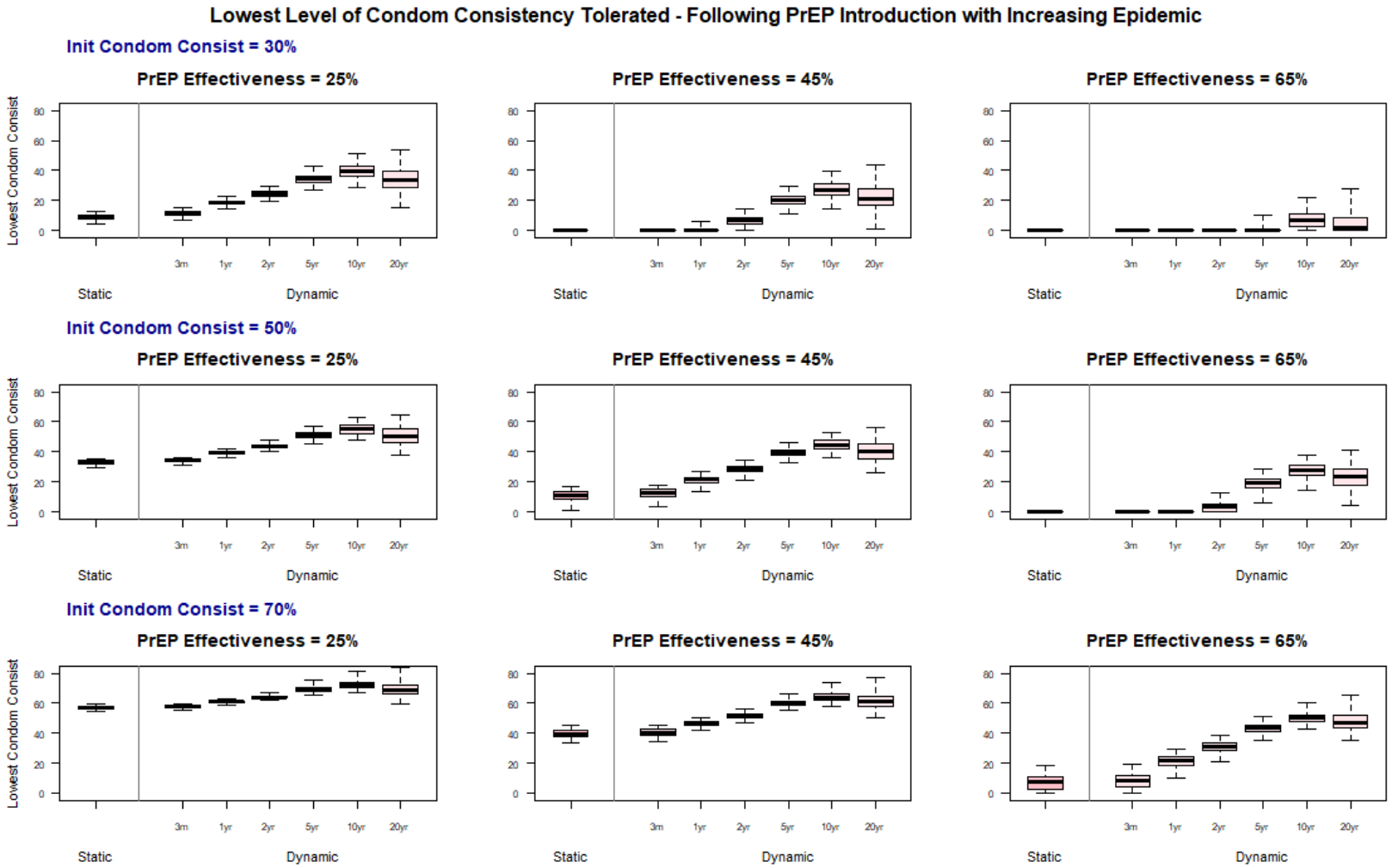

Figure 2: Boxplots showing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45% and 65%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

Comparison of static and dynamic model outcomes

Under the scenario that PrEP is introduced at *Epidemic Equilibrium*, the percentage reductions in condom consistency estimated by the static and dynamic models are very similar up to a time-horizon of one year. By five years, the model predictions remain consistent to within 25% relative difference between medians (<35% between credible intervals (CrIs)), and by 20 years to within 35% between medians (≤100% between CrIs) (*Appendix 3: Supplementary Materials Table S2a).* The differences between the percentage reductions in condom consistency predicted by the static and dynamic models are less consistent over time where initial condom consistency is higher (≥50%) and PrEP use-effectiveness is lower (≤45%). This is consistent with our previous work based on the static model, which indicated that reductions in condom consistency should be of greatest concern for FSW with high initial condom consistencies achieving low levels of PrEP use-effectiveness[9]. However, the results suggest that the magnitude of concern predicted by the static model was understated over the long-term.

Under the *Increasing Epidemic* scenario, the differences between the percentage reductions in condom consistency predicted by the models are more pronounced over time. By five years the relative difference between model medians is less than 10% (<25% between CrIs) at high levels of PrEP use-effectiveness (85%) but up to 100% (100% between CrIs) at low levels of PrEP use-effectiveness (25%). By 20 years, the differences between the models start to decrease in response to the natural plateau of the underlying epidemics (*Appendix 3: Supplementary Materials Table S2b)*.

For both epidemic scenarios, removing ART, circumcision and STIs from the models under the structural sensitivity analysis led to bigger differences between model outcomes in situations where PrEP use-effectiveness is low (≤45%) and initial condom consistency is at least 30% (<45% relative difference between CrIs by 5 years, and <50% relative difference by 20 years) (*Appendix 3: Supplementary Materials Tables S3a and Sb, Figures S9-S12)*. Introducing PrEP in 2030 under the *Fully Endemic* rather than in 2015 in the *Epidemic Equilibrium* scenario led to differences under the same situations, although the magnitude of differences was smaller (<25% relative difference between CrIs by 5 years, and <35% between by 20 years) (*Appendix 3: Supplementary Materials Table S4, Figures S13 and S14)*. Additional analysis comparing the model outcomes by scenario is set out in *Appendix 3: Supplementary Materials, Additional Assessment of Results* section.

Comparison of policy conclusions between static and dynamic models

To explore the contexts in which the qualitative conclusions made on the basis of static models may be appropriate to guide HIV policy making, we list three policy conclusions derived based on the static model[9], and assess their validity under dynamic model formulation.

1. *Condom use can be reduced to zero without increasing HIV risk, if the level of HIV risk reduction achieved through PrEP is at least high as the maximum risk reduction possible through condom use*

This conclusion holds under the dynamic model in the *Epidemic Equilibrium* scenario, as well as in the *Increasing Epidemic* scenario, other than at high levels of initial condom consistency (70%), where after five years the dynamic model predicts that a reduction in condom consistency to zero may start to lead to an increase in HIV risk (Figures 1 & 2; *Appendix 3: Supplementary Materials Table S2a &S2b and Figures S6 & S8*).

2. *Reductions in condom consistency are especially well tolerated where:*

   i. *Higher levels of PrEP use-effectiveness are achieved (e.g. ≥65%)*

Figure 3 shows the lowest levels of condom consistency tolerated calculated using the static and dynamic models for PrEP use-effectiveness levels of 65% and 85%. The lowest levels of condom consistency are shown for initial condom consistencies of 10% (in blue), 30% (in orange), 50% (in pink), and 70% (in green). The dotted lines represent median estimates and shaded areas represent the 95% CrIs. The top row depicts the *Epidemic Equilibrium* scenario, and bottom row the *Increasing Epidemic* scenario.

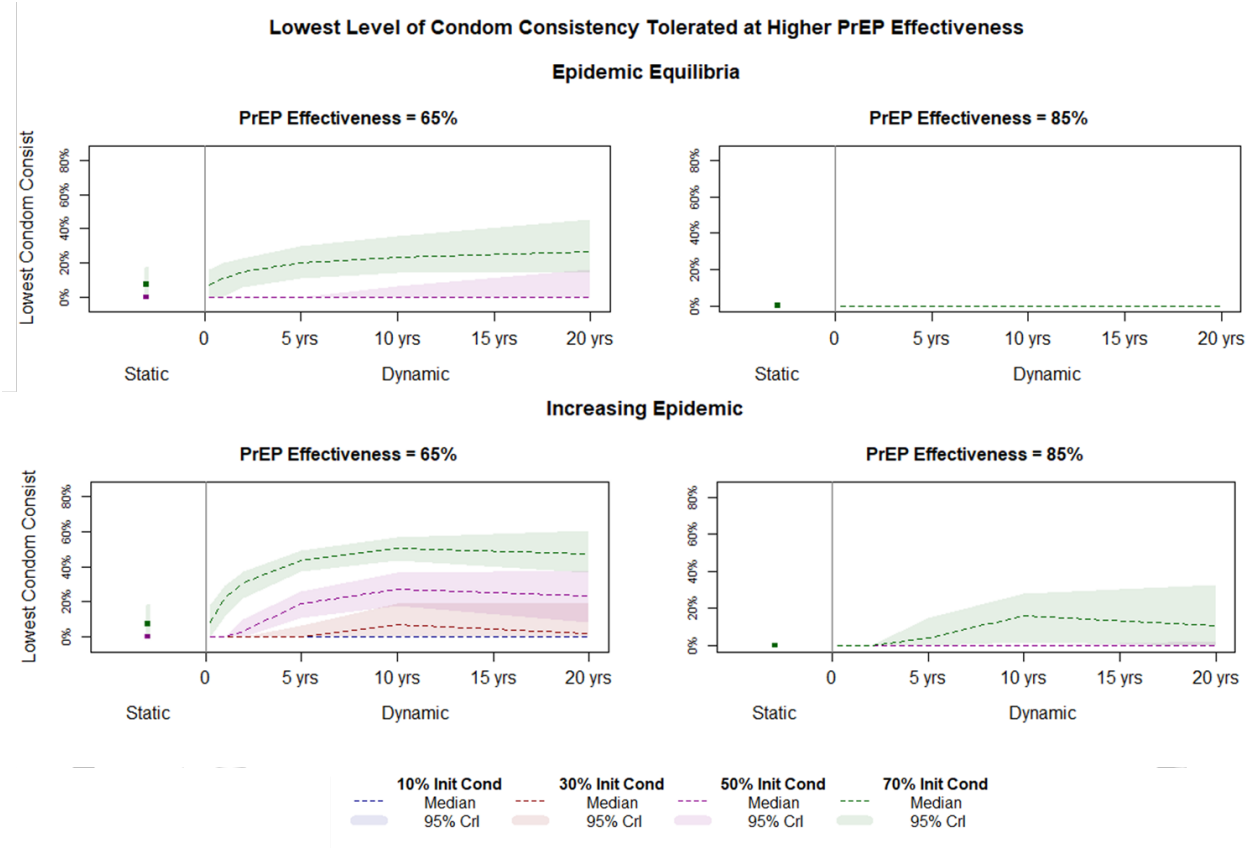

Figure 3: Lowest level of condom consistency tolerated at higher levels of PrEP use-effectiveness, for both scenarios Epidemic Equilibrium and Increasing Epidemic.

The lowest levels of condom consistency tolerated on PrEP are depicted for PrEP use-effectiveness levels of 65% (left) and 85% (right). Each graph shows the lowest level of condom consistency estimated by the static model, and by the dynamic model over a time horizon of 3 months to 20 years, corresponding to initial condom consistencies of 10%, 30%, 50% and 70%. The first row of graphs corresponds to the scenario Epidemic Equilibrium and the second row of graphs corresponds to the scenario Increasing Epidemic. The dotted lines are median estimates and shaded areas are 95% CrIs (colour coding in legend). Where the median results corresponding to lower initial condom consistencies cannot be seen on the graph, it indicates that the estimated lowest level of condom consistency is 0%. Where the 95% CrI cannot be seen on the graph, it indicates that the 95% CrI is very close to or exactly the same as the median.

With PrEP use-effectiveness of at least 65%, the static model predicts that median reductions in condom use of at least 85% will be possible without increasing HIV risk. The dynamic model broadly supports this conclusion, with less than 25% relative difference between the model medians and CrIs after five years, and less than 35% relative difference after 20 years in the *Epidemic Equilibrium* scenario. Importantly, under the *Increasing Epidemic* scenario, these differences are much more pronounced, with up to 60% relative difference between medians and CrIs after five years, and up to 65% relative difference (85% between 95% CrIs) after 20 years.

For initial condom consistencies of up to 50%, the static model predicts that FSW on PrEP with use-effectiveness of at least 65% can stop using condoms completely without increasing HIV risk. This is consistent with the dynamic model conclusions under the *Epidemic Equilibrium* scenario. Under the

Increasing Epidemic scenario, this only holds where PrEP use-effectiveness is at least 85% (rather than 65%) (Figure 3; *Appendix 3: Supplementary Materials Table S2a & Sb*).

ii. Or where initial condom consistencies are low (e.g. <50%).

Figure 4 shows the lowest levels of condom consistency tolerated after PrEP introduction, calculated using the static and dynamic models for initial condom consistencies (before PrEP introduction) of 10% and 30%. The lowest levels of condom consistency tolerated are shown corresponding to PrEP use-effective of 25% (in green), 45% (in pink), 65% (in orange), and 85% (in blue). The dotted lines represent median estimates and shaded areas represent the 95% CrIs. The top row depicts the *Epidemic Equilibrium* scenario, and bottom row the *Increasing Epidemic* scenario.

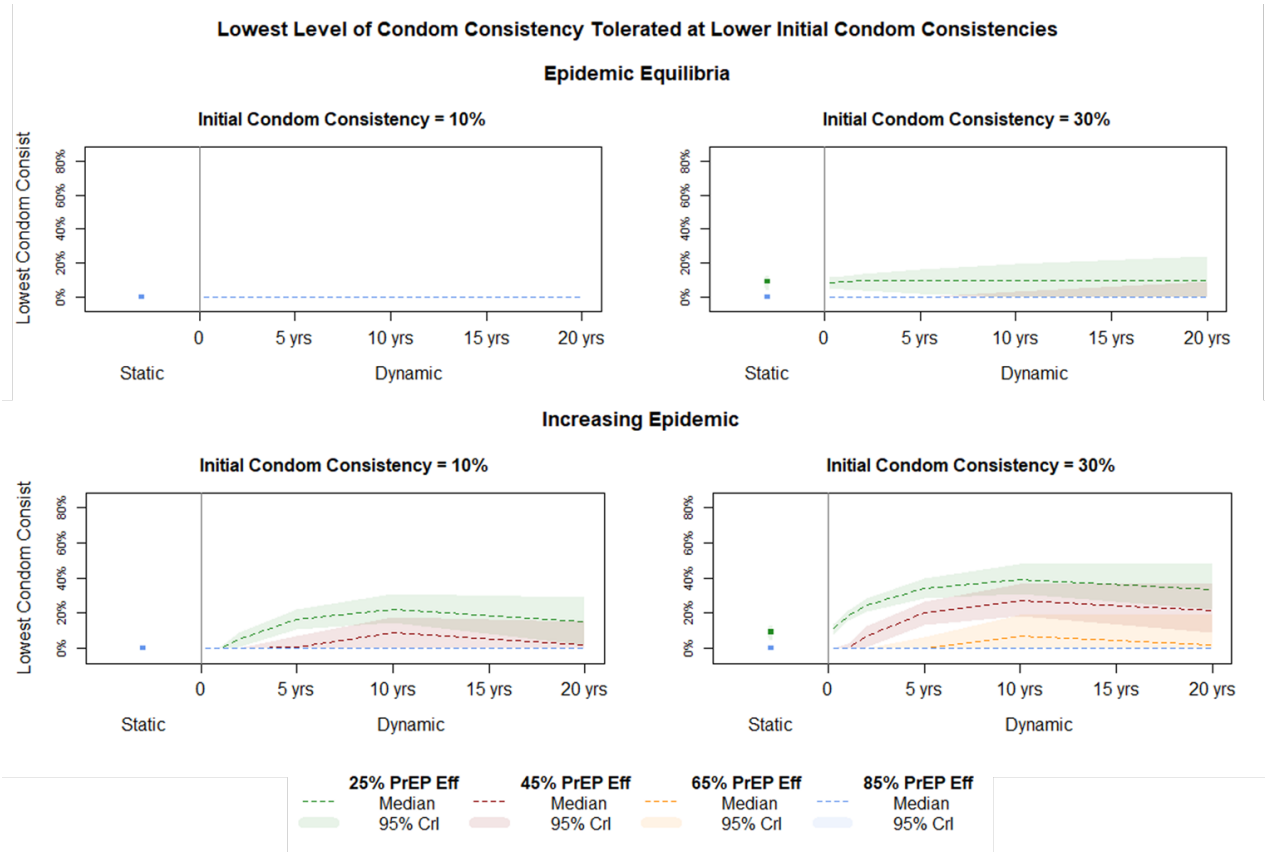

Figure 4: Lowest level of condom consistency tolerated at lower levels of initial condom consistency, for both scenarios Epidemic Equilibrium and Increasing Epidemic.

The lowest levels of condom consistency tolerated on PrEP are depicted for initial condom consistencies of 10% (left) and 30% (right). Each graph shows the lowest level of condom consistency estimated by the static model, and by the dynamic model over a time horizon of 3 months to 20 years, corresponding to PrEP use-effectiveness levels of 25%, 45%, 65% and 85%. The first row of graphs corresponds to the scenario Epidemic Equilibrium and the second row of graphs corresponds to the scenario Increasing Epidemic. The dotted lines are median estimates and shaded areas are 95% CrIs (colour coding in legend). Where the median results corresponding to specific levels of PrEP effectiveness cannot be seen on the graph, it indicates that the lowest level of condom consistency tolerated is 0%. Where the 95% CrI cannot be seen on the graph, it indicates that the 95% CrI is very close to or exactly the same as the median.

Under the *Epidemic Equilibrium* scenario the dynamic model supports the outcomes of the static model especially well in the short term, with relative difference between medians of less than 5% after five years (<25% between the 95% CrIs), and less than 5% relative difference by 20 years (<70% between 95% CrIs). Under the *Increasing Epidemic* scenario, the model differences are large over time, e.g. estimates from the dynamic model of the lowest level of condom consistency tolerated are up to double the levels estimated by the static model after 5 years (Figure 4; *Appendix 3: Supplementary Materials Table S2a & S2b*).

3. *Even with the achievement of low levels of PrEP use-effectiveness (e.g. ≤45%), reductions in condom consistency are possible without increasing HIV risk.*

As with the static model, under the *Epidemic Equilibrium* scenario the dynamic model predicts that some decreases in condom consistency on PrEP will always be possible without increasing HIV risk over the 20-year time horizon, even for lower levels of PrEP use-effectiveness of up to 45%. This holds true under the *Increasing Epidemic* scenario up to a five-year time horizon.

Discussion

Main findings of this study

This study demonstrates that there are contexts in which static models can provide useful deductions to guide policy making around the introduction of a new HIV intervention. Static models may have advantages to guide programming over short-medium time horizons in certain settings. However, over longer timeframes, static models may not sufficiently emphasize situations of programmatic importance, especially in contexts where underlying epidemics are not at equilibrium. PrEP is likely to be of benefit in reducing HIV risk in high-burden settings, even if moderate reductions in condom use occur.

What is already known on this topic

It is well established that dynamic models are more appropriate to address policy questions where it is important to account for the downstream effects of population interactions and evolving contextual factors over time.[5,6,26,27] Both static and dynamic models have been used to inform policy making in the field of HIV.[10,11,13,39,40] Existing studies have cautioned that static models may underestimate the contribution of epidemic drivers to HIV transmission over time.[18,28] However, to date, no study has assessed the epidemic contexts and timeframes over which simple static models may suffice to inform decision making in the field of HIV, especially in the context of the introduction of new prevention interventions.

What this study adds

This study compares the outcomes of a static model with the outcomes of a matched dynamic model, applied to different epidemic contexts across time horizons. Both models are used to assess the absolute and percentage reductions in condom consistency that can be tolerated, without HIV risk increasing, following introduction of PrEP for FSW. We found that over short-medium time-horizons of up to five years, the static model approximates the outcomes of the dynamic model fairly consistently. Over longer timeframes of up to 20 years, there are contexts in which the reductions in condom use predicted by the static model do not hold under the dynamic model formulation; particularly where initial condom consistency is reasonably high (≥50%) and/or PrEP use-effectiveness is low (≤45%). The differences between the two models are greater where the underlying HIV epidemic is increasing (Figure 1 & 2, *Appendix 3: Supplementary Materials Tables S2a*

& S2b). The structural sensitivity analysis (removing model parameters relating to ART, circumcision and STIs) showed bigger differences between model outcomes in situations where PrEP use-effectiveness is low (≤45%) and initial condom consistency is at least 30%. Introducing PrEP where the underlying HIV epidemic is fully endemic in 2030 (rather than at equilibrium in 2015) led to differences under the same situations, although smaller in magnitude. The difference between the models' outcomes arise predominantly from the dynamic model's ability to capture changes in HIV prevalence over time, which is highlighted where PrEP use-effectiveness is insufficiently high enough to mask greater reductions in condom use.

Nonetheless, the broad-stroke policy conclusions predicted by the static model hold under the dynamic model formulation. Specifically, in high HIV burden contexts, PrEP for FSW is likely to be of benefit in reducing HIV risk even if reductions in condom use occur; that reductions in condom consistency can be better tolerated by FSW achieving high levels of PrEP effectiveness or with low baseline condom consistencies; and efforts to promote condom use will be especially critical for FSW with high levels of baseline condom consistency but who are anticipated to adhere less well to PrEP.

Simple, static models have a structural advantage over dynamic models, as they can usually be more easily analytically manipulated to deduce conclusions to guide policy making. These take-aways are often additional to those that can be gleaned through numeric and graphic assessment of either model's outcomes. Noting that model results are usually discounted over longer time-horizons due to uncertainty in underlying assumptions or implementation contexts, there may be merits for using static models to guide the introduction of new HIV interventions over short-medium time horizons, especially where the underlying HIV epidemic is well-evolved. Static models may also be better suited to guide the roll out of interventions intended for short term-use, such as PrEP, which is intended to cover seasons of risk.[31]

In contexts with increasing epidemics, dynamic models may be more appropriate to guide the programming of interventions for long-term use. Building on the conclusions in Mishra and colleagues,[18] this study underscores that decision maker reliance on the magnitude of intervention effectiveness assessed through static models, such as the UNAIDS Modes of Transmission model,[10] should be cautioned in contexts where HIV prevalence is increasing, e.g. in the relevant sub-epidemics in Eastern Europe, South East Asia, the Middle East and South America, especially in relation to high burden (e.g. key) populations.

Future studies could extend this model comparison to other infectious diseases to understand the conditions under which static models are sufficient to inform policy making. This may be especially pertinent for diseases where there is limited understanding of key components required in dynamic

model construction (e.g. transmission dynamics or their quantification), but comparably better understanding of the narrower information set needed to formulate static models.

Limitations of this study

There are several limitations to this study. The models used in this analysis are simplified formulations of static and dynamic models, to facilitate comparison. They do not account for different levels of PrEP coverage or population heterogeneity, relying instead on population averages. For the same reason, these two populations were explored in isolation without accounting for interactions with wider societal groups. Assessment of the effects of behavioural disinhibition are limited to FSW, not the downstream effects on partner populations.

The analysis does not explicitly explore potentially important correlations between risk factors and PrEP effectiveness. However, the impact of correlations between initial condom consistency and PrEP adherence can be easily deduced through the scenarios explored (*Figures 1 & 2).*

The data used to characterise the FSW and their partner population in Hillbrow, South Africa, is limited by age and in some cases reliance on self-reports of sexual behaviour, which are susceptible to under-reporting. Data uncertainty is addressed to some extent through the uncertainty analysis.

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4.4 Implications for Thesis

Research Paper 2 concludes that broad-stroke conclusions of Research Paper 1 regarding the reductions in condom consistency tolerated without HIV risk increasing following the introduction of PrEP for high-risk women do indeed hold under dynamic formulation. Specifically, in high HIV burden contexts, PrEP for high-risk women is likely to be of benefit in reducing HIV risk even if reductions in condom use occur; reductions in condom consistency can be better tolerated by FSWs achieving high levels of PrEP effectiveness or with low baseline condom consistencies; and efforts to promote condom use will be especially critical for FSW with high levels of baseline condom consistency but who are anticipated to adhere less well to PrEP.

However, the paper concludes that over longer time horizons (upwards of 5 years) the static model under-emphasises the specific situations that may be of programmatic importance. Specifically, where a high-risk woman's initial condom consistency is reasonably high ($\geq$50%) and/or PrEP use-effectiveness is low ($\leq$45%), the levels of reduction in condom use predicted by the static model do not hold under the dynamic formulation. This is especially the case where the underlying HIV epidemic is still increasing.

The results of Research Paper 2 indicate that there are merits in using static models to inform policy making around the introduction of an HIV prevention intervention in high-burden contexts over short-medium time horizons, especially where the underlying HIV epidemic is well-evolved. This is a pertinent conclusion, considering the relative benefits of static models over dynamic models for use in policy making (including ease of communication, understanding, adoption and critiquing), as well as that some HIV prevention interventions are intended for short-term use (as in the case of PrEP, which is intended for seasons of risk). However, in contexts with increasing epidemics, dynamic models are more appropriate to guide the programming of HIV prevention interventions for long-term use.

Chapter 5

5. Research paper 3: Time to scale up PrEP beyond the highest-risk populations? Modelling insights from high-risk women in sub-Saharan Africa

5.1 Introduction to Research Paper 3

Research paper 3 aims to respond to thesis objectives 4 and 5 by exploring strategies for PrEP scale up across high-risk women at population-level, weighing overall HIV infection reduction and cost-effectiveness. To explore how these strategies may differ by epidemic and implementation context, Research Paper 3 applies this analysis to 3 country contexts in sub-Saharan Africa with different epidemic profiles and levels of HIV burden: South Africa (20.4% adult HIV prevalence[1]), Zimbabwe (12.7% adult HIV prevalence[1]) and Kenya (4.7% adult HIV prevalence[1]).

The contexts in which the models are being applied are stable generalised high prevalence HIV epidemics[2]. The timeframe for the analysis was taken to be 1 year, given that PrEP is intended to cover seasons of risk and that few PrEP demonstration programs have achieved significant retention in women in this context beyond the first 12 months.[3,4] Given the conclusions of Research Paper 2 that static models are sufficiently robust to guide decision making around the introduction of an HIV prevention intervention in high HIV burden contexts over short-medium time horizons where the underlying HIV epidemic is well-evolved, and in view of their comparative merits to inform policy making, this study adopted static rather than dynamic models of HIV risk.

At the time of undertaking this study, PrEP roll out in all three countries was focused on the highest-risk individuals, including female sex workers[5–7], who face significantly higher individual HIV risk[2] than women in the general population. As such, female sex workers were considered the benchmark for assessment of cost-effectiveness and infections averted when assessing PrEP scale-up across a more broadly defined group of women at risk in these contexts[8–10]: to adolescent girls and young women aged 15-24 years (AGYW), to women 25-34 years, and to women 35-49 years.

It is hoped that the conclusions of Results Paper 3 will help inform priority setting as policy makers in sub-Saharan Africa consider scaling-up PrEP across a more broadly defined group of women at risk, accounting for both population-level impact and cost-effectiveness.

5.2 Cover Sheet

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Hannah Grant
Principal Supervisor	Professor Graham Medley
Thesis Title	The scale-up of PrEP for HIV prevention in high-risk women in sub-Saharan Africa: use of mathematical modelling to inform policy making

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

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Lancet HIV
Please list the paper's authors in the intended authorship order:	Hannah Grant, Gabriela B. Gomez, Katharine Kripke, Ruanne V. Barnabas, Charlotte Watts, Graham F. Medley and Zindoga Mukandavire
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	

Student Signature: [redacted] **Date:** 14/11/19

Supervisor Signature: [redacted] **Date:** 14 November 2019

5.3 Research Paper 3

Time to scale up PrEP beyond the highest-risk populations? Modelling insights from high-risk women in sub-Saharan Africa

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Abstract

Background: HIV burden in sub-Saharan Africa remains highest in women. PrEP is an effective HIV prevention measure, currently prioritized for those at highest risk, such as female sex workers (FSW), for whom it is most cost-effective. However, the greatest number of HIV infections in sub-Saharan Africa occur in women in the general population. As countries consider wider PrEP scale-up, there is need to weigh population-level impact with cost-effectiveness to inform priority-setting in the context of resource constraints.

Methods: We developed mathematical models of HIV risk to women and derived tools to guide PrEP programming. The models were fitted to South Africa, Zimbabwe and Kenya, which span a range of HIV burdens in sub-Saharan Africa. The impact, cost and cost-effectiveness of PrEP scale-up for adolescent girls and young women (AGYW), women 25-34 years and women 35-49 years were assessed, accounting for the low program retention levels reported in demonstration projects.

Findings: PrEP could avert substantially more infections a year among women in general population than among FSW. The greatest number of infections could be averted annually among AGYW in South Africa (24-fold the number as for FSW). In Zimbabwe, the greatest number of infections could be averted among women 25-34 years (8-fold that as for FSW), and in Kenya similarly between AGYW and women 25-34 years (3-fold that as for FSW).

Conclusions: PrEP has the potential to substantially reduce the numbers of new HIV infections in HIV-endemic countries in sub-Saharan Africa, even considering low levels of PrEP program retention in women. This will necessitate PrEP being made widely available beyond those at highest individual risk, including to women in the general population. Wide scale roll out will require continued integration of PrEP into a range of national services and at community level, in order to significantly bring down the costs and improve cost-effectiveness.

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Author Contributions: ZM, CW, GM, GBG and RB inspired the study. HG and ZM designed the study. HG undertook the modelling analyses and drafted the manuscript. GBG developed the cost model. ZM, GM, CW, GBG, KK and RB reviewed and provided feedback on the draft manuscript.

Declaration of Interests: The authors declare no conflicts of interest.

Background

Women remain the most affected by the global HIV epidemic. In sub-Saharan Africa, the region with the greatest HIV burden, 59% of new adult infections are among women[2]. In 2017, a quarter of all new infections in the region were among adolescent girls and young women (AGYW) aged 15-24 years[2], whilst female sex workers (FSW) are up to 20 times more likely to be HIV positive than women in the general population[11].

Oral pre-exposure prophylaxis (PrEP) has shown HIV prevention efficacy in randomised controlled trials[12]. It is hoped PrEP will address some of the drivers of HIV in women, which include lack of agency to negotiate sex and condom use[2]. Aside from women in sero-discordant relationships[13], PrEP demonstration projects have faced challenges in retaining women[3,4,14], raising concerns about the ability of programs to avert infections when scaled-up[2]. A recently completed PrEP demonstration project among FSW in South Africa reported 22% 12-month program retention rates[3]. In spite of promising 3-month retention levels[15], early results from programming in Kenya[4,16] and Zimbabwe[17] show even lower retention rates in AGYW than FSW.

As PrEP is rolled out in countries in line with 2016 normative guidance, its use has been prioritised for populations at substantial risk of HIV[18]. Among women in sub-Saharan Africa, PrEP is being prioritized for FSW and, in certain contexts, AGYW[19] (including through PEPFAR DREAMS programmes[20,21]). PrEP programs are being hosted by services tailored for groups at highest risk of infection, or in general services with screening tools used to identify those most at risk[18,22]. Increasingly, there is pressure for countries to move away from focused programs for key populations, towards universal access to PrEP as part of a rights-based approach to health[23]. The language of PrEP programming is shifting to refer to populations that could benefit from PrEP, rather than to focus on individual risk[23].

Whilst FSW are typically the women at highest HIV risk[19], HIV incidence among women in the general population varies significantly by age range across countries in sub-Saharan Africa[19]. To date, six of the seven finalised population-based HIV impact assessments (PHIA) undertaken in PEPFAR-supported sub-Saharan African countries reveal higher levels of incidence in women 25-34 years or 35-49 years than in AGYW[24–30]. Policy makers are now having to weigh the potential benefits and challenges of scaling up PrEP for groups of women at lower individual levels of risk, but in whom the total number of new infections is greater due to vast differences in population sizes[2].

Decisions around PrEP scale-up are taking place in a context of limited external resources for HIV, constraints in domestic budgets and a global push for countries to prioritize resources to reach the 90-90-90 treatment targets[2]. These decisions mirror those previously faced by policy makers in determining whether to scale up antiretroviral treatment for individuals at higher CD4 counts, balancing comparatively lower benefits for individuals with potential for greater population-level prevention effects[18].

Several modelling studies have evaluated the cost-effectiveness and impact of PrEP for high-risk populations in sub-Saharan Africa[31–33]; between key populations or key populations and men/ women in the general population[33–35]; relative to other HIV prevention interventions[36–38]; and relative to the scale up of antiretroviral treatment (ART)[39–41]. Studies typically find PrEP to be less cost-effective than other established prevention interventions, such as condoms, or scaling up early ART, but cost-effective as part of a combination prevention approach for those at greatest risk. Studies have not systematically accounted for the low levels of PrEP program retention recently seen in women in sub-Saharan Africa[31–38,42,43]. No study to date has assessed the scale-up of PrEP from higher- to lower-risk women population groups in sub-Saharan Africa, weighing cost-effectiveness on an individual basis with the need to avert the greatest number of infections at a population level.

It is in this context we undertake our study, which aims to highlight key considerations to feed into policy decision making, as countries consider scaling-up PrEP across a more broadly defined group of women at risk in sub-Saharan Africa, accounting for individual- and population-level impact and cost-effectiveness. We use case studies of three HIV-endemic countries in sub-Saharan Africa: South Africa, Zimbabwe and Kenya. These countries were chosen as they span a range of HIV burden levels in the region, each have adopted a national PrEP strategy[5–7], and have been at the forefront of PrEP roll-out in sub-Saharan Africa[23].

Methods

As the contexts in which the models are being applied are stable generalised high prevalence HIV epidemics[2], we adopted static mathematical models of HIV risk[44–46]. Static models have the advantage of being a comparatively easier tool for use and communication with policy makers, and have been shown to be robust to inform policy making around the introduction of new HIV interventions over short-medium time horizons in stabilised epidemics[47].

The mathematical models take the Bernoulli formulation of HIV risk[47], where the sexual partners of high-risk women are assumed to come from population i in which the proportion HIV infected is p_i. High-risk women are assumed to have C_i partners from each population per year, with whom they have an average n_i sex acts per year each. Condoms are assumed to be used with partners from each population with consistency γ_i. Upon introduction, high-risk women from group j are assumed to adhere to PrEP at an average level α_j, which corresponds to a level of HIV risk reduction, θ_{α_j}. We used the estimates for women from the Partners Demonstration Project[48] to relate levels of PrEP adherence to levels of HIV risk reduction. High-risk women from group j enrolled in PrEP projects are assumed to have a 12-month retention level r_j. The models account for STI levels, levels of viral load suppression due to ART in HIV positive partners, and male circumcision. Analyses were conducted over a one-year timeframe, as PrEP is intended to cover 'seasons' of HIV risk (rather than long-term use), and few PrEP demonstration programs have achieved significant retention in women in this context beyond the first 12 months[3,4]. All models were programmed in R version 3.3.2.

Simple tools to help guide PrEP programme decision making

First, three simple tools were developed to inform programme decision making using a basic set of information typically available to PrEP programmes[49].

Heatmaps to estimate HIV incidence in women

Heatmaps were developed to help decision makers estimate the annual HIV incidence in women by number of monthly sex acts, average condom use and underlying epidemic setting. We demonstrated four different example epidemic settings: underlying HIV prevalence in partner populations of 5%, 10%, 20% and 40%. In many sub-Saharan African contexts, 5% HIV prevalence is illustrative of HIV prevalence in males 15-24 years, 5-20% the HIV prevalence in males 25-49 years,

and 20-40% the HIV prevalence in the clients of FSW (*Appendix 4: Supplementary Materials: Table S2).*

Simple rule to draw insights around relative cost-effectiveness of PrEP

A simple rule was developed to help policy makers draw qualitative program insights around conditions under which it may be equally cost-effective to roll out PrEP in a lower-risk group (e.g. AGYW) as in a higher-risk group (e.g. FSW). Cost-effectiveness is defined as the incremental cost of PrEP for a woman retained at level r_j in a PrEP program over a 12-month period, divided by the risk reduction achieved on PrEP when adhered to at level α with retention r_j over the 12-month period. In the absence of willingness-to-pay thresholds, relative cost-effectiveness was assessed by comparing these estimates of cost per infection averted between populations.

Heatmaps to estimate the relative unit cost at which PrEP scale-up from higher- to lower-risk women is cost-effective

Heatmaps were developed to help decision makers estimate the relative unit cost at which it will be cost-effective to scale up PrEP from a comparatively higher- (e.g. FSW) to comparatively lower-risk woman (e.g. AGYW), also using the number of monthly sex acts, average condom use and underlying epidemic setting. Different epidemic settings were illustrated by taking HIV prevalence in the higher-risk women's partner population of either 20% or 40%. For each of these scenarios, HIV prevalence in the lower-risk women's partner population was then simulated at 1/4, 1/2, 3/4 and 1 times the prevalence of the higher-risk women's partner population (i.e. 5%, 10%, 15% and 20%; and 10%, 20%, 30% and 40% respectively). These scenarios span a range of epidemic settings in sub-Saharan Africa[19].

It was assumed that the higher-risk group had 22% PrEP program retention levels and all women retained had PrEP adherence levels of 70-85% (corresponding to risk-reduction of 73-99%[48]), consistent with the South African TAPS demonstration project in FSW[3]. PrEP program retention for the lower-risk group was simulated between $\pm$25% of the 22% retention levels of the higher-risk group (i.e. 16.5%-27.5%), consistent with the difference between AGYW and FSW retention in Kenya[4]. For lower-risk women retained in the PrEP program, it was assumed that PrEP adherence was the same as the higher-risk group.

Country case studies

Assessment of cost-effectiveness and impact of scaling-up PrEP

To highlight key considerations to feed into decision making as countries consider scaling-up PrEP beyond those at highest-individual risk, we assessed the cost-effectiveness and impact of scaling-up PrEP for women across a spectrum of high HIV risk in South Africa, Zimbabwe and Kenya. Given the significantly higher individual HIV risk faced by FSW[2] FSW were taken as the benchmark for assessment. In comparison, we considered the scale-up of PrEP to three groups at high HIV risk in the general population[8–10]: AGYW (aged 15-24 years), women 25-34 years and women 35-49 years. No further targeting of PrEP was assumed. Women aged 50+ were not evaluated given the paucity of information available to parameterise and fit the models in all three country contexts[24,50–53].

FSW were assumed to have partners drawn from two populations: regular partners and clients. AGYW were assumed to have partners drawn from their own age group and the 25-34 years age group, given that 17% and 14% women 15-19 years report relationships with men at least 10 years older in Zimbabwe[51] and Kenya[52] respectively, and 36% South African women 15-19 years report relationships with men at least 5 years older[8]. Women 25-34 years and women 35-49 years were assumed to have partners drawn from their own age groups given the lack of data to suggest otherwise. However, this assumption was explored further through the structural sensitivity analysis. Data ranges to parameterise the models were drawn from the literature and fitted to the latest national estimates of HIV incidence by group[1,24,54–60] using Bayesian Monte Carlo Filtering with Latin Hypercube Sampling, assuming uniform prior distributions, yielding at least 200 fits across the four groups for each country.

FSW were assumed to have 12-month PrEP program retention and adherence levels consistent with the South African TAPS demonstration project[3]. AGYW, women 25-34 years and women 35-49 years were assumed to have program retention levels between $\pm$25% of these 12-month FSW retention levels[4], and the same adherence levels as FSW retained in the program. To explore the role of adherence, the parametric uncertainty analyses were repeated with 1) 25% lower HIV risk-reduction across all groups, and 2) 25% lower HIV risk-reduction across AGYW, women 25-34 years and women 35-49 years (but unchanged among FSW).

We estimated the unit costs of PrEP program delivery per person retained after 12-months (Table 1). We assumed FSW were offered PrEP through programmes with outreach and community mobilisation components and all other women were offered PrEP through sexual and reproductive health services, with AGYW having larger counselling components. Service delivery costs were taken

from demonstration projects and previous costing publications in Kenya[61,62] and South Africa[3]. For Zimbabwe, non-tradable components of the South African estimates were transferred using purchasing power parities[63] following standard methods[64]. Drug costs were assumed to be USD57-80 per year, spanning internationally traded values with freight and distribution[65], and highest reported prices in demonstration projects. All published costs were adjusted to USD 2017[66].

Country	**Population**	**Unit cost** (min - max)	Service delivery excl. drugs	Drugs only (min - max)
South Africa	FSW	190 - 210	130	57 – 80
South Africa	AGYW (15-24 years)	149 - 169	89	57 – 80
South Africa	Women (25-34 years)	128 - 148	68	57 – 80
South Africa	Women (35-49 years)	87 - 107	27	57 – 80
Zimbabwe	FSW	293 - 317	237	57 – 80
Zimbabwe	AGYW (15-24 years)	219 - 243	163	57 – 80
Zimbabwe	Women (25-34 years)	181 - 204	124	57 – 80
Zimbabwe	Women (35-49 years)	106 - 130	50	57 – 80
Kenya	FSW	399 - 423	343	57 – 80
Kenya	AGYW (15-24 years)	358 - 382	302	57 – 80
Kenya	Women (25-34 years)	294 - 318	238	57 – 80
Kenya	Women (35-49 years)	185 - 209	129	57 – 80

Table 1: *Cost estimates per person retained on PrEP after 12-months by population and country. Costs in USD 2017.*

Structural sensitivity analysis

Whist the literature only provides evidence of women aged 15-25 years having male partners from an older population group in these three settings, we explored how the model outcomes change if women aged 25-34 years are also assumed to have male partners from an older population group (35-49 years) with higher HIV prevalence. This model structural sensitivity analysis was

parameterised illustratively assuming 50% the number of partners a year from the male population 35-49 years as had by women 35-49 years (in addition to their partnerships with males 25-34 years).

Further information on model structure, parameterization, calibration and costs are set out in the *Appendix 4: Supplementary Materials.*

Results

Simple tools to help guide PrEP programme decision making

Heatmaps to estimate HIV incidence in women

The estimated annual HIV incidence in women, by number of monthly sex acts and average condom use, is shown in Figure 1. The estimates are shown for four cases: underlying HIV prevalence in partner population of 5%, 10%, 20% and 40%.

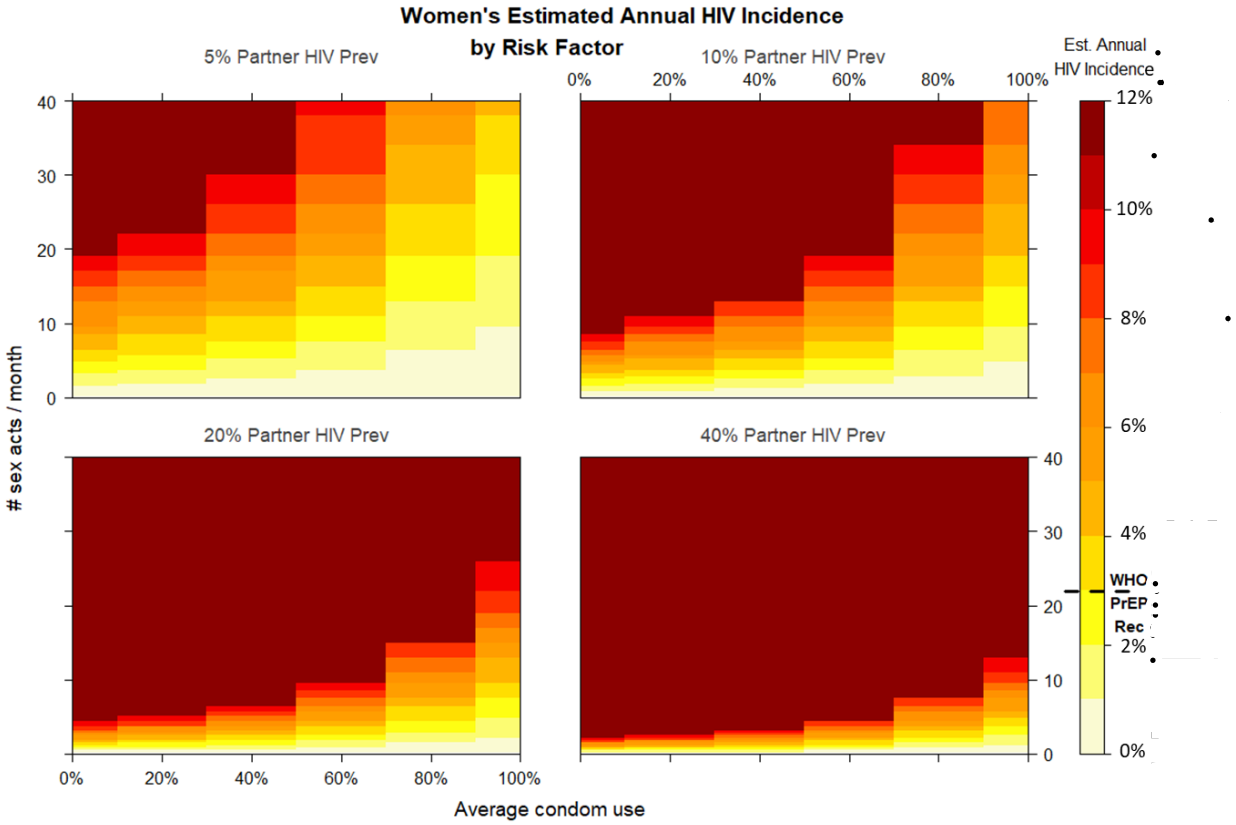


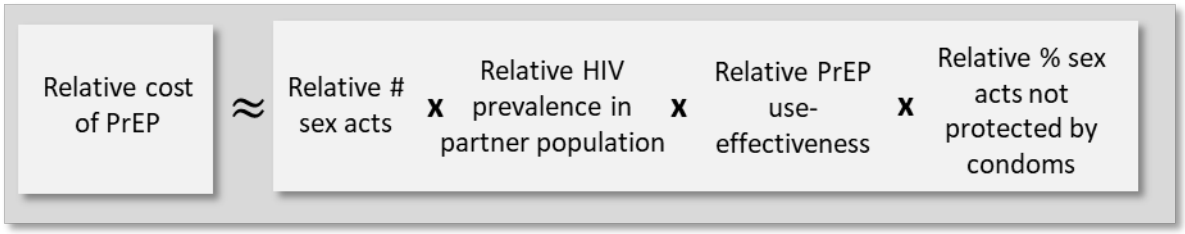
Figure 1: Women's estimated HIV incidence by risk factor.
The heatmaps show the estimated annual HIV incidence in women according to their number of sex acts per month (number of partners multiplied by average number of sex acts with each per month), and average condom use. The estimated annual HIV incidence is shown by colour (according to the colour key on the right-hand side of the graph) in incidence increments of 1% or 1 per 100 person years. An annual incidence of at least 3% or 3 per 100 person years is coloured light orange and corresponds to the WHO recommended threshold for PrEP eligibility18. The 4 heatmaps correspond respectively (left to right, top to bottom) to underlying partner HIV prevalence of 5%, 10%, 20% and 40%. The heatmaps are calculated using equation (S1.1) from the Appendix 4: Supplementary Materials, assuming that a women's partners are drawn from a single population and no women are on PrEP.

Figure 1 shows that where women's partners come from a population with HIV prevalence of up to 5%, women will be below the 3%[18] WHO-recommended HIV incidence threshold for PrEP where the

number of sex acts a month is up to 10 and average condom use is at least 50% (areas shaded yellow in the heatmap). As the underlying HIV prevalence in the partner population increases, women will need higher levels of condom consistency or to engage in fewer sex acts a month to be below the WHO incidence threshold for PrEP (areas shaded orange-red). Where women's partner population have a prevalence of 40%, women will almost uniformly be above the threshold for PrEP.

Simple rule to draw insights around relative cost-effectiveness of PrEP

To help policy makers draw qualitative program insights around conditions under which it may be equally cost-effective to roll out PrEP in a lower-risk group as in a higher-risk group, we derived the simple rule set out in Equation 1. This rule can be approximated based on information typically estimated by PrEP programs[49]. The relative measures stated are for lower-risk women compared to higher-risk women.



Equation 1: Simple rule to draw insights around the relative cost at which PrEP will be equally as cost-effective to scale up in a lower-risk group as it will be in the high-risk group.
All relative measures refer to the low-risk group in comparison to the high-risk group and pertain to the same time period. The relative cost of PrEP is the unit cost of PrEP per individual retained in the program over the given time period. The number of sex acts is the number of partners multiplied by the average number of sex acts with each over the given time period. The use-effectiveness of PrEP is the HIV-risk reduction through use of PrEP at a given level of adherence, for a population with a given average program retention level49. This rule holds under the condition that the prevalence in the partner population multiplied by the average number of sex acts with each partner per unit of time, multiplied by the basic risk of HIV transmission through peno-vaginal sex, the average proportion of sex acts not protected with condoms and PrEP is much less than 1. This simple rule can be approximated using data collected in PrEP programs49. Further details on the derivation of this rule and associated conditions are given in the Appendix 4: Supplementary Materials.

Heatmaps to estimate the relative unit cost at which PrEP scale-up from higher- to lower-risk women is cost-effective

The relative cost at which PrEP will be equally as cost-effective to scale up in the lower-risk group as it will be in the higher-risk group, is demonstrated in four scenarios shown in Figure 2: underlying HIV prevalence in the lower-risk women's partner population of 10%, 20%, 30% and 40%, and with HIV prevalence in the higher-risk women partner population of 40% (approximately that of FSW clients in higher-burden settings). The equivalent figure corresponding to a lower HIV prevalence in

the higher-risk women's partner population of 20% is given in *Appendix 4: Supplementary Materials – Figure S4.*

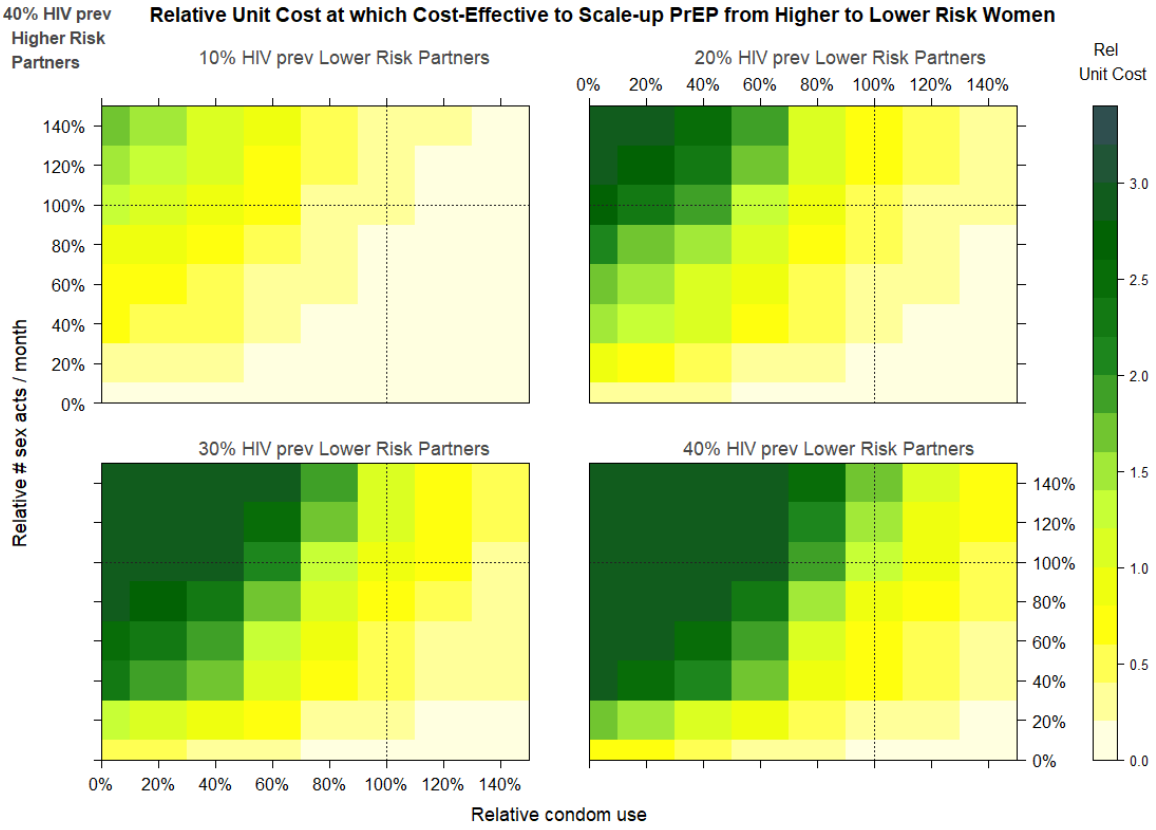


Figure 2: Relative unit cost at which it is cost-effective to scale up PrEP from a higher- to lower-risk women group. *The heatmaps show the relative unit cost at which it is cost-effective to scale up PrEP from a higher- to a lower-risk group. The relative unit cost at which PrEP is cost-effective is shown by the relative average condom use in the lower-risk group compared to the higher-risk group (x-axis), and the relative number of sex acts a month for women in the lower-risk group compared to the higher-risk group (y-axis). The unit cost of PrEP in the lower-risk group relative to the higher-risk group at which PrEP is equally cost-effective between the two groups is shown by colour, according to the colour key on the right-hand side of the graph. A colour within the yellow spectrum denotes that the relative unit cost of PrEP in the lower-risk group relative to the higher-risk group has to be less than 1 for it to be equally as cost cost-effective. A colour within the green spectrum denotes that the relative unit cost of PrEP in the lower-risk group relative to the higher-risk group will be greater than 1 for it to be equally as cost cost-effective. The 4 heatmaps correspond respectively (left to right, top to bottom) to underlying partner HIV prevalence of 10%, 20%, 30% and 40% in the lower-risk group's partner population and all of them corresponding to 40% HIV prevalence in the higher-risk women's partner population. The heatmaps are calculated using equation (S1.5) from the Appendix 4: Supplementary Materials, assuming that women's partners are drawn from a single population each. The higher-risk group are assumed to have 12-month PrEP program retention levels of 22%3 and adherence levels of 70-85% (corresponding to a risk reduction of 73-99%48). The PrEP program retention levels for the lower-risk group were simulated between +/- 25% the retention of the higher-risk group4. For those lower-risk women retained in the PrEP program, it was assumed that PrEP adherence was the same as the higher-risk group.*

Where HIV prevalence in the lower-risk women's partner population is 10%, the results show that irrespective of both women's condom use, the unit cost of PrEP in the lower-risk group will have to be much lower than in the higher-risk group for PrEP roll-out to be equally as cost-effective (areas

shaded yellow), other than where the numbers of monthly sex acts in the lower-risk group exceeds that of the higher-risk group (areas shaded green). As HIV prevalence increases in the lower-risk women's partner population relative to the higher-risk women's partner population, PrEP will be equally cost-effective between the two groups at increasingly higher unit costs for the lower-risk group relative to the higher-risk group.

Country case studies

The model fits to HIV incidence for South Africa, Zimbabwe and Kenya are given in *Appendix 4: Supplementary Materials: Figures 1-3.*

Figure 3 shows the maximum unit cost of PrEP for AGYW, women 25-34 years and women 35-49 years, relative to the unit cost of PrEP for FSW, for scale-up to be equally as cost-effective as it is in FSW. This is shown for South Africa (blue), Zimbabwe (orange) and Kenya (green). As comparators, the estimated current relative unit costs are shown (cream).

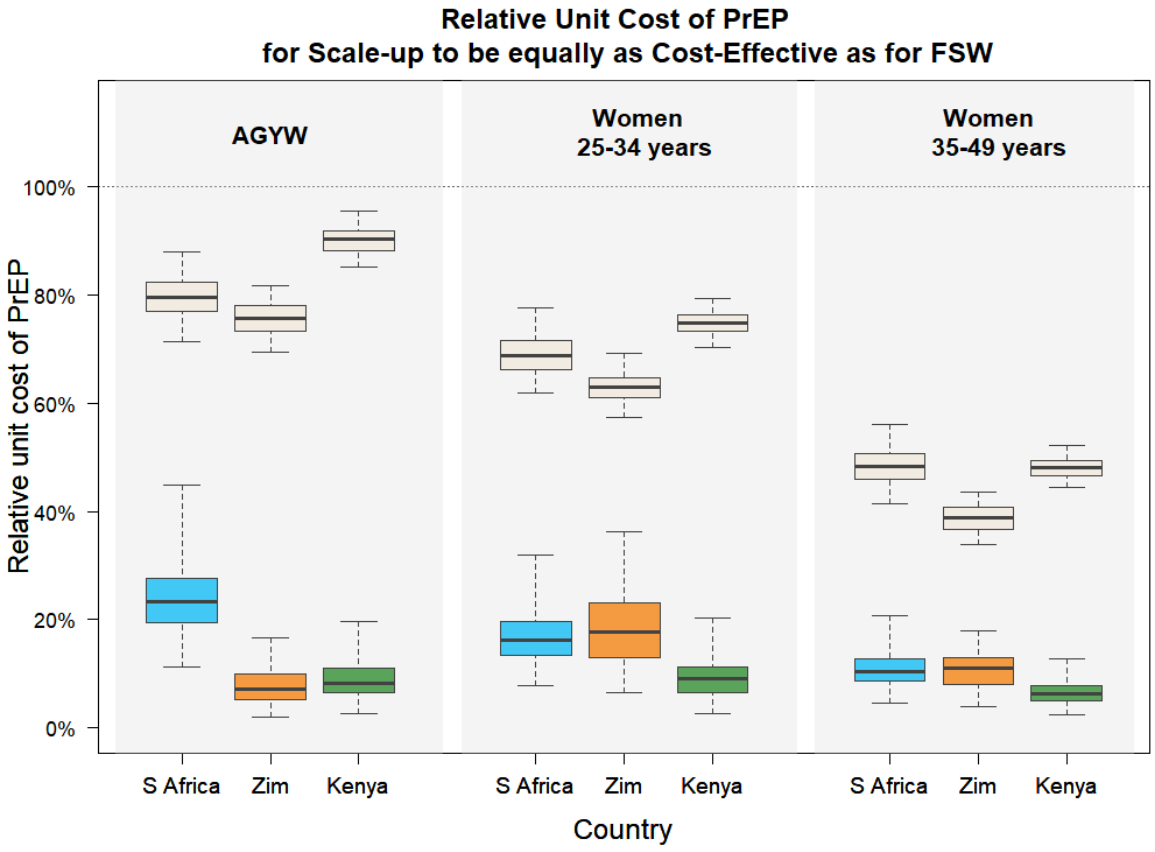


Figure 3: Relative unit cost of PrEP for scale-up to be equally as cost-effective as for FSW.
The boxplot shows the maximum unit cost of PrEP per year for AGYW, women 25-34 years or women 35-49 years relative to the unit cost of PrEP for FSW, for PrEP scale-up in these populations to be equally as cost-effective as it is for FSW (bright-coloured boxes). The maximum relative unit costs are shown, grouped left to right, for AGYW, women 25-34 years or women 35-49 years. Within each age grouping, the results are show by country, left to right, for South Africa (in blue), Zimbabwe (in orange) and Kenya (in green). The maximum relative unit costs are calculated using equation (S2.5) from Appendix 4: Supplementary Materials and assume that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project[3]. As comparisons, current estimates of the unit costs of PrEP for AGYW, women 25-34 years and women 35-49 years, relative to the unit cost of PrEP for FSW are shown for all countries (in cream), calculated using data from Table 1. The abbreviations used in the graph are as follows: AGYW denotes adolescent girls and young women 15-24 years, S Africa denotes South Africa and Zim denotes Zimbabwe.

For example, in the case of AGYW in South Africa, Figure 3 shows that PrEP will be equally cost-effective for AGYW as for FSW at a maximum median relative unit cost of 23.3 % (95% CrI: 13.3%, 36.8%) (furthest left blue boxplot). The current estimated unit cost of PrEP in AGYW relative to FSW in South Africa is median 79.8 % (95% CrI: 73.0%, 87.0 %) (furthest left cream boxplot). If the cost of PrEP for AGYW dropped by median 70.8% (95% CrI: 53.2%, 83.4 %) it would be equally as cost-effective as for FSW (*Appendix 4: Supplementary Materials: Table S3*).

Otherwise, across all other scenarios in all three countries, the unit cost of PrEP for AGYW, women 25-34 years and women 35-49 years would have to drop between median 71.8-91.0% (95% CrIs spanning: 50.8%, 96.5%) to be equally as cost-effective.

Figure 4 illustrates the estimated number of infections that could be averted a year due to PrEP in each high-risk women population group, in each country, for every $100,000 available for PrEP programming. Additional analyses, including the proportion of HIV infections that could be averted a year for every $100,000 allocated to each population group are shown in *Appendix 4: Supplementary Materials: Tables S4, S5* and *Figure S5*.

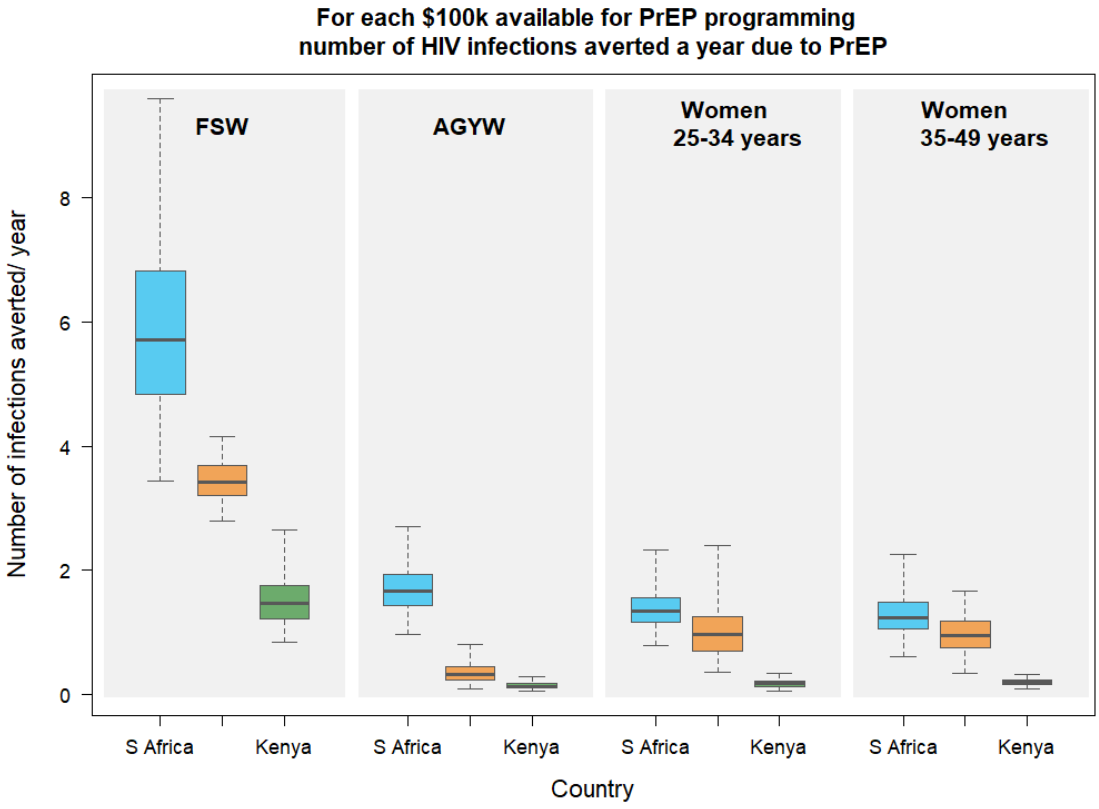


Figure 4: Boxplot of the number of HIV infections that could be averted a year due to PrEP, for each $100k available for PrEP programming.
The boxplot shows, for each $100k available for PrEP programming a year for FSW, AGYW, women 25-34 years and women 35-49 years, the total number of infections that could be averted a year due to PrEP. The number of infections that could be averted a year for each $100k available for PrEP are shown, grouped left to right, for FSW, AGYW, women 25-34 years or women 35-49 years. Within each age grouping, the results are shown by country, left to right, for South Africa (in blue),

Zimbabwe (in orange) and Kenya (in green). The number of infections averted a year is calculated using equation (S2.10) from Appendix 4: Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project3. The unit costs of PrEP for each high-risk women group are as stated in Table 1. These estimates hold until PrEP saturation (determined by retention levels and population size) has been reached in the smallest population group – in this case, FSW. After this point, no additional financial resources will be able to reduce infections per year in this population group.

Given the differences in relative population sizes, Figure 5 demonstrates the relative number of infections that could be averted a year with PrEP at equal coverage levels in AGYW, women 25-34 years and women 35-49 years as in FSW. These results correspond to Table S8 in the *Appendix 4: Supplementary Materials*.

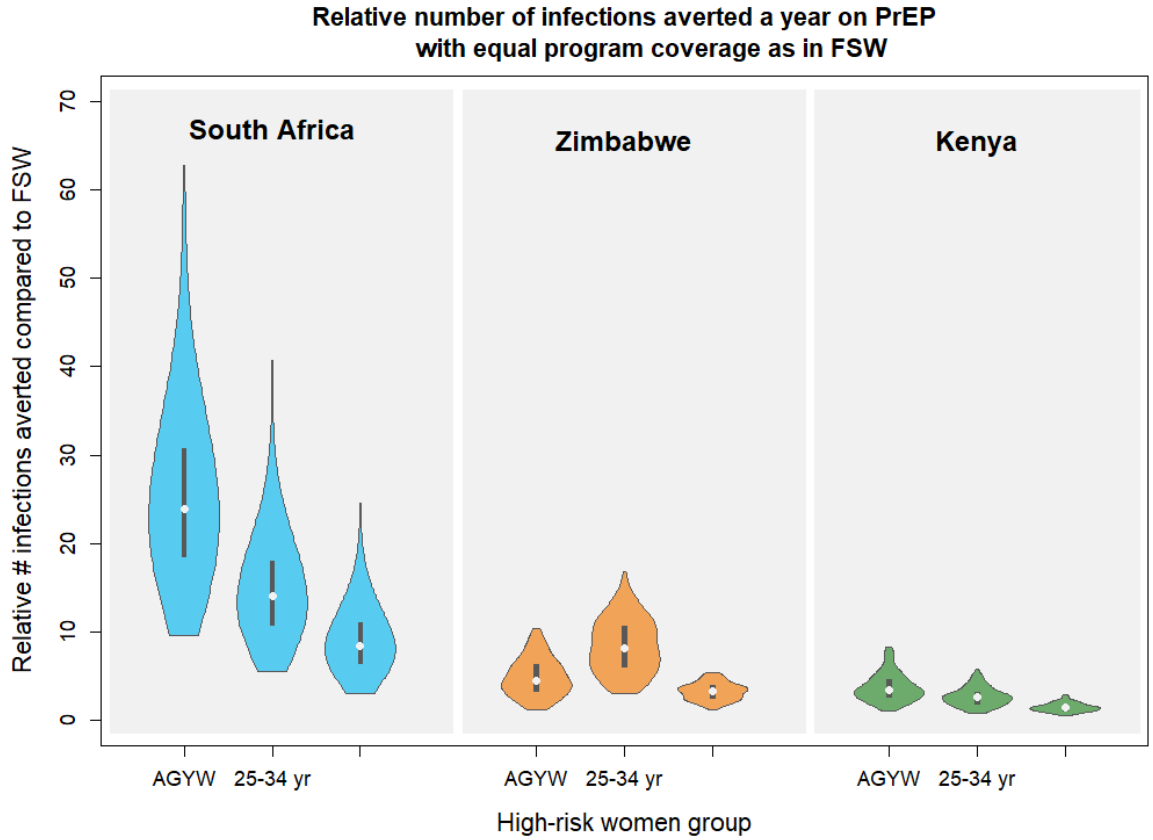


Figure 5: Violin plot of the relative number of infections averted a year on PrEP with equal program coverage as in FSW. *The violin plot shows the relative number of infections that could be averted a year in HIV negative AGYW, women 25-34 years or women 35-49 years, compared to in FSW, if PrEP were scaled up at the same coverage levels as in HIV negative FSW. The relative number of infections that could be averted are shown, grouped left to right, for South Africa (in blue), Zimbabwe (in orange) and Kenya (in green). In the violin plots, the white dots represent the median values, the thick black vertical lines represent the interquartile range, the vertical length of the violin represents the range of values and the width of the violin represents the frequency with which those values occur. The relative number of infections that could be averted are calculated using equation (S2.9) from Appendix 4: Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project3. The abbreviations used in the graph are as follows: AGYW denotes adolescent girls and young women 15-24 years, 25-34 yr denotes women 25-34 years and 35-49 yr denotes women 35-49 years in each country.*

In comparison to the number of infections averted annually in FSW in South Africa, a median 24 times (95% CrI:12, 45) the number of HIV infections could be averted in AGYW, median 14 times (95% CrI:7, 27) in women 25-34 years, and median 8 times (95% CrI:4, 17) in women 35-49 years, if PrEP were rolled out at the same coverage levels across populations.

In Zimbabwe, a median 4 times (95% CrI:2, 9) the number of annual HIV infections could be averted in AGYW, median 8 times (95% CrI:3, 14) in women 25-34 years, and median 3 times (95% CrI:2, 5) in women 35-49 years, in comparison to FSW with equal PrEP program coverage.

In Kenya, a median 3 times (95% CrI:2, 8) the number of HIV infections could be averted in AGYW, median 3 times (95% CrI:1, 5) in women 25-34 years, and median 1 times (95% CrI:1, 3) in women 35-49 years, in comparison to FSW with equal PrEP program coverage.

Sensitivity analyses

Repeating the analyses shown in Figure 3 (relative unit cost for PrEP to be equally as cost effective) and Figure 5 (relative number of infections averted a year with equal program coverage) with 25% reduced adherence-related HIV risk-reduction across all female groups led to <0.01% change across the scenarios (*Appendix 4: Supplementary Materials: Tables S9 and S10)*. Repeating these analyses with 25% reduced adherence-related HIV risk reduction among all non-FSW women groups led to <0.3% change across the scenarios (*Appendix 4: Supplementary Materials: Tables S11 and S12).*

Repeating the analyses in Figures 3 and 5 under the structural sensitivity analysis, exploring the case that women 25-34 years have partners from the 35-49 year age group in addition to their own age group, led to <1% change across scenarios (*Appendix 4: Supplementary Materials: Tables S13 and S14).*

Discussion

This is the first study to assess the potential impact and cost-effectiveness of PrEP scale-up across different high-risk women population groups among countries in sub-Saharan Africa, to highlight key considerations for policy decision making. PrEP should be offered to women at highest HIV risk, such FSW, for whom it is most cost-effective. However, only by extending PrEP to women at comparatively lower risk will new HIV infections reduce substantially.

We developed three simple tools to guide PrEP programming, applicable to any setting using a basic set of information typically available to implementers. First, heatmaps (Figure 1) to estimate the annual HIV incidence in women, by number of monthly sex acts, average condom use and underlying epidemic setting. Second, a simple rule (Equation 1) to gain qualitative program insights around the relative cost at which PrEP will be equally as cost-effective between two groups of women with different HIV risk factors and behaviours. Third, heatmaps (Figure 2) applying the relative cost-effectiveness estimates to different epidemic settings.

By adapting the models to three countries spanning the spectrum of high HIV burden contexts in sub-Saharan Africa, we have seen that the unit costs of PrEP delivery for AGYW, women 25-34 years and women 35-49 years would have to reduce considerably (by estimated median 70.8-91.0% across scenarios) for scale-up to these populations to be as cost-effective as for FSW. Indeed, on an individual basis, PrEP is most cost-effective for FSW than any other high-risk women population group, with a greater number of infections averted a year for every $100k available for PrEP programming in all three country contexts (Figure 4).

However, rolling out PrEP widely for women in the general population has potential to substantially impact on the countries' HIV epidemics. In South Africa, PrEP has the potential to avert approximately 24 times the number of infections annually in AGYW as in FSW when scaled up at equal coverage levels, and approximately 14 and 8 times the number in women 25-34 and 35-49 years respectively. In Zimbabwe approximately 8 times the number of infections could be averted annually in women 25-34 years as in FSW, and approximately 4 and 3 times the number in AGYW and women 35-49 years respectively. In Kenya, approximately 3 times the number of infections could be averted annually in AGYW and in women 25-34 years as in FSW, and around the same number in women 35-49 years as in FSW. The wide variability in the violin plot estimates of the relative number of infections averted by population group (Figure 5) highlight that decisions around PrEP scale-up will need to depend on the specific characteristics of the groups under consideration.

By quantifying the impact that can be achieved through PrEP scale-up across high-risk women groups in each of the three country contexts, this study highlights the potential importance of PrEP roll-out at population level, even considering low levels of program retention and adherence. It underscores the value of universal access to PrEP in sub-Saharan Africa as part of a rights-based approach to health. Policy makers will need to weigh these prospects against affordability, in view of current program costs, budget constraints and program sustainability (although given PrEP is intended to cover seasons of risk, rather than for long term use, it may be more feasibly scaled back over time as population incidence decreases).

Scaling up PrEP for women in the general population has the potential to drive cost reductions through economies of scale, in turn improving cost-effectiveness, allowing more women to be reached with the same budget. Doing so will require countries to continue to integrate PrEP into a range of health, non-health and community services for women in the general population[5–7], which in some instances (e.g. education) may be challenging in local cultural contexts. Advocates' efforts will be important in further reducing drug prices, as will the prioritization of resources for prevention by decision makers. Long-acting PrEP formulations, currently under investigation[67–69], may also help improve cost-effectiveness, if they are able to increase HIV prevention use-effectiveness through improved product adherence and retention in comparison to daily oral pill formulations.

Limitations

This study was conducted using static mathematical models, given their comparative ease for use in policy making. Static models can be more easily tailored to individual settings, necessitating a narrower and more readily available set of data in comparison to the more complex dynamic models typically used to inform HIV decision making. However, they do not capture downstream infections averted in partner populations and the wider society. Many studies have shown that introducing HIV prevention interventions to high-risk groups has greatest impact on reducing onwards transmission early in epidemics when prevalence is low and the basic reproductive rate is high, than in endemic high-burden contexts[70,71], such as those in which our model is applied[2]. Therefore, if the study were extended to look at the impact of PrEP beyond its recipients, these estimated infections averted would be minima, costs per infection averted maxima, and modest changes would be expected comparing the relative impact between high-risk populations.

Much of the data used to characterise high-risk women are limited by age and lack of reliable data on numbers of partners and numbers of sex acts. Sexual behaviour data is subject to under-reporting, and when collected for the general population through demographic health surveys, reporting as percentages makes it difficult to derive meaningful limits or statistic distributions for the underlying data. HIV incidence and prevalence data are not always available for the same population for the same year. As PHIA surveys[72] in PEPFAR-supported sub-Saharan African countries continue to be rolled out over the coming years, these data will become more readily and consistently available to repeat these analyses across high-burden countries. Cost estimates are limited by assumptions on how subgroups are reached. Whilst a strength of this study is heterogeneity in programmatic costs, our estimates are limited by the scarcity of empirical data in these settings. Data uncertainty is addressed to some extent through the uncertainty analysis.

This study parameterises models using population averages for broadly defined groups for whom data is readily available in the literature. It does not account for significant behavioural heterogeneity that exists within each of these groups nor in differences in HIV burden at local-levels, potentially masking important risk groups and population interactions. Accordingly, reported population mixing between women 15-19 years and men 5-10 years older in these countries was approximated to be represented by AGYW (15-24 years) drawing partners from male populations 15-24 years and 25-34 years. Lack of available data to parameterize women 50 years+ meant that it was not possible to explore the scale-up of PrEP to this population group. Where available data permits, these analyses could be tailored to reflect greater or different heterogeneity between sub-populations and at sub-national level. Lastly, the study also does not explicitly account for other PrEP program cascade factors, such as uptake. Doing so would affect the relative estimates of PrEP effectiveness where at least one of the female populations have materially different levels of program uptake than the others.

Conclusion

PrEP has the potential to significantly reduce the numbers of new HIV infections in HIV-endemic countries in sub-Saharan Africa, even considering low levels of PrEP program retention in women. This will necessitate PrEP being made widely available beyond those at highest individual risk, including to women in the general population. Wide-scale roll out will require integration of PrEP into a wide range of national services and at community level, in order to significantly bring down the costs and improve cost-effectiveness.

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5.4 Implications for Thesis

The conclusions of Research Paper 3 indicate that PrEP has the potential to significantly reduce the numbers of HIV infections at population-level, if it is scaled up widely for women beyond those at highest individual risk. This is noteworthy, considering the low levels or PrEP program retention accounted for: 22% retention after 1 year in female sex workers, and within ±25% of this (i.e. 16.5%-27.5%) for all other women.

The female population groups in which PrEP has the potential to reduce the greatest number of infections differs by country according to their underlying incidence profiles. In South Africa, it is estimated that PrEP has the potential to avert the most number of infections in AGYW as compared to FSW (approximately 24 times the number annually), followed by women 25-34 years (approximately 14 times the number) and then women 35-49 years (approximately 8 times the number). By contrast, in Zimbabwe, it is estimated that the greatest number of infections could be averted annually in women 25-34 years (approximately 8 times the number as in FSW), followed by AGYW and women 35-49 years (approximately 4 and 3 times the number as in FSW respectively). In Kenya, roughly the same number of new infections could be averted annually in AGYW and women 25-34 years (approximately 3 times the number of infections as in FSW respectively), followed by women 35-49 years (approximately the same number as in FSW).

Policy makers will have to balance this important potential for infection reduction at population level, with their ability to pay for PrEP scale-up. Using current estimates of cost of PrEP delivery by population group, and given the significantly greater HIV risk faced by FSW in comparison to other female groups in the general population, PrEP provision remains significantly more cost-effective for FSW across the three country contexts explored. The unit cost of PrEP delivery for AGYW, women 25-34 years and women 35-49 years would need to drop significantly by between median 70.8%-91.0% across all three country contexts to be as cost-effective as for FSW.

Scaling up PrEP at population level by integration into a range of national and community services has the potential to drive cost reductions, improving cost-effectiveness on an individual basis for AGYW, women 25-34 years and women 35-49 years. However, achieving cost-parity with the cost of PrEP for FSW (other than potentially for AGYW in South Africa) is likely to be challenging for these countries in the near term.

Policy makers in sub-Saharan Africa can easily adapt the models and tools used in this Research Paper to estimate the relative cost-effectiveness and potential impact of PrEP for different risk populations by country context. It is hoped that this information will then help these decision

makers weigh available resources with the potential for impact of PrEP at population level in an effort to maximise HIV infections averted.

Chapter 6

6. Discussion

6.1 Main findings

This PhD thesis set out to address the following aim and objectives:

Aim: to use mathematical modelling to inform policy making around the scale-up of PrEP for women across a spectrum of high HIV risk in sub-Saharan Africa, accounting for heterogeneities in HIV risk factors and PrEP programme outcomes

Objectives:

1. To assess the potential effectiveness of PrEP in reducing HIV infections among high-risk women in sub-Saharan Africa
2. To explore the extent to which behavioural disinhibition may outweigh the potential benefits of PrEP
3. To assess the robustness of conclusions made on the basis of static modelling techniques to incorporation of dynamic effects, to contribute to understanding around the importance of modelling complexity to inform HIV policy making
4. To explore strategies for the scale-up of PrEP across high-risk women at population-level, weighing considerations around HIV infection reduction and cost-effectiveness
5. To evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa, to explore how the approach to PrEP scale-up may differ by epidemic and implementation context

An assessment of the research conclusions in relation to the thesis objectives is set out in the following section.

Objective 1: To assess the potential effectiveness of PrEP in reducing HIV infections among high-risk women in sub-Saharan Africa

This objective was assessed in Chapters 3, 4 and 5 as a critical step on the modelling pathway to investigation of subsequent thesis objectives, e.g. around the effects of behavioural disinhibition and strategies for PrEP scale-up. The modelling undertaken in all three chapters, through both static and dynamic model formulations, concluded that PrEP has the potential to reduce new HIV infections among women across a spectrum of risk in sub-Saharan Africa. However, its ability to do so is dependent on women's PrEP programme cascade metrics, including PrEP programme uptake, retention and adherence. PrEP will only be effective at reducing HIV risk for a woman if it is made available to her, she has access to it, commences taking the drug, is retained in the programme during her season of risk and adheres to it. It also depends on the level of any behavioural disinhibition following commencement of PrEP relative to other HIV risk factors and her use-effectiveness of PrEP (level of HIV risk reduction achieved through taking PrEP with given retention and adherence levels). The analytical derivations in Research Paper 1 (Chapter 2, Equation 2.7) have illustrated that as long as the use-effectiveness of PrEP is at least the same as that achieved with condoms prior to introduction of PrEP, PrEP will always be beneficial in reducing HIV risk. Once the precise relationship between PrEP adherence and use-effectiveness has been established for women, this will facilitate understanding of the levels of weekly PrEP pill adherence needed compared to baseline levels of condom consistency (for which there is a linear relationship between use and effectiveness) to achieve the same levels of HIV risk reduction.

Objective 2: To explore the extent to which behavioural disinhibition may outweigh the potential benefits of PrEP

This objective was assessed first through Research Paper 1 (in Chapter 3) using a static model and the results then verified through Paper 2 (in Chapter 4) using a dynamic model formulation. The papers conclude that should behavioural disinhibition occur, the extent to which the protective effects of PrEP will outweigh increased HIV risk through reductions in condom use depends on the use-effectiveness of PrEP and the change in use of condoms following PrEP commencement. The effects of behavioural disinhibition would be more pronounced for women at higher underlying risk of HIV owing to other non-condom related risk factors.

The methodological approaches undertaken through both Research Papers agree in their broad-stroke policy conclusions to guide decision making at country level. These are, that in high HIV

burden contexts, PrEP for high-risk women is likely to be of benefit in reducing HIV risk even if reductions in condom use occur; that reductions in condom consistency can be better tolerated by high-risk women achieving high levels of PrEP use-effectiveness or with low baseline condom consistencies; and efforts to promote condom use will be especially critical for high-risk women with high levels of baseline condom consistency but who are anticipated to adhere less well to PrEP.

The exact use-effectiveness threshold at which PrEP is a beneficial additional HIV prevention approach for high-risk women (considering any reductions in condom consistency following PrEP introduction) depends on other underlying epidemiological and behavioural HIV risk factors. In the case of FSW in inner-city Johannesburg, if PrEP is introduced in a context where the underlying HIV epidemic has reached HIV equilibrium, over short-medium time horizons of up to 5 years, it is estimated that up to 85% reduction in condom consistency can be tolerated, as long as 65% use-efficacy is achieved with PrEP. 65% PrEP use-efficacy corresponds to adherence levels of more than 4 tablets out of 7 a week, according to the Partners Demonstration Project analysis in women[1]. If the underlying epidemic were still to be increasing in inner-city Johannesburg, the level of reduction in condom consistency tolerated with 65% PrEP use-effectiveness would drop from 85% to 34% after 5 years on PrEP.

As highlighted in our recent Commentary for the Lancet HIV (Appendix 5), there are further aspects in relation to behavioural disinhibition on PrEP that would benefit investigation. These include community-level behavioural disinhibition (reductions in condom use in those *not* using PrEP, which has recently been reported among MSM communities in Australia[2]); patterns of behavioural disinhibition in relation to intermittent PrEP regimens (i.e. between and after episodes of PrEP); and alternate strategies for STI prevention among PrEP takers with low baseline condom use.

Objective 3: To assess the robustness of conclusions made on the basis of static modelling techniques to incorporation of dynamic effects, to contribute to understanding around the importance of modelling complexity to inform HIV policy making

This objective was assessed through Research Paper 2 (Chapter 4). Research Paper 2 compared the results of matched static and dynamic model formulations in exploring the impact of the introduction of a new HIV prevention intervention (in this case, PrEP) for women at high HIV-risk in SSA, using the case study of FSW in inner-city Johannesburg. Research Paper 2 explored the extent to which the broad-stroke conclusions made on the basis of the static model held under the dynamic model formulation. The paper explores the extent to which specific numeric predictions of the

reductions in condom consistency tolerated on PrEP made through the static model remained robust under the dynamic model formulation. This was assessed different epidemic contexts (where the underlying HIV epidemics in the respective populations are still increasing, at equilibrium, and fully endemic in the populations) and over time horizons of three months to 20 years.

Research Paper 2 concluded that the overarching policy conclusions made on the basis of the static model remained true under the dynamic model formulation. This is a noteworthy conclusion given the comparative advantages of static models for use by policy makers[3,4].

Regarding the consistency of the numeric predictions between the two models, Research Paper 2 found that over short-medium time-horizons of up to five years, the static model approximates the outcomes of the dynamic model fairly consistently. However, over longer timeframes of up to 20 years, the static models may underemphasize situations of programmatic importance, especially in contexts where underlying epidemics are increasing. In particular, the model comparison found that the reductions in condom use predicted by the static model do not hold under the dynamic model formulation where initial condom consistencies are reasonably high (≥50%) and/or PrEP use-effectiveness is low (≤45%), with the differences greater where the underlying HIV epidemic is increasing. The difference between the models' outcomes arise principally from the dynamic model's ability to capture changes in HIV prevalence over time, highlighted where PrEP use-effectiveness is insufficiently high enough to mask greater reductions in condom use.

Objective 4: To explore strategies for the scale-up of PrEP across high-risk women at population-level, weighing considerations around HIV infection reduction and cost-effectiveness

This objective was explored through Research Paper 3 (Chapter 5), which assessed the potential individual-level cost-effectiveness and population-level impact (number of infections averted) of PrEP, for women across a spectrum of high risk: AGYW, women 25-34 years, women 35-49 years and FSW. In the absence of willingness to pay thresholds, relative cost-effectiveness was assessed by comparing estimates of cost per infection averted between high-risk women populations. Research Paper 3 devised three simple tools to guide implementers in assessing strategies for PrEP scale-up at country level, applicable to any setting, using a basic set of information available to implementers[5].

The first tool helps implementers estimate the annual HIV incidence in women, using information on average number of monthly sex acts, average condom use and underlying epidemic setting. The second tool helps implementers to estimate the relative cost at which PrEP will be equally as cost-effective between two groups of women according to their HIV risk factors and risk behaviours. The

third simple tool helps implementers assess the relative unit cost at which PrEP will be equally as cost-effective for lower-risk women as women at comparatively higher-risk, also using information on average number of monthly sex acts, average condom use and underlying epidemic setting.

The Research Paper then assessed strategies for PrEP scale-up across these four groups of high HIV-risk women in three different country implementation contexts in SSA. It concluded that to maximise cost-effectiveness, PrEP should be offered to women at highest HIV risk, such FSW. However, to maximise the number of HIV infections averted at population-level, and significantly impact the HIV epidemics in SSA, PrEP should be rolled out for women in the general population at comparatively lower HIV-risk, but in whom the number of HIV infections are in total greater annually, due to vast differences in population size. The relative magnitude of potential infections averted on PrEP annually in each of the 4 high-risk women groups differs by country context, according to underlying HIV risk factors (epidemiological and behavioural), relative population sizes and PrEP programme outcomes in each of the groups. As such, so would the order of prioritization of high-risk women groups for PrEP scale-up in each of these country contexts.

Wide-scale roll out of PrEP for groups of women in the general population has the potential to drive cost reductions through economies of scale, improving cost-effectiveness and allowing more women to be reached with the same financial resources. This will require the integration of PrEP into a range of health, non-health and community services for women, which in some instances may be challenging considering local cultural contexts (e.g. integration into education settings for AGYW).

Accordingly, strategies for scale-up of PrEP for women across a spectrum of high HIV-risk can be determined using the analytical tools developed for this study, allowing decision makers to assess relative cost-effectiveness and relative number of infections averted at population level. These strategies will also need to account for the contextual considerations outlined in the study, including potential scope for PrEP cost-reduction through economies of scale, potential for integration of PrEP into a wide range of national services and at community level to research each of these groups of women and other relevant contextual, political and cultural factors.

Objective 5: To evaluate strategies for PrEP scale-up in more than one country setting in sub-Saharan Africa, to explore how the approach to PrEP scale-up may differ by epidemic and implementation context

This objective was explored through Research Paper 3 (Chapter 5), which applied analytical tools to assess the potential cost-effectiveness and population-level impact of PrEP across the 4 groups of

women at high risk of HIV in three different implementation contexts in SSA. Specifically, strategies for PrEP scale-up were applied to three HIV endemic countries in SSA that span a range of HIV burden levels in the region: South Africa (20.4% adult HIV prevalence), Zimbabwe (12.7% adult HIV prevalence) and Kenya (4.7% adult HIV prevalence)[6]. The analysis showed that in all three country contexts, PrEP is most cost-effective for FSW, for whom HIV risk is higher than all the other female population groups considered.

Looking at the potential impact of PrEP population-level in reducing the greatest number of new HIV infections annually, the relative magnitude of potential infections averted across the 4 high-risk women groups differs by country context. In South Africa, PrEP has the potential to avert approximately 24 times the number of infections annually in AGYW as in FSW when scaled up at equal coverage levels, and approximately 14 and 8 times the number in women 25-34 and 35-49 years respectively. In Zimbabwe, approximately 8 times the number of infections could be averted annually in women 25-34 years as in FSW, and approximately 4 and 3 times the number in AGYW and women 35-49 years respectively. In Kenya, approximately 3 times the number of infections could be averted annually in AGYW, 3 times in women 5-34 years as in FSW, and the same number in women 35-49 years.

PrEP has the potential to avert significant numbers of new HIV infections annually in each of these countries with high HIV incidence among women, even considering low levels of PrEP program retention seen in among women in sub-Saharan African settings. This will necessitate PrEP being made widely available beyond those at highest individual risk. In each of these three countries, strategies for PrEP scale-up for women across risk-groups in the general population will account for the relative number of infections that could be averted annually between each group, resource availability, the potential scope for PrEP cost-reduction through economies of scale, political will, the potential for PrEP to be integrated into a wide range of national services and at community level to research each of these groups of women and other relevant contextual and cultural factors.

6.2 Contributions of Thesis

The contributions of this thesis are summarised below, grouped as 1) contributions to HIV policy making and PrEP programming, and 2) contributions to methods.

6.2.1 Contributions to HIV policy making and PrEP programming

This thesis has demonstrated that PrEP is likely to be a beneficial HIV prevention tool for women across a spectrum of high HIV-risk in sub-Saharan Africa, accounting for heterogeneities in HIV risk factors and PrEP programme outcomes. This holds, even if reductions in condom use occur on PrEP. This is an important take away, given the critical need for the scale-up of new HIV prevention approaches to address the incredibly high levels of HIV incidence in women across a spectrum of HIV risk in SSA[7], the concerns that behavioural disinhibition may outweigh the HIV-protective effects of PrEP[8–12] and in view of the low levels of PrEP programme retention and drug adherence observed in studies to date for women at high-HIV risk in SSA[13–20].

This research guides PrEP programmers and policy makers that in high HIV burden contexts, reductions in condom consistency can be better tolerated by women achieving high levels of PrEP use-effectiveness or with low baseline condom consistencies. It has demonstrated that efforts to promote condom use will be especially critical for high-risk women with high levels of baseline condom consistency but who are anticipated to adhere less well to PrEP.

This research has built on the work by Foss et al[21] in relation to the introduction of an HIV- and STI-efficacious microbicide, which also found that there are likely to be contexts in which reductions in condom use can be tolerated (depending on the efficacy and use-effectiveness of the microbicide), and that particular concern should be paid to individuals with high baseline levels of condom use anticipated to have challenges in using microbicides consistently. This thesis has gone further, however, in several ways. First, it explored the effect of reductions in condom consistency with two different partner populations of FSW, finding that condom consistency with regular partners could be reduced to zero, and reductions in condom consistency with clients still be tolerated whilst achieving 50% HIV risk reduction, with levels of PrEP use-effectiveness of at least 55%. This is of note given the incentives for FSW to reduce condom consistency with clients[22], and challenges with condom use between FSW and regular partners[23]. It has accounted for an important element of the PrEP programme cascade, retention, within the Bernoulli HIV risk equation, finding that in spite of the low levels of retention among women observed among demonstration projects[13,14,20], PrEP has the potential to substantially impact the annual number of new HIV infections annually among

women in sub-Saharan Africa. It has also explored the epidemic contexts and timeframes over which the results of the static model formulation hold, having accounted for the dynamics of population interactions (further assessment of this below).

To help assess strategies for PrEP scale-up in resource-constrained environments beyond women at highest HIV-risk in sub-Saharan African society, accounting for heterogeneities in women's risk factors and PrEP programme outcomes, this research has contributed a number of analytical tools, three country case studies and noted associated implementation considerations. It has demonstrated that PrEP will always be most cost-effective for those women, such as FSW, who are at highest HIV risk in sub-Saharan African contexts. However, to maximise the number of HIV infections averted at population-level, and significantly impact the HIV epidemics in SSA, PrEP will need to be rolled out for women within the general population.

Having assessed PrEP roll out across 4 population groups across a spectrum of risk in SSA (AGYW, women 25-34 years, women 35-49 years and FSW), this research has demonstrated that strategies for PrEP scale-up for women across risk-groups in the general population need to be informed by 1) the relative number of infections that could be averted annually between each group with PrEP, 2) the relative cost-effectiveness of PrEP between these population groups; 3) resource availability and the potential scope for PrEP cost-reduction through economies of scale, and 4) the potential for PrEP to be integrated into a wide range of national services and at community level to reach each of these groups of women, as well as other relevant contextual, political and cultural factors.

Case studies are illustrated for three countries in SSA, South Africa, Zimbabwe and Kenya, all of which are currently weighing PrEP roll out beyond those at highest individual HIV-risk[24–26], and represent different implementation settings across a spectrum of HIV burden in the region[7]. It is hoped that this research will help inform in-country deliberations around PrEP scale-up.

More generally, this research provides decision makers with a number of relatively simple analytical and pictorial tools to guide programming in implementation contexts. These include the simple analytical relations outlined in Research Paper 1 (Chapter 3) to guided assessment of the conditions under which reductions in condom use will be tolerated on PrEP. They also include the tools set out in Research Paper 3 to help PrEP implementers estimate the annual HIV incidence in women and the relative cost at which PrEP will be equally as cost-effective between two groups of women at different levels of HIV risk, using a limited set of information typically available in implementation settings[5]. Many of the static models used in this PhD could relatively easily be carried out or adapted by implementers with limited analytical background and limited experience with programming tools – for example the relatively simple Excel-based static model from Research Paper 1.

To the best of my knowledge this research is the first to have assessed 1) the extent to which behavioural disinhibition can be tolerated without increasing HIV risk following the introduction of PrEP, and 2) the scale-up of PrEP across high-risk women population groups in SSA, whilst considering heterogeneities in HIV risk factors and PrEP program outcomes. The analytical approaches carried out in this research could easily be adapted to assess new PrEP formulations as they become available[27], or indeed adapted to other new HIV prevention interventions, populations or implementation settings.

Finally, this research will give assurance that static models of HIV risk are likely to be robust in assessing the introduction of new HIV prevention interventions in high-burden settings where the underlying HIV epidemics are at equilibrium, especially over short-medium time horizons of up to 5 years. There is therefore scope for static models, which are simpler to devise, parametrise and communicate, to be used more routinely to inform decision making in such contexts. Where such tools are to be implemented in contexts where the underlying HIV epidemics are still increasing, policy makers are advised to instead rely on dynamic modelling tools.

6.2.2 Contributions to methods

To the best of my knowledge, this research is the first to examine the extent to which the conclusions of static models remain robust to the incorporation of dynamic effects when considering the introduction of a new HIV prevention intervention, across differing time horizons and epidemic contexts. This methodological question was explored using the topical open question surrounding tolerated reductions in condom use following the introduction of PrEP[8–12], and using the pertinent case study of FSW in inner-city Johannesburg, a population at very high levels of HIV[28].

This research has demonstrated that over short-medium time-horizons of up to five years, the static model approximates the outcomes of the dynamic model fairly consistently. However, over longer timeframes of up to 20 years, the static models may underemphasize situations of programmatic importance, especially in contexts where underlying epidemics are not at equilibrium. In particular, the model comparison found that the predictions of the static model do not hold well under the dynamic model formulation over longer time horizons in specific contexts - where initial condom consistencies are reasonably high ($\geq$50%) and/or PrEP use-effectiveness is low ($\leq$45%), with the differences greater where the underlying HIV epidemic is increasing. The difference between the models' outcomes arises principally from the dynamic model's ability to capture changes in HIV prevalence over time, highlighted where PrEP use-effectiveness is insufficiently high enough to mask

greater reductions in condom use. Importantly, the key policy conclusions made on the basis of the static model held well under the dynamic model formulation.

This research will contribute to the evolving and limited literature base seeking to assess the minimum level of modelling complexity needed to appropriately address HIV policy questions[29–31]. It provides reassurance that in high HIV-burden contexts where the underlying HIV epidemics are at equilibrium, static models are sufficiently robust to inform decision making around the introduction of new HIV prevention interventions over short-medium time horizons. This is noteworthy considering the comparative advantages of simpler models outlined in this thesis, including that they are typically easier to communicate to, be understood and owned by policy makers; their reduced data requirements and speed of development compared to dynamic models; and their ease of use to deduce broad principles to help guide decision making[3,4,30–33].

These conclusions have direct implications for the use of existing simple static models used to guide decision making in HIV, in view of the epidemic context and timeframe the analysis is applied to. For example, it underscores the conclusions of Mishra and colleagues[34] that the UNAIDS Models of Transmission model, used to inform HIV prevention resource allocation at country and sub-national levels, should be cautioned in epidemic contexts where HIV prevalence is increasing beyond very short timeframes.

6.3 Limitations

This section focuses on overarching limitations across the body of research undertaken in this thesis.

6.3.1 Accounting for uncertainty and fitting to data in Research Paper 1

Research Paper 1 adopted a simple static model that could easily be evaluated in Excel, along with a very simple approach to assess parametric uncertainty, with the idea that the simplicity of the approach would more intuitive to and more easily understood by policy makers. This was undertaken by taking maximum and minimum values of each parameter from the literature and repeating the analyses with exclusively maximum value and exclusively minimum values, to give upper and lower bounds for model outcomes. The HIV risk model was not fitted to HIV incidence data.

This approach to accounting for parametric uncertainty, whilst being a simple approach that was hoped to be intuitive to and replicable by policy makers, is rudimentary. In general, this approach cannot be relied upon to give true upper and lower bounds due to the interactions of non-linear modelling terms. More appropriate yet simple Bayesian approaches, though slightly less intuitive, could include assigning each parameter an underlying distribution, drawing a large number of samples from each, and use these parameter sets to build up uncertainty ranges around model outcomes.

As the risk model was not fitted to HIV incidence data, there cannot be confidence that the specific numeric outcomes of the model apply well to the implementation context for FSW in inner-city Johannesburg. The static model adopted in Research Paper 2, which was fitted to data, did confirm the broad overall trends (not specific numeric values) of the static model used in Research Paper 1. However, simple fitting approaches could have been used, such as undertaking the refined approach to parametric uncertainty suggested above, and selecting only parameter sets that gave outcomes (in the absence of the PrEP intervention) matching estimates of HIV incidence for the population.

6.3.2 Model structural uncertainty

The uncertainty analyses undertaken in all three Research Papers overall focused more strongly on parametric rather than model structural uncertainty. Model structural uncertainty was accounted for to some extent in Research Paper 1 by exploring one vs two partner population groups for FSW (though the outcomes not specifically compared) and comparing the model outcomes with or

without accounting for STIs in the model equations. In Research Paper 2, model structural uncertainty was explored by assessing the model's sensitivity to heterogeneity in the number of parameters. This was undertaken by removing all parameters related ART, circumcision and STIs, re-running the analyses and comparing the conclusions. In Research Paper 3, model structural uncertainty explored the assumption (based on available data) that only AGYW have partners drawn from an older age group, and looked at how the results change if women 25-34 years were assumed to have partners also from the 35-49 year group.

Where model structural uncertainty is not fully explored, this means that there cannot be confidence the model outcomes are not affected by the choice of model structure. One important model structural uncertainty analysis that could be undertaken is exploring model sensitivity to heterogeneity in populations and their interactions, for example, by more fully exploring multiple or greater age disaggregation around partner populations (where relevant) and including the underlying general population in models – see below for further interrogation of population heterogeneity.

6.3.3 Population and demographic heterogeneity

Population heterogeneity

All the models developed for this research adopted simplified representations of heterogeneity in population groups and their interactions. For example, whilst Research Papers 1 and 3 adopted two partner populations for FSW, regular partners and clients, Research Paper 2 assumed only clients. In practice, research has shown that FSW's partner populations usually include at least a third group, regular clients or boyfriends[23,28,35]. This is an important partner group in terms of HIV risk, as they are often individuals at high HIV-risk and with whom condom consistency is typically low as a reflection of the regular nature of the relationship[23,28,35]. In Research Paper 3, for the main analysis, AGYW and FSW are assumed to have partners drawn from two populations and women 25-34 years and 35-49 years partners drawn from single populations each. In none of the Research Papers were other underlying population groups accounted for, such as women and men in the general population for Research Papers 1 and 2, and women and men 50+ years in Research Paper 3. Furthermore, FSW, as well as the three additional general population female groups addressed in Research Paper 3 are far from homogenous groups[7,23,36–38]. Though Research Paper 3 accounted for risk heterogeneity through uncertainty analysis, further disaggregation of these groups may reveal important trends to inform programming.

Women in serodiscordant couples were not included in within the broader definition of women at high HIV-risk in this research. Whilst they are at significantly elevated risk of HIV, this was undertaken considering that many countries are rolling out distinct programmes in conjunction with ART services to give PrEP to the HIV negative partner as a short-term bridge to HIV viral suppression in the HIV positive partner[25,39–41], so many not be considered for PrEP resource allocation within the same category as 'other' high-risk women, as well as women in serodiscordant relationship's comparatively improved outcomes through the PrEP programme cascade vis-à-vis other groups of high-risk women[42,43]. This was a subjective choice, and it could be argued that women in serodiscordant relationships should have been included in the group of women defined as at high HIV-risk for the purposes of the analyses undertaken. The models adopted across the Research Chapters could easily be adapted to include women in serodiscordant relationships in future work.

In reality, individuals at risk have partners drawn from many different populations, and by not accounting for these heterogeneous populations and their partner formations, important routes of HIV transmission may be under accounted for, and therefore the research may fail to bring out important groups to be prioritized for HIV prevention interventions. The level of population heterogeneity accounted for in a model is a difficult balance between addressing important populations for programming, with availability of data to parameterise these groups and their interactions. It must also consider the ability of policy makers and implementers to implement recommendations that in reality may be too focused on narrow population groups that are either difficult to identify in practice or by doing so risks having adverse effects such as perpetuating stigma around narrowly defined risk groups.

Demographic heterogeneity

This research also has limitations in the demographic heterogeneity accounted for. First, the research has focused on countries in South and East Africa, due to their comparative elevated levels of HV burden at population level, but not addressed any case studies from west and central Africa. Nonetheless there are many female populations at high HIV-risk in west and central Africa, who could perhaps benefit through such modelling to inform policy making around PrEP. It would also be interesting to compare the conditions under which static models are sufficiently robust to inform policy making around the introduction of a new HIV prevention intervention for high-risk women, as undertaken in Research Paper 2, but in the context of lower-HIV burden settings.

Additionally, HIV epidemics are incredibly diverse at sub-national levels, and in many settings, down to the level of localities of hundreds of metres, such as the fishing communities on the shores of Lake Victoria, where the transactional practice of sex-for-fish is a significant driver of HIV transmission[44,45]. Whilst the research of Research Papers 1 and 2 were undertaken in a specific geographic location (Hillbrow in inner-city Johannesburg), the settings for Research Paper 3 were at national level. Whilst this was undertaken to inform dialogue at national levels, and the models can be easily tailored to more specific geographies. However, doing so risks conclusions being made on the basis of population averages and applied to settings with very different epidemiologic, as well as other risk factor, realities. For example, in Kenya, at county level alone (a low level of demographic disaggregation), the county with the highest average adult HIV prevalence, Siaya (21.0%), has prevalence levels 210 times higher than the county with the lowest average adult HIV prevalence, Wajir (0.1%) (2018 estimates)[46].

Both these issues of population and demographic heterogeneity are part of a wider challenge in the use of mathematical models to inform policy making and programme implementation – that models are always a simplified version of reality, and therefore always wrong. The underlying tension in use of models to inform decision making in reality is the need to capture sufficient heterogeneity, as well as complexity, to accurately reflect the question and context at hand, with the availability of reliable data to parameterise models, as well as models and their conclusions being well understood and adopted by decision makers, and their outcomes being sufficiently specific, but not too specific to be applied in view of the realities of implementation contexts.

6.3.4 Static models and downstream effects of interventions

As stated throughout the Research Papers, use of static models limits the assessment of the effect of an intervention (in this case PrEP) to the population for whom risk is being assessed. Static models do not capture the downstream effects of interactions between populations and therefore cannot make deductions about the effect of PrEP being taken by a high-risk woman on infections averted in their partner populations. In fact, all three Research Papers (including Research Paper 2 which compares the outcomes of static and dynamic models) do not assess secondary infections averted in partner and wider population groups as a result of PrEP for high-risk women. This is a limitation as deductions are made only on the basis of assessing primary, rather than secondary, or even tertiary infections prevented.

6.3.5 Data availability

A significant challenge and limitation in parametrising the models in all three Research Papers has been the availability, as well as age, of data. Much sexual behaviour data is limited by being self-reported and therefore subject to under-reporting[47,48]. Many national surveys (such as demographic health surveys) report important data categorically (e.g percentage of women who have 2+ partners in the last 12 months[49]), making it difficult to derive meaningful parameter ranges (e.g. in this case, *the of the numbers of partners over the last 12 months*). Data is not always available disaggregated by the three female general population groupings used in Research Paper 3 for all parameters and all countries. For example, in Research Paper 3, data to parametrise Zimbabwean AGYW's number of sex acts a year with both partner groups had to be parameterised using South African data, due to lack of data availability for their Zimbabwean counterparts.

Data to parameterise key populations, in this case FSW, is limited by age, as well as under- reporting in all three implementation contexts explored. The population most challenging to parametrise are the clients of sex workers, as there is very little data on them as a distinct group in these contexts. As such, data gaps were filled by relying on data from long-distance truck drivers and male migrant worker populations, population groups which are known clients of FSW in these settings[50,51].

PrEP programme cascade data, in particular retention and adherence data is limited by availability in SSA for women, especially non-FSW general population groups. At the time of undertaking research for the first Research Paper, no data were available for women relating the numbers of weekly PrEP doses to levels of HIV risk reduction, so data for MSM and TGW was relied on in the model interpretation, which has since been shown to be unrealistic, since women require higher levels of PrEP drug levels to achieve the same levels of HIV risk reduction as men[52]. To date, there is still not the same level is disaggregation available for women, as for men, relating number of daily PrEP tablets to levels of HIV risk reduction. Also, at the time of undertaking Research Paper 1, no data were available relating PrEP cascade factors in general to levels of HIV risk reduction for female populations (other than the early RCTs which were stopped early for futility, assumed owing to lack of adherence[53]). Accordingly, the model accounted only for levels of HIV-risk reduction, assumed to be associated with unknown levels of PrEP adherence, but in nomenclature this also should have referred to other programme cascade factors including retention and uptake.

Finally, data for fitting models to HIV prevalence and incidence is limited by age, in particular in Kenya. As the population-based HIV impact assessment (PHIA) surveys[54] are further rolled out over the coming years across countries in SSA, updated data will become available. Altogether the challenges in availability and them being up-to-date limits the accuracy of the model results.

6.4 Key area not addressed through research: structural factors

Role of structural factors in HIV prevention for high-risk women in SSA

Structural factors are important drivers of HIV in women in sub-Saharan Africa. At a macro-level these drivers arise due to harmful social and economic policies and conditions, cultural norms, religious practices, political and legal factors[55,56]. At community-level these drivers affect women's access to education, economic opportunities and healthcare, affect societal gender norms, perpetuate stigma and lead to power imbalances between men and women[55,56]. At an individual level, these factors contribute to HIV acquisition through women engagement in transactional sex and sex work, gender-based violence, lack of agency to negotiate partner selection and sex, safe sex, uptake of health and HIV prevention services and interventions (such as condoms or PrEP, or the treatment of STIs)[55,56].

It is incredibly difficult to assess the contribution of structural factors to HIV transmission, or indeed the relative contribution of structural factors versus other behavioural and epidemiologic risk factors. Researchers including Remme et al[57,58], Shannon et al[59] and Cluver et al[60,61] have done some impressive, formative work to assess the potential impact of one or more concurrent structural interventions to address predominantly individual-level as well as community-level structural drivers of HIV women (including cash transfers, gender empowerment programmes, free school meals, violence reduction programmes) across a spectrum of women at high HIV risk, including AGYW and FSW. Their studies report the potential impact and cost-effectiveness of such interventions according to epidemic context, as well as the multiplicative impact and cost benefits of more than one structural intervention concurrently implemented. They note the additive impact of these interventions on outcome and impact indicators of importance to other development sectors prioritized in the SDGs[62], such as education, economic development and social protection, or to other sectors within health, including sexual and reproductive health, mental health, and a wide range of communicable diseases[57–61].

At present, the majority of normative core HIV prevention interventions focus on biomedical approaches (such as VMMC, ART, PEP, condoms, harm reduction services), including the mainstay of UNAIDS's five pillar programmes of HIV prevention[63], with PrEP being the newest addition. In the policy space, it is comparatively easier to justify HIV prevention funding for biomedical rather than structural interventions, as their effect on individual HIV risk is well documented, their effect typically easier to quantify through intervention trials, and they tend to be more straightforward to implement[64–67]. When rolled out at wide scale through implementation programmes, the impact of biomedical interventions can be more directly measured over short time horizons (e.g. VMMC

performed, condoms delivered, viral suppression due to ART), making them easier for international donors and domestic politicians to justify to their funders and funding bases[64–67]. By contrast, structural interventions to affect macro-level policy and cultural change can take many years, and their effect difficult to attribute and quantify[55,56]. Indeed, the majority of donor financing for HIV is spent on biomedical interventions[68,69]. However, biomedical interventions tend address the proximate symptoms of the drivers of HIV, not their upstream causes.

Through my time spent working on HIV prevention programmes in Kenya and South Africa, as well as through keen interest in the literature, it has been my overwhelming sense that structural factors, have perhaps the greatest influence on HIV acquisition among women in SSA. However, as a policy maker, I have repeatedly felt under-equipped with concrete, numerical evidence to make the case for the importance of addressing structural factors and for structural programmes to be scaled up at global, national and local levels.

If I were to undertake research again to address the disproportionate HIV incidence among women across a spectrum of risk in SSA using mathematical modelling, I would therefore focus on structural factors where there is a comparative paucity of evidence[55]. Specifically, I would aim to contribute to quantification of the effect of structural factors at macro-, community- and individual-levels on HIV transmission, as well as the potential impact and cost-effectiveness of structural interventions to address these drivers, looking across the HIV, health and wider development sectors in assessing the contribution of structural interventions to broader global development goals[62]. I would especially focus on interventions to address macro-level factors, since these are the origin of structural drivers down to individual level[55] and have been comparatively under-explored compared to individual- and community-level drivers[55,67,66]. Modelling could also be used to assess the complementarity of structural interventions to support and enhance the use of PrEP to address HIV risk among women across a spectrum of risk in SSA.

This modelling could be done in conjunction with trials or demonstration projects, or as standalone research, by algebraically characterising the effect of structural interventions upon relevant parts of the HIV risk equation and prevention cascade, as well as equivalent risk equations and cascades for the health and cross-sectoral outcomes under exploration. For example, in the case of HIV, certain structural interventions could be considered to act upon condom use, the rate of partner change, the basic risk of transmission (e.g. if it reduces the risk of physiological trauma through intercourse[70]), the prevalence of HIV and STIs in partner populations (e.g. if it affects the population from which partners are drawn), and PrEP programme cascade metrics (e.g. uptake, retention and adherence). In the absence of empirical data to parametrise models, potential impact ranges for

structural interventions could be derived by simulating parameters across data ranges elicited through expert opinion[71–73]. Considering the outcomes of Research Chapter 2, if this research were applied to contexts where the underlying epidemics are stable among relevant partner populations, and the structural interventions deemed to affect change over shorter time horizons (such as through individual-level empowerment programmes, which have demonstrated behavioural changes over a number of months[55]), this modelling could be undertaken using static risk equations. Otherwise, and especially for structural interventions that affect change of longer time horizons (such as certain legal or policy changes[55]), dynamic models will be more appropriate.

Having done so, I would then be able to equip myself with a stronger evidence for making the appropriate case in my work for the prioritization of resources for interventions to address macro-, community- and individual-level structural factors, through the HIV sector, as well as in conjunction with other sectors, to address the unacceptably high burden of HIV incidence among women in SSA, as well as in other populations and geographies globally.

6.5 Areas for further research

Considering the aims and results of this thesis's research, its limitations and the outlined area of research not addressed by this thesis, the following are suggested areas for further research. These areas of research are grouped as *research to inform HIV policy making and PrEP programming*, and *research to inform methods*.

Research to inform HIV policy making and PrEP programming

- The dynamic model formulation set out in Research Paper 2 could be refined to assess the potential effects of community behavioural disinhibition following the introduction of PrEP for high-risk women in SSA. Whilst community-level behavioural disinhibition has thus far only been reported in MSM communities[2], the fact that few PrEP OLE, demonstration and implementation projects among women in SSA have been completed and reported results to date, means this cannot be ruled out as a potential consequence of PrEP introduction for women across a spectrum of risk in SSA.
- The potential effects of behavioural disinhibition in relation to strategies for intermittent (rather than daily) PrEP use among women at high risk of HIV in SSA could be explored using either the static or dynamic model outlined in Research Papers 1 and 2, depending on whether the timeframe for evaluation is up to 5 years, or longer.
- The South Africa, Zimbabwean and Kenyan case studies outlined in Research Paper 3 could be further refined with in-country policy makers in the context of country-specific HIV prevention or PrEP budgets, considering the actual scope for PrEP cost-reduction through economies of scale, the potential for PrEP integration into a wide range of national services and at community level, and relevant contextual, political and cultural factors in order to finalise in-country strategies for PrEP scale-up.
- The methods outlined in Research Paper 3 could be used to assess strategies for PrEP scale-up in other country contexts or across other populations at risk of HIV. This could be undertaken by policy makers, requiring only limited support from modellers. The models could be applied across contexts with greater population and geographic heterogeneity to evaluate PrEP scale-up across more narrowly defined risk groups and geographic locations.
- The methods outlined in Research Paper 3 could also be applied to assess strategies for the scale-up of newer, long-acting PrEP formulations, such as microbicides, injections and implants.

Given that longer-acting formulations intend to improve PrEP program outcomes by strengthening critical stages of the PrEP cascade, such as uptake and retention[74–76], it will be important that these cascade stages are reflected in the model equations. The model equations would need be adapted to include, for example, PrEP uptake, in addition to retention and use-effectiveness.

Research to inform methods

- The static versus dynamic model comparison undertaken in Research Paper 2 could be repeated in lower-HIV burden contexts, such as west and central Africa, or concentrated epidemic settings, such as in the relevant Asian and eastern and central European settings, to assess the broader epidemic conditions under which static models are sufficiently robust to inform policy making around the introduction of a new HIV prevention intervention for populations at risk of HIV.
- The static versus dynamic model comparison undertaken in Research Paper 2 could be explored in the context of declining epidemics in underlying population groups, for applicability to current and future contexts where the epidemics are on a trajectory to decline. Extrapolating the conclusions of Research Paper 2, I would hypothesise that the changing rates of HIV prevalence in declining epidemics would mean that beyond short timeframes, dynamic models are most appropriate for estimating the impact of new HIV interventions. However, this would need to be confirmed through such research.
- The mathematical properties of the static and dynamic models in Research Paper 2 could be compared to further understand the differences in model limit behaviour. For example, the basic reproduction number could be derived for the dynamic model based on first principles and for the static model based the intuitive approach (as outlined in the section on *static vs dynamic models* in the Background chapter) to determine the relationship between equilibria states; compare what they highlight about epidemic control efforts; and understand the extent to which the dynamic model is controlled by model parameters versus initial conditions.
- The static versus dynamic model comparison undertaken in Research Paper 2 could be applied to other infectious diseases, such as tuberculosis, where there is a more limited understanding of transmission dynamics, and thus harder to meaningfully build and parameterise dynamic transmission models. Should there be contexts in which static models are sufficiently robust to inform policy making for these diseases, this information would support policy makers and

modellers in building and adopting simpler models for decision making, which may be less data and time intensive and therefore cheaper to devise, and more user friendly.

- The role of model complexity could be explored in relation to other methodological attributes considered in model development to inform HIV policy making. One such example would be to explore the contexts in which discrete models are sufficiently robust in relation to their continuous counterparts. This would be an interesting study, since simple discrete models (such as those in the family of SIR models) can be evaluated using simple computing tools, such as excel, by counting the number of individuals in each compartment after each time step. Equivalent matched models evaluated in continuous time, however, require the use of more advanced programming approaches, as well as adopting more complex methodological approaches (such as advanced calculus), for model solving, with which policy makers may be less comfortable. If such studies were undertaken across a range of model attributes, this would allow for an overall framework to be developed to guide policy makers and modellers around the minimum level of modelling complexity need to appropriately inform decision making in HIV and beyond.

- Rather than looking at the barriers to use of models to inform policy making from a model structure point of view, research could be undertaken to explore the barriers and best-practice approaches for effectively communicating models of all levels of complexity through approaches that encourage policy maker understanding, ownership and uptake.

- The results of Research Paper 2 could be further verified through other types of model structural uncertainty analyses, for example by exploring whether further population heterogeneity affects the Research Paper's conclusions, e.g. by accounting for FSW regular partners and boyfriends in addition to clients, as well as men and women in the general population.

- Modelling approaches could be developed to quantify of the effect of structural factors at macro-, community- and individual-levels on HIV transmission, as well as the potential impact and cost-effectiveness of structural interventions to address these drivers, particularly the under-explored area of macro-level structural drivers. Impact and cost-effectiveness could usefully be assessed beyond the HIV sector alone, across other health and non-health sectors, to assess the contribution of structural interventions to broader global development goals[62]. The models developed through this research could be adapted to assess the complementarity of structural interventions to support and enhance the use of PrEP to address HIV risk among

women across a spectrum of risk in SSA. This modelling could then be used to inform resource allocation across sectors at global, national and sub-national levels.

6.6 Conclusion

PrEP is likely to be of benefit in reducing HIV risk in women across a spectrum of HIV-risk in sub-Saharan Africa, even if reductions in condom use occur. This conclusion is made having accounted for heterogeneities in women's HIV risk factors and PrEP programme outcomes, including the low levels of PrEP programme retention and adherence reported in studies. PrEP will be most cost-effective for individuals at great HIV risk, such as FSW. However, it has potential to significantly reduce the number of new infections at population-level if made widely available beyond those at highest individual risk, including to women in the general population. Strategies for PrEP scale-up will need to weigh the potential cost-effectiveness and population-level impact of PrEP with the potential for PrEP integration into a wide range of national services and at community level, in order to significantly bring down the costs and improve cost-effectiveness in resource-constrained environments.

Static models can be sufficiently robust to inform policy making around the introduction of new HIV prevention interventions in high HIV-burden settings over short-medium time horizon of up to 5 years, where underlying HIV epidemics have reached equilibrium. Over longer timeframes, and in contexts where the underlying HIV epidemics are still evolving (other than over short time horizons of less than a year), static models may under-emphasize situations of programmatic importance and dynamic models will be more appropriate to guide decision making.

6.7 References to Chapter 6

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Appendix 1: Ongoing, planned and completed PrEP OLE, demonstration and implementation projects among women in Sub-Saharan Africa

Ongoing, Planned and Completed PrEP Open Label, Demonstration and Implementation Projects in Women in Sub-Saharan Africa							
Trial/Project	**Sponsor/ Funder**	**Type/Category**	**Location**	**Population**	**Design/Key questions**	**Status**	**Status Details**
HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study	Wits RHI, HPTN; DAIDS, NIAID, NIMH	Demonstration Project	South Africa; Zimbabwe	AGYW aged 16-25 years	The goal of this study is to evaluate whether HIV-uninfected sub-Saharan African women ages 16-25 who are at high risk for HIV infection will initiate PrEP and achieve sufficient adherence using scalable adherence support interventions to achieve HIV prevention benefits from this promising biomedical prevention intervention.	Ongoing	Ongoing; started June 2016. Expected completion October 2018.
MTN-034/IPM 045/REACH	MTN; IPM; NIH; NIAID, NIMH, NICHHD	Clinical Trial	South Africa, Kenya, Zimbabwe, Uganda	AGYW aged 16-17 years	Participants will be randomized to product sequence and will use a silicone elastomer vaginal matrix ring (VR) containing 25 mg of dapivirine (DPV) to be replaced each month for a total period of 6 months of use, as well as take oral emtricitabine/tenofovir (FTC/TDF) tablets daily for a 6 month product use period. The primary purpose of this trial is to collect safety and adherence data over the course of study product use. The study will also examine the acceptability of the study products.	Ongoing	Ongoing; started January 2019.
EMPOWER (Enhancing Methods of Prevention and Options for Women Exposed to Risk) Consortium	Wits RHI, LSHTM; USAID	Demonstration Project	South Africa, Tanzania	AGYW aged 16-24 years	An initiative of STRIVE, a research consortium investigating the social norms and inequalities that drive HIV, that integrates violence prevention and combination prevention, including PrEP. Aims to assess whether it is feasible, acceptable, and safe to offer oral PrEP as part of a combination prevention package that addresses gender-based violence (GBV) and HIV.	Completed	Completed; ended December 2017.
IMPAACT 2009 (DAIDS ID 30020): Pharmacokinetics, Feasibility, Acceptability and Safety of Oral Pre-Exposure Prophylaxis for	International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network	Observational study	Zimbabwe, South Africa, Malawi, Uganda	AGYW aged 16-24 years	Parallel, observational cohort study of HIV-uninfected pregnant adolescents and young women (aged 16-24). The study is designed to characterize adherence over time among women who initiate once daily oral PrEP during pregnancy and continue in the first 6 months following delivery, and to compare pregnancy outcomes among women who take PrEP and women who decline PrEP during the antenatal period.	Ongoing	Ongoing; started February 2019.

Primary HIV Prevention during Pregnancy and Breast Feeding in Adolescents and Young Women							
POWER (Prevention Options for Women Evaluation Research)	University of Washington ICRC, Carnegie Mellon, DTHF, Harvard U., KEMRI, RTI, Wits RHI; USAID	Demonstration project	Kenya, South Africa	AGYW aged 16-24; women 25-29 years	Assesses women's preferences for using microbicides and PrEP through demonstration projects with strategic pilots of delivery strategies, first with oral PrEP. Project will characterize choice, uptake, early adherence and identify cost-effective delivery models, including assessment of repeat HIV testing, decision-making within partnerships, and the interface with reproductive health services.	Ongoing	Ongoing; started July 2015. Expected completion June 2020.
CAPRISA 082: Prospective Study of HIV Risk Factors and Prevention Choices in Young Women in KwaZulu-Natal, South Africa	USAID; CAPRISA	Observational study	South Africa	AGYW aged 18-24; women 25-30 years	Observational study looking at: 1) demographics, 2) HIV risk perception and behavioural assessment, 3) acceptability assessment of expanded HIV prevention options. Data on PrEP uptake, adverse events, usage, barriers, PrEP cycling, adherence by pill count and drug levels will be collected.	Completed	Completed; study closed February 2018.
CAPRISA 084: A demonstration project of daily oral PrEP as part of sexual reproductive health services for young women at high risk of acquiring HIV in KwaZulu- Natal	USAID; CAPRISA	Demonstration project	South Africa	AGYW aged 18-24; women 25-31 years	This PrEP demonstration project will identify in two high HIV burden districts in KwaZulu-Natal: who is likely to use PrEP; how PrEP will be used (understanding pill taking practices); barriers to consistent adherence; how PrEP will change current behavioural practices for HIV prevention (risk compensation); and what support and training is required for service providers.	Completed	Completed; study closed November 2018.
Gender-Specific Combination HIV Prevention for Youth in High Burden Settings (MP3-Youth)	NIH	Demonstration Project	Kenya	AGYW, adolescent men	To evaluate the feasibility and acceptability of a gender-specific combination HIV prevention package for youth in high burden settings. The study aims to pilot a combination package of gender-specific interventions in western Kenya in a mobile health delivery format using integrated services delivery. Interventions include: Male-Specific Intervention Package (HIV counselling and testing; facilitated linkage to	Completed	Completed; study closed April 2016.

					care for HIV-positive; condoms; VMMC); Female-Specific Intervention Package (HIV counselling and testing; facilitated linkage to care for HIV-positive; contraception/family planning; PrEP; conditional cash transfer).		
Church of Scotland Demonstration Project	Church of Scotland Hospital	Demonstration Project	South Africa	Adolescent girls, Pregnant Women	Aims to recruit pregnant teenagers at their first ANC visit and enrol them into comprehensive support program, including PrEP, with the aim of improving outcomes for the mothers and babies. Central focus will be assisting young mothers to return to school, prevent acquisition of HIV and postponing further pregnancies. Other adherence strategies will be investigated as well.	Planned	Planned.
PrEP Implementation for Mothers in Antenatal Care (PrIMA)	NIH, NIAID	Cluster randomized controlled trial	Kenya	Adolescent women, women, serodiscordant couples	This cluster randomized controlled trial aims to determine the best model for optimized PrEP delivery in pregnancy by using existing highly accessed MCH systems as a platform for efficiently delivering PrEP to pregnant women. Twenty ANC clinics in Western Kenya (Siaya and Homa Bay counties) were randomized, ten to universal and ten to targeted PrEP administration. Overall, 4000 women will be enrolled (200 women per clinic) and followed through nine months postpartum. The primary outcome is HIV incidence at nine months postpartum and additional outcomes (PrEP uptake, PrEP continuation and adherence). We are also collecting data on psychosocial factors that may influence uptake, adherence, and retention, birth and infant outcomes, partner HIV-status knowledge, and sexual behaviour information.	Ongoing	Ongoing; started in May 2016. Expected completion June 2020.
3Ps for Prevention Study (Perception, Partners, Pills)	DTHF; University of Washington; funded by NIMH, BMGF	Demonstration project	South Africa	AGYW	Demonstration project in Masiphumilele (Cape Town) assessing uptake to oral PrEP and effect of conditional incentives based on drug levels on adherence to oral PrEP. Through BMGF supplemental funding, PrEP demand creation campaign is being developed with McCann South Africa and PrEP uptake will be enumerated.	Ongoing	Ongoing; started February 2017.
DREAMS	PEPFAR, BMGF, Nike Foundation	Implementation Project	Kenya, South Africa, eSwatini, Uganda, Lesotho, Tanzania,	AGYW	Partnership to reduce HIV infections among AGYW; extends beyond health sector to address poverty, gender inequality, sexual violence, lack of education; PrEP implementation component included.	Ongoing	Ongoing.

			Zambia, Zimbabwe				
Monitoring Pre-Exposure Prophylaxis in Young Adult Women (MPYA)	NIMH	Demonstration Project	Kenya	AGYW	This protocol describes a longitudinal study of young Kenyan women at high risk for HIV who will be offered HIV pre-exposure prophylaxis (PrEP) for up to two years. Adherence will be monitored in all women with the next generation Wisepill; half will be randomized to receive short message service (SMS) reminders. The technical function, acceptability, cost, and validity of the next generation Wisepill device coupled to SMS reminders will be determined among this cohort of young Kenyan women. Additionally, SMS will be used for longitudinal assessment of risk perception and its alignment with PrEP adherence.	Ongoing	Ongoing; started June 2016. Expected completion May 2020.
MSF AGYW PrEP Demo Program	MSF	Open Label Study	South Africa	AGYW	Clinic-based SRH club for delivery of PrEP to young women in Khayelitsha.	Ongoing	Ongoing; started June 2017.
Choices For Adolescent Methods Of Prevention In South Africa (CHAMPS)	NIAID	Demonstration Project	South Africa	AGYW, Adolescent Men	CHAMPS consists of three pilot projects: three pilots: MACHO interrogates adolescent men's attitude to circumcision; Pluspills investigates PrEP; UChoose investigates preferred types of prevention utilizing contraception as the surrogate in 16-17 year-old women.	Completed	Completed; still providing PrEP.
I-TECH DREAMS Project	CDC/PEPFAR	Implementation Project	Namibia	AGYW, Pregnant women	I-TECH, International Training and Education Center for Health at the University of Washington, is funded by CDC/PEPFAR to implement a DREAMS- like intervention in two regions of Namibia. The DREAMS-like intervention includes provision of PrEP to 15-24 year old AGYW.	Ongoing	Ongoing; started October 2017. Expected completion February 2019.
PrEP Implementation in Young Women and Adolescent girls-DREAMS Innovation Challenge (PrIYA)	DREAMS managed by JSI	Implementation Project	Kenya	AGYW, Pregnant women	PrIYA is an implementation project to integrate delivery of oral PrEP in Maternal and Child Health and Family Planning clinics and to evaluate how to efficiently reach women who might benefit from PrEP. PrIYA is funded through the DREAMS Innovation Challenge.	Completed	Completed March 2019.
UNICEF PrEP Demo Program	UNITAID	Demonstration Project	Brazil, South Africa, Thailand	Sexually active adolescents	Combination HIV prevention interventions including oral PrEP.	Planned	Planned.
PEPFAR	PEPFAR	Implementation Project	17 Countries in SSA, 3 Asian, 2	At risk individuals	Provides PrEP to adults and adolescents at risk of HIV infection.	Ongoing	Ongoing.

			Caribbean, 1 European				
LVCT Health and SWOP Kenya (IPCP-Kenya)	LVCT, SWOP; WHO, UNAIDS, Georgetown, LSHTM, Imperial College; funded by BMGF	Demonstration Project	Kenya	FSW (18 and older), MSM (18 and older), young women at high HIV risk (15 -29)	Introduces PrEP to combination prevention interventions. Feasibility study assessing consumer perceptions, cost, delivery options, potential barriers and opportunities for introduction and adherence completed. Acceptability among target populations, cost, menu of combination interventions and feasible delivery options established. Delivers PrEP as part of combination prevention to 2,100 participants over 12 months in preliminary stages. The project will define criteria for PrEP indication among targeted populations, adherence strategies, health system requirements and model impact of PrEP in Kenya.	Completed	Completed October 2017.
Benin Demonstration Project with CHU de Québec (Canada)	BMGF	Demonstration Project	Benin	FSW	To assess feasibility and usefulness of integrating TasP and PrEP to combination prevention package offered to FSWs in Benin; identify best way to successfully implement TasP and PrEP in this setting and to ensure their adoption by national policymakers as part of the HIV prevention package for FSWs.	Completed	Completed; still providing PrEP.
Senegal Demonstration Project with Reseau Africain De Recherche Sur Le Sida, University of Washington, and Westat	BMGF	Demonstration Project	Senegal	FSW	Two phase project including a formative research phase followed by a prospective study of PrEP with TDF/FTC to assess changes in HIV incidence and prevalence in FSW followed at IHS, and Pikine, Mbao, Rufisque and Diamniadio Health Centers over 12 months during the implementation of PrEP and compare that to detailed historical data in this population dating back to 1985.	Completed	Completed; ended December 2016.
The TAPS Demonstration Project	BMGF	Demonstration project	South Africa	FSW	Evaluates whether oral PrEP and immediate treatment can be rolled out within a combination prevention and care approach tailored to needs of 400 HIV-negative and 300 HIV-positive FSW. Study sites include Hillbrow and Pretoria.	Completed	Completed; no longer providing PrEP to former participants.
Sisters Antiretroviral therapy Programme for Prevention of HIV –an Integrated Response (SAPPH-Ire)	DFID; UNFPA	Demonstration Project	Zimbabwe	FSW, AGYW	Seeks to enhance HIV treatment and prevention among highway-based sex workers at 7 sites by increasing uptake and frequency of testing, demonstrate acceptability and feasibility of delivering PrEP, maximize retention in care, promote timely initiation of ART for those eligible, and maximize adherence to both ART and PrEP. The evaluation will be in a representative population-based sample of	Completed	Completed.

					2,800 sex workers, with an estimated 1,000 to 1,500 targeted to take PrEP, after 18 months.		
LINKAGES Malawi	PEPFAR, USAID	Demonstration Project	Malawi	FSW, MSM	TBD	Ongoing	Ongoing.
Pangaea SHAZ! Hub Drop-in Centre	PEPFAR	Implementation Project	Zimbabwe	FSW, Young Women Who Sell Sex, MSM, TGW, Adolescents, Women, Men Serodiscordant Couples, Pregnant women	This is a youth drop-in centre based in Chitungwiza (30km) from the capital, Harare. The site also serves as a research site.	Ongoing	Ongoing.
Bridge to Scale Implementation Project (Jilinde Project)	BMGF, Jhpiego	Implementation Project	Kenya	FSW, MSM, AGYW, Discordant Couples, General population, PWID	This project aims to outline and demonstrate an effective model for Pre- exposure Prophylaxis (PrEP) scale-up as an HIV-prevention intervention in low-resource settings.	Ongoing	Ongoing; started November 2016.
MSF Swaziland PrEP Demonstration Project	MSF	Demonstration Project	eSwatini	FSW, MSM, TGW, TGM, Adolescents, Women, Men, Serodiscordant couples	This study is working to expand the evidence base related to the feasibility, acceptability, and tolerability of daily oral pre-exposure prophylaxis (PrEP) among key populations in Eswatini.	Ongoing	Ongoing; started September 2017. Results expected June 2019.
Expanding Options for HIV Prevention Through Pre-exposure Prophylaxis in Hhohho Region, Swaziland (Sihlomile)	Heidelberg Institute of Public Health; Mylan	Demonstration Project	eSwatini	FSW, MSW, MSM, TGW, AGYW, Adolescent Men, High Risk Women & Men, Serodiscordant couples	An 18-month observation cohort study with the overall aim to assess the operationalization of oral Pre-exposure prophylaxis (PrEP) in Swaziland as an additional HIV combination prevention method among population groups and individuals at high risk of HIV infection.	Ongoing	Ongoing; started August 2017. Expected completion January 2019.
SAUTI	USAID, PEPFAR	Demonstration Project	Tanzania	FSW, Serodiscordant couples,	The aim of the proposed project is to generate data on the implementation models, uptake, feasibility and acceptability HIV self-testing and PrEP in Tanzania through	Ongoing	Ongoing; started

				partners of FSW	community services provision to inform future policy and program development. The project goal is to achieve the UNAIDS first 90, and ensure populations with high risk of acquiring HIV remain negative. This project will target KVPs in selected areas.		October 2017.
LINKAGES Swaziland: Providing Access to HIV Pre Exposure Prophylaxis (PrEP) for those at High Risk in Swaziland	PEPFAR, USAID	Demonstration Project	eSwatini	FSW, Women, Men, MSM, TGW, TGM, AGYW, Adolescent men, Serodiscordant couples	Rates of HIV remain high among women in general, as well as key populations such as, adolescent and young women, FSW and men who have sex with men. PrEP for HIV prevention represents a new option for those at high risk and vulnerable to HIV infection to protect themselves from HIV. This study proposes to offer PrEP to key populations and people at high risk of HIV infection through existing service platforms through a demonstration project to determine whether it can be scaled up in a national programme.	Ongoing	Ongoing; started June 2017. Expected completion January 2019.
Technical Support to Enhance HIV/AIDS Prevention and Opportunities in Nursing Education (TSEPO)	USAID	Implementation Project	Lesotho	High Risk Individuals	TBD	Ongoing	Ongoing.
Partners Demonstration Project	NIMH/NIH, USAID and BMGF	Demonstration Project	Kenya, Uganda	Men, Women, Serodiscordant Couples	Evaluates HIV prevention preferences among approximately 1,000 HIV serodiscordant couples, adherence to PrEP and ART and interface of reproductive health priorities and ART-based prevention. Will implement PrEP as “bridge” to ART, providing PrEP to HIV-negative partner until the HIV- positive partner has initiated ART.	Completed	Completed.
PrEP Operational Research Project	MSF	Demonstration Project	Mozambique	MSM, FSW	Operating in the "corridor," a busy trade route frequented by truckers that runs through Mozambique, Malawi, and Zimbabwe. MSF is providing HIV screening and care to sex workers, drivers, and MSM in the region.	Ongoing	Ongoing; started in 2016. Expected completion October 2018.
EQUIP PrEP Demo in Namibia	TBD	Demonstration Project	Namibia	MSM, PWID, FSW	EQUIP has launched a PrEP demonstration project specifically focused on treatment approaches that effectively respond to Key Population needs and support Test & Start services.	Ongoing	Ongoing.

SEARCH (Sustainable East Africa Research in Community Health)	BMGF	Demonstration Project	Kenya, Uganda	People at high risk of HIV	This is the PrEP extension of the SEARCH study which is underway in over 320,000 participants in Kenya and Uganda.	Ongoing	Ongoing; recruitment began April 2017.
Seasonal Use of PrEP in Mozambique - Short course pre-exposure prophylaxis (PrEP) for female partners of migrant miners in the Gaza Province of Mozambique	BMGF through WHO	Demonstration Project	Mozambique	Women	The overall aim of the proposed study was to assess the feasibility and acceptability of providing short term daily oral PrEP (once daily FTC/TDF 200mg/300mg) as a potential HIV prevention tool to HIV-negative female partners of male miners in Gaza Province, Mozambique. Additional objectives were also to identify facilitators and barriers to uptake and adherence with short term once daily PrEP for HIV prevention among female partners of miners; to assess safety of PrEP use in terms of adverse events requiring discontinuation of PrEP and social harms; to evaluate effect of PrEP on sexual behaviours among participants and to assess correlation between self- reported adherence, adherence measured by pill count and drug level.	Completed	Completed in 2017.

Table S1: Ongoing, Planned and Completed PrEP Open Label, Demonstration and Implementation Projects in Women in Sub-Saharan Africa.

For all ongoing, planned or completed PrEP open label demonstration and implementation projects for women in sub-Saharan Africa, the table set out the study name, sponsor/ funder, project type, population, key study questions and project status. The table does not include studies for women classified within the populations of people who in inject drugs (PWID) and serodiscordant couples. The following acronyms are used: FSW = female sex worker, MSM = men who have sex with men, AGYW = adolescent girls and young women, TGW = transgender women, TGM = transgender men, TasP = treatment as prevention. The table is reproduced from AVAC (May 2019 list – latest available in October 2019)[1].

References to Appendix 1

1. AVAC Global Advocacy for HIV Prevention. Ongoing and Planned PrEP Open Label, Demonstration and Implementation Projects [Internet]. 2019 [cited 2019 Aug 14]. Available from: https://www.avac.org/sites/default/files/resource-files/ongoing_planned_oralPrEP_studies_april2019.pdf

Appendix 2: Supplementary Materials to Research Paper 1

Supplementary Materials to: When are declines in condom use while using PrEP a concern? Modelling insights from a Hillbrow, South Africa case study

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Supplementary Methods

The HIV risk from a single partner population to FSW with consistency of condom use γ_1, adhering to PrEP at level α is given by:

$$\pi(\gamma_1, \alpha) = 1 - \Big(p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m$$

S1

In the absence of PrEP($i.e\ \alpha = 0$) the HV risk equation (S1) becomes

$$\pi(\gamma_0, 0) = 1 - \Big(p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m$$

S2

It is more beneficial to take PrEP as a supplementary prevention method if the condition $\pi(\gamma_1, \alpha) < \pi(\gamma_0, 0)$ is satisfied, which simplifies to

$$\Big(p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m < \Big(p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m$$

S3

From equation (S3), the condition for PrEP to be beneficial in terms reducing HIV risk is given by

$$\frac{(1 - \varepsilon\gamma_1)}{(1 - \varepsilon\gamma_0)} < (1 - b_\alpha)$$

S4

The introduction of PrEP will therefore be of significance if the relative HIV risk reduction factor due to condom use after the introduction of PrEP is less than the HIV risk reduction afforded by PrEP. Equation (S4) can also be arranged to give:

$$b_\alpha > \frac{\varepsilon(\gamma_0 - \gamma_1)}{(1 - \varepsilon\gamma_1)}$$

S5

Equation (S5) gives us the level of effectiveness that must be attained for PrEP to be of benefit in reducing HIV risk, considering any change in condom consistency. We also note from equation (S5) that the risk reduction for PrEP to be beneficial at any level of adherence $\alpha > 0$ happens at $\gamma_0 = \gamma_1$: condom consistency remains unchanged. It is independent of the number of partners, sex acts and partner HIV prevalence.

From equation (S5) we derive the critical PrEP effectiveness corresponding to critical adherence level α^*, which serves as the break-even point for beneficence of PrEP for HIV prevention with regard to any change in condom consistency:

$$b_{\alpha^*} = \frac{\varepsilon(\gamma_0 - \gamma_1^*)}{(1 - \varepsilon\gamma_1^*)}$$

S6

Considering the extreme scenario of 100% condom migration on PrEP, this intervention will not increase HIV risk for FSWs as long as the achieved effectiveness of PrEP exceeds that of condoms at the consistency prior to PrEP introduction:

$$\varepsilon\gamma_0 < b_\alpha \leq 1$$

S7

This can also be seen as the condition under which PrEP will *always* be beneficial as an additional HIV prevention approach in reducing HIV risk.

Simple rearrangement of equation (S6) gives the break-even value of condom consistency after introduction of PrEP such that HIV risk is not increased:

$$\gamma_1^* = \frac{(\varepsilon\gamma_0 - b_\alpha)}{\varepsilon(1 - b_\alpha)}$$

S8

Extension of the simple HIV risk equations (S1) and (S2) to consider the case of two partner populations gives the refined HIV risk using PrEP and condoms as:

$$\Pi(\gamma_1, \alpha) = 1 - \left(p_c\left(1 - \beta(1 - \varepsilon\gamma_1^c)(1 - b_\alpha)\right)^{n_c} + (1 - p_c)\right)^{m_c} * \left(p_r\left(1 - \beta(1 - \varepsilon\gamma_1^r)(1 - b_\alpha)\right)^{n_r} + (1 - p_r)\right)^{m_r}$$

S9

And in the absence of PrEP (i.e. $\alpha = 0$):

$$\Pi(\gamma_0, 0) = 1 - \left(p_c\left(1 - \beta(1 - \varepsilon\gamma_0^{c})\right)^{n_c} + (1 - p_c)\right)^{m_c} * \left(p_r\left(1 - \beta(1 - \varepsilon\gamma_0^{r})\right)^{n_r} + (1 - p_r)\right)^{m_r}$$

S10

Returning to the case of a single partner population, the simple HIV risk equations (S1) and (S2) can also be extended to account for the increased risk of HIV transmission resulting from exposure to STIs. For a FSW using PrEP and condoms, their HIV risk is refined to:

$$\pi(\gamma_1, \alpha) = 1 - \Big(sp\big(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - s)p\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - p)\Big)^m$$

S11

And in the absence of PrEP:

$$\pi(\gamma_0, 0) = 1 - \Big(sp\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s)p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m$$

S12

PrEP is thus beneficial in reducing HIV risk, considering possible changes in condom use and increased exposure to STIs, if $\pi(\gamma_1, \alpha, \delta) < \pi(\gamma_0, 0, \delta)$, which simplifies as:

$$s\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s)\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n < s\big(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 - s)\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n$$

S13

Finally equations (S11) and (S12) are extended to account for both FSW partner populations, considering exposure to STIs. HIV risk using PrEP and condoms is then:

$$\Pi(\gamma_1, \alpha, \delta) = 1 - \Big(sp_c\big(1 - \delta\beta(1 - \varepsilon\gamma_1^{c})(1 - b_\alpha)\big)^{n_c} + (1 - s)p_c\big(1 - \beta(1 - \varepsilon\gamma_1^{c})(1 - b_\alpha)\big)^{n_c} + (1 - p_c)\Big)^{m_c} * \Big(sp_r\big(1 - \delta\beta(1 - \varepsilon\gamma_1^{r})(1 - b_\alpha)\big)^{n_r} + (1 - s)p_r\big(1 - \beta(1 - \varepsilon\gamma_1^{r})(1 - b_\alpha)\big)^{n_r} + (1 - p_r)\Big)^{m_r}$$

S14

And in the absence of PrEP given by:

$$\Pi(\gamma_0, 0, \delta) = 1 - \left(sp_c\left(1 - \delta\beta(1 - \varepsilon\gamma_0^c)\right)^{n_c} + (1 - s)p_c\left(1 - \beta(1 - \varepsilon\gamma_0^c)\right)^{n_c} + (1 - p_c)\right)^{m_c} * \left(sp_r\left(1 - \delta\beta(1 - \varepsilon\gamma_0^r)\right)^{n_r} + (1 - s)p_r\left(1 - \beta(1 - \varepsilon\gamma_0^r)\right)^{n_r} + (1 - p_r)\right)^{m_r}$$

S15

Sensitivity analysis

For the sensitivity analysis exploring the case where the probability that at least one person in the partnership has an STI, s, changes following the introduction of PrEP, we take s_0, to be the probability that at least one person in the partnership has an STI prior to the introduction of PrEP and s_1, to be the probability that at least one person in the partnership has an STI following the introduction of PrEP.

In order to obtain conservative results in terms of change in condom consistency tolerated following the introduction of PrEP, it is assumed that STIs are present in *all* partnerships where reductions in condom consistency occur following the introduction of PrEP, and these STIs are transmitted through the sex act if not already present in both partners. Therefore the probability that at least one person in the partnership has an STI following the introduction of PrEP, s_1, will increase at the same rate as the change in condom consistency tolerated for HIV risk not to increase on PrEP. In other words, $s_1 = s_0 * \left(1 + (\gamma_0 - \gamma_1)\right)$.

In order to undertake the sensitivity analyses, equations **S11** to **S15** are evolved as follows:

For a single partner population, accounting for the increased risk of HIV transmission resulting from exposure to STIs, where the probability that at least one person in the partnership has an STI is assumed to change in accordance with change in condom consistency, HIV risk using PrEP and condoms (evolution of S**11**) is:

$$\pi(\gamma_1, \alpha, s_1) = 1 - \left(s_0\left(1 + (\gamma_0 - \gamma_1)\right)p\left(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\right)^n + (1 - s_0\left(1 + (\gamma_0 - \gamma_1)\right))p\left(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\right)^n + (1 - p)\right)^m$$

S16

And in the absence of PrEP (evolution of **S12**) is:

$$\pi(\gamma_0, 0, s_0) = 1 - \Big(s_0 p\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s_0)p\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n + (1 - p)\Big)^m$$

S17

PrEP is thus beneficial in reducing HIV risk, considering possible changes in condom use and increased exposure to STIs, if (evolution of **S13**):

$$\begin{aligned} s_0\big(1 - \delta\beta(1 - \varepsilon\gamma_0)\big)^n + (1 - s_0)\big(1 - \beta(1 - \varepsilon\gamma_0)\big)^n \\ < s_0\big(1 + (\gamma_0 - \gamma_1)\big)\big(1 - \delta\beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n + (1 \\ - s_0\big(1 + (\gamma_0 - \gamma_1)\big)\big)\big(1 - \beta(1 - b_\alpha)(1 - \varepsilon\gamma_1)\big)^n \end{aligned}$$

S18

Considering both FSW partner populations, accounting for the increased risk of HIV transmission resulting from exposure to STIs, where the probability that at least one person in the partnership has an STI is assumed to change in accordance with change in condom consistency, HIV risk using PrEP and condoms (evolution of S**14**) is:

$$\begin{aligned} \Pi(\gamma_1, \alpha, \delta, s_1) = 1 \\ - \Big(s_0\big(1 + (\gamma_0 - \gamma_1)\big)p_c\big(1 - \delta\beta(1 - \varepsilon\gamma_1^c)(1 - b_\alpha)\big)^{n_c} + (1 \\ - s_0\big(1 + (\gamma_0 - \gamma_1)\big)\big)p_c\big(1 - \beta(1 - \varepsilon\gamma_1^c)(1 - b_\alpha)\big)^{n_c} + (1 - p_c)\Big)^{m_c} \\ * \Big(s_0\big(1 + (\gamma_0 - \gamma_1)\big)p_r\big(1 - \delta\beta(1 - \varepsilon\gamma_1^r)(1 - b_\alpha)\big)^{n_r} + (1 \\ - s_0\big(1 + (\gamma_0 - \gamma_1)\big)\big)p_r\big(1 - \beta(1 - \varepsilon\gamma_1^r)(1 - b_\alpha)\big)^{n_r} + (1 - p_r)\Big)^{m_r} \end{aligned}$$

S19

And in the absence of PrEP (evolution of **S15**) is:

$$\begin{aligned} \Pi(\gamma_0, 0, \delta, s_0) = 1 - \Big(s_0 p_c\big(1 - \delta\beta(1 - \varepsilon\gamma_0^c)\big)^{n_c} + (1 - s_0)p_c\big(1 - \beta(1 - \varepsilon\gamma_0^c)\big)^{n_c} + (1 - p_c)\Big)^{m_c} \\ * \Big(s_0 p_r\big(1 - \delta\beta(1 - \varepsilon\gamma_0^r)\big)^{n_r} + (1 - s_0)p_r\big(1 - \beta(1 - \varepsilon\gamma_0^r)\big)^{n_r} + (1 - p_r)\Big)^{m_r} \end{aligned}$$

S20

Parameter	Symbol	Baseline value (range: low risk-high risk)	References
Sexual behaviour data			
Proportion of client partner population HIV infected	p_c	0.26 (0.23-0.29)	[1](Black African Men, 25-49, South Africa)
Proportion of regular partner population HIV infected	p_r	0.26 (0.23-0.29)	[1] (Black African Men, 25-49, South Africa)
Initial condom consistency with regular partners	γ_0^r	0.1	Mid-point of (0.15-0.05) from [2](main partnerships, per sex act, Hillbrow)
Initial condom consistency with clients	γ_0^c	Varied across a spectrum of simulated values in each analysis, from 30% upwards	
Probability at least one person in the partnership has an STI	s	0.15 (0.15, 0.3)	[3](prevalence of Chlamydia trachomatis & Neisseria gonorrhoea in Hillbrow FSWs); [4](FSW STI prevalence, Durban)
Number of client partners, per 3 month period	n_c	105 (rounded) (78-126)	[2](mean monthly reported number of clients per FSW, Hillbrow; multiplied by 3)
Number of regular partners, per 3 month period	n_r	1 (0.37-2)	[3](mean reported number of current partners, rounded), [5](number of main sexual partners, FSWs Hillbrow)
Average number of sex acts – per client, per 3 month period	m_c	1 (1-1.2)	[3](number of sexual encounters per client, Hillbrow)
Average number of sex acts – per regular partner, per 3 month period	m_r	24 (mid-point) (12-36)	[2](mean monthly frequency of sex acts in main partnerships, Hillbrow; multiplied by 3)
Transmission Probabilities			
Condom HIV risk reduction efficacy per sex act	ε	0.85 (0.90-0.80)	[6](with consistent use), [7](with consistent use)
Probability of HIV transmission, male to female, through peno-vaginal sex	β	0.001 (0.00078,0.00199)	[8](basic risk male-to-female peno-vaginal), [9](Per-act HIV-1 transmission probability 95% CI)

Multiplicative increase in per sex act probability of HIV transmission in the presence of an STI	δ	3.7 (2-6);	[10](combined study effectiveness estimate across STDs, and range spanning individual STD combined study effect estimates)
PrEP HIV risk reduction effectiveness, corresponding to adherence level α	b_α	0.35; 0.45; 0.55; 0.65; 0.75; 0.85; 0.95 (see note below table)	Spanning spectrum of trial estimates [11–15,16] corresponding to varying levels of adherence

Table S1: Model parameter values.
The unbracketed numbers shown in the 'base value' column are the values that have been used to parameterise the model for the base, or core, analyses of this study. The numbers shown in brackets represent the values used in the sensitivity analyses looking at the outcomes for high and low risk FSW, with the left-hand bracketed value corresponding to the low risk scenario and the right hand bracketed value corresponding to the high risk scenario.

Further notes to Table S1: Specifically, in the case of $\boldsymbol{b_\alpha}$, a range of values were used in the base analyses, to represent a spectrum of possible levels HIV risk reduction effectives achieved corresponding to differing levels of PrEP adherence ($\boldsymbol{\alpha}$).

In the single partner population analyses these values of $\boldsymbol{b_\alpha}$ were simulated in increments of 10%, roughly spanning the range of HIV risk reduction estimated through the iPrEx OLE[17] study, which provides the most comprehensive evidence base available to date linking PrEP adherence to HIV risk reduction through drug concentrations found in participants' dried blood spots. The study reported that:

- *An estimated drug dosing of <2 tables a week led to an estimated HIV risk reduction compared to no adherence of 53%;*
- *An estimated drug dosing of 2 to 3 tablets a week led to an estimated HIV risk reduction of 87%; and*
- *An estimated drug dosing of 4 to 6 tablets a week led to an estimated HIV risk reduction of 100%*

However, noting that the iPrEx OLE study was conducted in a different study population (MSM and transgender women) than considered in this study, we started $\boldsymbol{b_\alpha}$ from a slightly lower baseline of 35%.

In the *two partner population* analyses, for simplicity three levels of $\boldsymbol{b_\alpha}$ were simulated: 55%, 75% and 95%, roughly spanning the lower and upper values of $\boldsymbol{b_\alpha}$ observed in the iPrEx OLE study, as well as the midpoint of these values.

Supplementary Results

Single partner population, accounting for increased STI exposure

γ^0	35% PrEP Effectiveness				45% PrEP Effectiveness				55% PrEP Effectiveness				65% PrEP Effectiveness				75% PrEP Effectiveness				85% PrEP Effectiveness			
	% reduction condom consistency tolerated		Change in tolerance, considering no STI effect		% reduction condom consistency tolerated		Change in tolerance, considering no STI effect		% reduction condom consistency tolerated		Change in tolerance, considering no STI effect		% reduction condom consistency tolerated		Change in tolerance, considering no STI effect		% reduction condom consistency tolerated		Change in tolerance, considering no STI effect		% reduction condom consistency tolerated		Change in tolerance, considering no STI effect	
	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)	Base	(LR, HR)
90%	17%	(-4%,4%)	0%	(-4%,4%)	25%	(-6%,7%)	0%	(-6%,7%)	38%	(-9%,10%)	0%	(-9%,10%)	57%	(-13%,15%)	0%	(-13%,15%)	92%	(-22%,8%)	0%	(-22%,8%)	100%	(0%,0%)	0%	(0%,0%)
85%	21%	(-4%,5%)	0%	(-4%,5%)	31%	(-6%,7%)	0%	(-6%,7%)	47%	(-9%,11%)	0%	(-9%,11%)	71%	(-14%,16%)	0%	(-14%,16%)	100%	(-8%,0%)	0%	(-8%,0%)	100%	(0%,0%)	0%	(0%,0%)
80%	25%	(-4%,5%)	0%	(-4%,5%)	39%	(-7%,8%)	0%	(-7%,8%)	58%	(-10%,11%)	0%	(-10%,11%)	87%	(-15%,13%)	0%	(-15%,13%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)
75%	31%	(-5%,5%)	0%	(-5%,5%)	47%	(-7%,8%)	0%	(-7%,8%)	69%	(-11%,12%)	0%	(-11%,12%)	100%	(-11%,0%)	0%	(-11%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)
70%	37%	(-5%,6%)	0%	(-5%,6%)	56%	(-8%,9%)	0%	(-8%,9%)	83%	(-11%,13%)	0%	(-11%,13%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)
50%	73%	(-7%,8%)	0%	(-7%,8%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)
30%	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)	100%	(0%,0%)	0%	(0%,0%)

Table S2: Percentage reduction in condom consistency tolerated for HIV risk not to increase on PrEP, and corresponding decreased tolerance having accounted for the effect of STIs - for various levels of PrEP effectiveness (b_α) achieved and baseline condom consistencies *(γ_0).*

For each level of PrEP effectiveness simulated, in the left-hand column, the table shows the % reduction in condom consistency tolerated, where STIs are accounted for in the HIV risk equations. The results are shown for the base case parameterization of the model, as well as the boundary cases explored through the first sensitivity analysis of high and low risk FSW.

In the right hand side columns for each level of PrEP effectiveness simulated, the table shows the absolute difference in % reduction in condom consistency tolerated, in the case that STIs are not accounted for in the HIV risk equations.

'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW, and the results calculated in the sensitivity analysis for the boundary parameter cases. The results corresponding to the Base case where the effect of STIs are considered are shown graphically in Figure 2 in the main text.

Single partner population, accounting for increased STI exposure

– Sensitivity analysis on STI prevalence following introduction of PrEP

γ^0	35% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			45% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		
	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)
90%	17%	(-4%,4%)	-2%	-12%	(-4%,-1%)	25%	(-6%,7%)	-3%	-12%	(-7%,-2%)
85%	21%	(-4%,5%)	-3%	-15%	(-5%,-2%)	31%	(-6%,7%)	-4%	-13%	(-8%,-4%)
80%	25%	(-4%,5%)	-3%	-12%	(-6%,-4%)	39%	(-7%,8%)	-6%	-16%	(-9%,-7%)
75%	31%	(-5%,5%)	-5%	-16%	(-6%,-6%)	47%	(-7%,8%)	-8%	-17%	(-10%,-11%)
70%	37%	(-5%,6%)	-6%	-16%	(-7%,-9%)	56%	(-8%,9%)	-10%	-18%	(-12%,-15%)
50%	73%	(-7%,8%)	-16%	-22%	(-14%,-25%)	100%	(0%,0%)	-16%	-16%	(-12%,-31%)
30%	100%	(0%,0%)	0%	0%	(0%,-9%)	100%	(0%,0%)	0%	0%	(0%,0%)

γ^0	55% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			65% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		
	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR, HR)	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR, HR)
90%	38%	(-9%,10%	-5%	-13%	(-10%,-4%)	57%	(-13%,15%	-10%	-18%	(-17%,-9%)
85%	47%	(-9%,11%	-7%	-15%	(-12%,-8%)	71%	(-14%,16%	-14%	-20%	(-19%,-16%)
80%	58%	(-10%,11%	-10%	-17%	(-14%,-13%)	87%	(-15%,13%	-18%	-21%	(-22%,-24%)
75%	69%	(-11%,12%	-14%	-20%	(-16%,-18%)	100%	(-11%,0%	-19%	-19%	(-20%,-28%)
70%	83%	(-11%,13%	-18%	-22%	(-19%,-25%)	100%	(0%,0%)	-5%	-5%	(-4%,-18%)
50%	100%	(0%,0%)	0%	0%	(0%,-3%)	100%	(0%,0%)	0%	0%	(0%,0%)
30%	100%	(0%,0%)	0%	0%	(0%,0%)	100%	(0%,0%)	0%	0%	(0%,0%)

γ^0	75% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			85% PrEP Effectiveness: % reduction condom consistency tolerated, assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		
	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR, HR)	Base	(LR, HR)	Base (Abs)	Base (Rel)	(LR, HR)
90%	92%	(-22%,8%)	-20%	-22%	(-28%,-22%)	100%	(0%,0%)	0%	0%	(0%,0%)
85%	100%	(-8%,0%)	-12%	-12%	(-18%,-18%)	100%	(0%,0%)	0%	0%	(0%,0%)
80%	100%	(0%,0%)	0%	0%	(0%,-7%)	100%	(0%,0%)	0%	0%	(0%,0%)
75%	100%	(0%,0%)	0%	0%	(0%,0%)	100%	(0%,0%)	0%	0%	(0%,0%)
70%	100%	(0%,0%)	0%	0%	(0%,0%)	100%	(0%,0%)	0%	0%	(0%,0%)
50%	100%	(0%,0%)	0%	0%	(0%,0%)	100%	(0%,0%)	0%	0%	(0%,0%)
30%	100%	(0%,0%)	0%	0%	(0%,0%)	100%	(0%,0%)	0%	0%	(0%,0%)

Table S3: Percentage reduction in condom consistency tolerated for HIV risk not to increase on PrEP, without and with change in STI prevalence following introduction of PrEP.
For each level of PrEP effectiveness achieved two sets of results are presented. In the left hand columns, as comparison points for the sensitivity analysis, the left hand column repeat the results for each PrEP effectiveness level (accounting for STIs) from Table S2 (in grey).

In the right hand columns, the results of the sensitivity analysis are presented, for the case that s changes following the introduction of PrEP in accordance with the reduction in condom consistency observed. Compared to the original results from Table S2, the table shows the change in % reduction condom migration tolerated in absolute and relative terms from the Base case. We also show the absolute % change for the boundary cases of Low Risk and High Risk FSW from the original Base case. (Abs) stands of absolute change and (Rel) stands for relative change. 'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW.

Two partner population, accounting for increased STI exposure

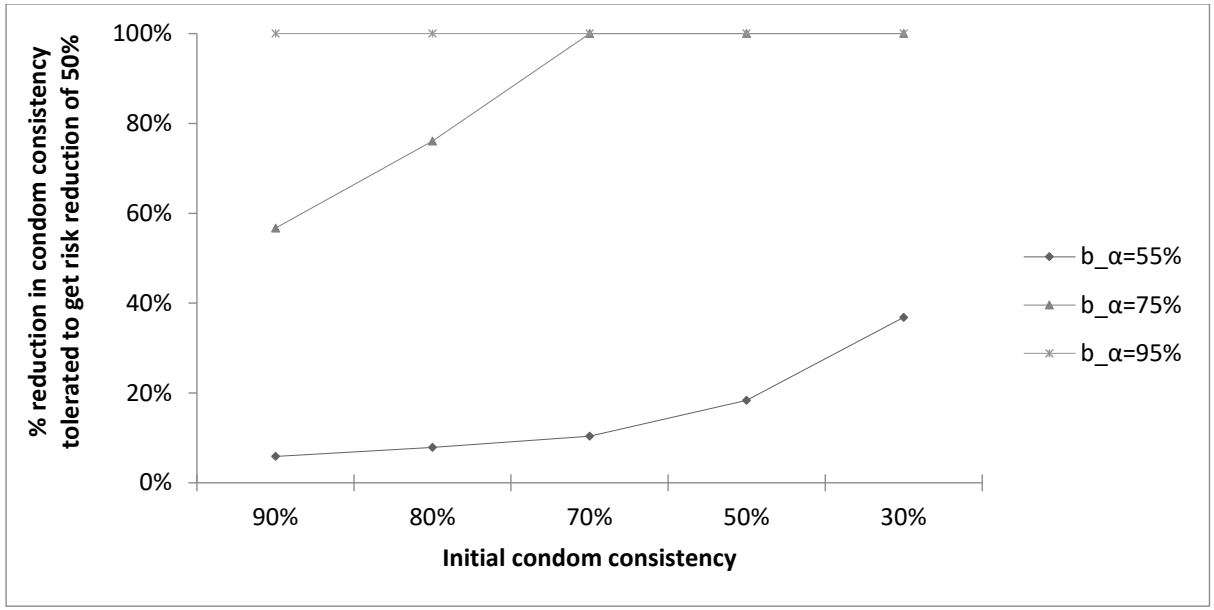

Figure S1: Percentage reduction in condom consistency tolerated to get risk reduction of 50%.

*Figure S1 shows the % reduction in condom consistency tolerated to get a risk reduction of 50% for three cases of PrEP effectiveness achiever: 55%, 75% and 95%, across a range of initial condom consistencies from 30% - 90%. b_α is the level of PrEP effectiveness achieved by a FSW. The results correspond to Table **1** in the main text, for the results accounting for STIs in the HIV risk equations.*

Two partner population, accounting for increased STI exposure

- *In the case that condom consistency with regular partners is reduced from 10% to 0% following the introduction of PrEP*

	55% PrEP Effectiveness								75% PrEP Effectiveness								95% PrEP Effectiveness							
	% reduction in condom consistency with clients tolerated to get overall HIV risk reduction of																							
	50%				90%				50%				90%				50%				90%			
γ^0	Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs		Accounting for STIs		Not accounting for STIs	
	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)	Base	(LR,HR)
90%	3%	**(-1%,-3%)**	4%	**(-1%,2%)**	-	-	-	-	54%	**(-26%,26%)**	55%	**(-26%,39%)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	54%	**(-25%,19%)**	54%	**(-26%,37%)**
80%	5%	**(-1%,-4%)**	5%	**(-1%,2%)**	-	-	-	-	73%	**(-29%,27%)**	74%	**(-29%,26%)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	73%	**(-28%,19%)**	74%	**(-29%,26%)**
70%	7%	**(-1%,-6%)**	8%	**(-2%,2%)**	-	-	-	-	98%	**(*,*)**	99%	**(*,*)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	97%	**(*,*)**	98%	**(*,*)**
50%	14%	**(-1%,-13%)**	15%	**(-2%,2%)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	100%	**(*,*)**	100%	**(*,*)**
30%	29%	**(-1%,-28%)**	31%	**(-3%,0%)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	-	-	-	-	100%	**(*,*)**	100%	**(*,*)**	100%	**(*,*)**	100%	**(*,*)**

Table S4: Maximum tolerated % reduction in condom consistency with clients to still achieve 50% or 90% reductions in HIV risk on PrEP, for different levels of PrEP effectiveness (b_α) achieved and condom consistency with regular partners assumed to be zero.

For each level of PrEP effectiveness demonstrated, the table shows the % reduction in condom consistency that could be tolerated, from varying levels of initial condom consistency, to achieve either 50% or 90% HIV risk reduction. The results are shown for both the case that STIs are accounted for in the HIV risk equations, as well as the case that they are not. The results are shown for the base case parameterization of the model, as well as the boundary cases explored through the first sensitivity analysis of high and low risk FSW.

The difference in assumptions taken to calculate the results for Table S4 compared to Table 1 in the main text is that for Table S4, condom consistency with regular partners is assumed to reduce from 10% to 0% following the introduction of PrEP, whereas in Table 1, condom consistency with regular partners is assumed to remain at 10% before and after introduction of PrEP.

b_α is the level of PrEP effectiveness achieved by a FSW. '–' indicates that achievement of the risk reduction is not possible. '' indicates full migration will still result in higher levels of risk reduction. 'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW, and the results calculated in the sensitivity analysis for the boundary parameter cases.*

Two partner population, accounting for increased STI exposure

- *Condom consistency with regular partners assumed to remain at 10% following the introduction of PrEP*

- *Sensitivity analysis on STI prevalence following introduction of PrEP*

	55% PrEP Effectiveness									75% PrEP Effectiveness									95% PrEP Effectiveness								
	% reduction in condom consistency with clients tolerated to get overall HIV risk reduction of																										
	50%					90%				50%					90%				50%					90%			
Initial condom consistency	Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		
	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)
90%	6%	(-3%,-3%)	-1%	-14%	(-3%,-4%)	-	-	-	-	-	57%	(-27%,26%)	-12%	-21%	(-29%,-11%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	56%	(-27%,19%)	-12%	-21%	(-29%,-14%)
80%	8%	(-3%,-5%)	-1%	-16%	(-3%,-6%)	-	-	-	-	-	76%	(-31%,24%)	-18%	-24%	(-34%,-21%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	75%	(-29%,20%)	-17%	-23%	(-33%,-24%)
70%	10%	(-3%,-6%)	-2%	-18%	(-4%,-8%)	-	-	-	-	-	100%	(*,*)	-26%	-26%	(-41%,-33%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	100%	(*,*)	-26%	-26%	(-41%,-39%)
50%	18%	(-4%,-13%)	-4%	-22%	(-5%,-15%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	100%	(*,*)	0%	0%	(0%,-7%)
30%	37%	(-6%,-29%)	-9%	-26%	(-9%,-33%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	-	-	-	-	-	100%	(*,*)	0%	0%	(0%,0%)	100%	(*,*)	0%	0%	(0%,0%)

***Table S5*: Maximum tolerated % reduction in condom consistency with clients (consistency with regular partners held constant) to still achieve 50% or 90% reductions in HIV risk on PrEP, for different levels of PrEP effectiveness achieved, assuming STI prevalence does not change with the introduction of PrEP; and change in this % reduction in the case STI prevalence does change with the introduction of PrEP.**

For each of the three levels of PrEP effectiveness simulated, two sets of results are presented. In the left hand columns, as comparison points for the sensitivity analysis, the left hand column repeats the results (accounting for STIs) from Table 1 in the main paper (in grey) – i.e. the two partner analysis where condom consistency with regular partners is assumed to be unchanged (at 10%) following the introduction of PrEP.

In the right hand columns, the results of the sensitivity analysis are presented, for the case that s changes following the introduction of PrEP in accordance with the reduction in condom consistency observed. Compared to the original results from Table 1, we show the change in % reduction condom migration tolerated in absolute and relative terms from the Base case. We also show the absolute % change for the boundary cases of Low Risk and High Risk FSW from the original base case. (Abs) stands of absolute change and (Rel) stands for relative change. 'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW.

Two partner population, accounting for increased STI exposure

- *In the case that condom consistency with regular partners is reduced from 10% to 0% following the introduction of PrEP*

- *Sensitivity analysis on STI prevalence following introduction of PrEP*

	55% PrEP Effectiveness									75% PrEP Effectiveness									95% PrEP Effectiveness								
	% reduction in condom consistency with clients tolerated to get overall HIV risk reduction of																										
	50%					90%				50%					90%				50%					90%			
γ^0	Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP			Assuming STI prevalence does not change		Change in % reduction, considering change in STI prevalence post PrEP		
	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)	Base	(LR,HR)	Base (Abs)	Base (Rel)	(LR,HR) (Abs)
90%	3%	(-1%,-3%)	0%	-14%	(-1%,-3%)	-	-	-		-	54%	(-26%,26%)	-11%	-21%	(-28%,-10%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	54%	(-25%,19%)	-11%	-21%	(-27%,-13%)
80%	5%	(-1%,-4%)	-1%	-16%	(-1%,-5%)	-	-	-		-	73%	(-29%,27%)	-17%	-24%	(-32%,-20%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	73%	(-28%,19%)	-17%	-24%	(-32%,-23%)
70%	7%	(-1%,-6%)	-1%	-18%	(-2%,-7%)	-	-	-		-	98%	(*,*)	-26%	-26%	(-39%,-33%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	97%	(*,*)	-25%	-26%	(-38%,-37%)
50%	14%	(-1%,-13%)	-3%	-22%	(-2%,-13%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	100%	(*,*)	0%	0%	(0%,-10%)
30%	29%	(-1%,-28%)	-8%	-26%	(-4%,-29%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	-	-	-		-	100%	(*,*)	0%	0%	(0%,0%)	100%	(*,*)	0%	0%	(0%,0%)

***Table S6*: Maximum tolerated % reduction in condom consistency with clients (consistency with regular partners assumed to reduce to zero following the introduction of PrEP) to still achieve 50% or 90% reductions in HIV risk on PrEP, for different levels of PrEP effectiveness achieved, assuming STI prevalence does not change with the introduction of PrEP; and change in this % reduction in the case STI prevalence does change with the introduction of PrEP.**

For each of the three levels of PrEP effectiveness simulated, two sets of results are presented. In the left hand columns, as comparison points for the sensitivity analysis, the left hand column repeats the results (accounting for STIs) from Table S4 (in grey) – i.e. the two partner analysis where condom consistency with regular partners is assumed to reduce from 10% to 0% following the introduction of PrEP.

In the right hand columns, the results of the sensitivity analysis are presented, for the case that s changes following the introduction of PrEP in accordance with the reduction in condom consistency observed (as well as condom consistency with regular partners reducing from 10% to 0% following the introduction of PrEP). Compared to the original results from Table s4, we show the change in % reduction condom migration tolerated in absolute and relative terms from the Base case. We also show the absolute % change for the boundary cases of Low Risk and High Risk FSW from the original Base case. (Abs) stands of absolute change and (Rel) stands for relative change. 'Base' refers to the main calculated results undertaken using the baseline parameter values. HR stands for high risk and LR stands for low risk FSW.

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Appendix 3: Supplementary Materials to Research Paper 2

Supplementary Materials to: Is modelling complexity always needed? Insights from modelling PrEP introduction in South Africa

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Supplementary Methods

Model Structure

Static formulation of HIV risk

Consistent with our previous work,[1] the static model of HIV risk takes the Bernoulli formulation, where the probability of the HIV virus being transmitted through each sexual contact is treated as an independent risk event. In our simplified population model, and to facilitate comparison between the static and dynamic models, female sex workers (FSW) are assumed to have a single partner population 'male partners', in which the proportion HIV infected is p. For simplicity, male partners are characterised as clients, rather than other partner types (such as regular partners). For a given time period, h, FSW are assumed to have C_m[1] partners, with whom they have an average of n_m sex acts each. h is taken as 3 months, corresponding to the minimum period after which an individual on PrEP must return to the provider to perform an HIV test to check for seroconversion (amongst other indicators).[2] We assume an average probability of HIV transmission, β_f, per sexual contact with an HIV infected male partner. It is assumed that all sex acts are peno-vaginal on the basis of available epidemiological data for FSW in Hillbrow.[3]

To assess the effect of any change in condom consistency (average proportion of sex acts in which a condom is used) following the introduction of PrEP, condoms are assumed to be used with consistency γ_0 prior to PrEP introduction and γ_1 after its introduction. We assume condoms to have an HIV risk reduction efficacy, ε, including slippage and breakage. The exact relationship between adherence and effectiveness of PrEP remains under investigation, especially for women.[4] As such, the equations assume an overall achieved level of 'PrEP use-effectiveness', b_α, corresponding to a given level of FSW PrEP adherence, α. In its most basic formulation, the Bernoulli model of HIV risk to FSW is:

$$\pi = 1 - \left(p\left(1 - \beta_f(1 - b_\alpha)(1 - \varepsilon\gamma)\right)^{n_m} + (1 - p)\right)^{C_m}$$

Where $\gamma = \gamma_0$ before the introduction of PrEP, and γ_1 after the introduction of PrEP.

1.1

[1] Static model parameters are denoted subscripts - *f* (for female) and *m* (for male) - as relevant, for ease of comparability with parameters in the dynamic model.

To account for changes in HIV risk owing to increased sexually transmitted infection (STI) exposure resulting through a decrease in condom consistency, it is assumed that s_1, the probability that at least one person in the partnership has an STI following the introduction of PrEP, increases proportionally to the absolute change in condom consistency; in other words $s_1 = s_0\big(1 + (\gamma_0 - \gamma_1)\big)$, where s_0 is the probability that at least one person in the partnership has an STI prior to the introduction of PrEP. Parameter δ is the multiplicative increase in per sex act probability of HIV transmission in the presence of an STI.

To account for antiretroviral (ART) coverage and male circumcision levels in this setting, ϑ_m is taken as the proportion of HIV+ partners that are on ART and ϱ is the average reduction in the probability of HIV transmission due to viral suppression on ART. The proportion of male population circumcised is denoted by τ and $\sigma_f$is the average reduction in probability HIV transmission to women, when the male partner has been circumcised.

Thus the HIV risk to a FSW, for a 3-month timestep, is given by the static model:

$$\pi_{static} = 1 - \big(p\psi_f + p\omega_f + (1-p)\big)^{C_m}$$

Or equivalently:

$$\pi_{static} = 1 - \big(1 + p(\psi_f + \omega_f - 1)\big)^{C_m}$$

Where:

$$\psi_f = (1-\tau)\begin{pmatrix} (1-\vartheta)s\Big(1-\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +(1-\vartheta)(1-s)\Big(1-\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +\vartheta s\Big(1-(1-\varrho)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +\vartheta(1-s)\Big(1-(1-\varrho)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \end{pmatrix}$$

and $\omega_f = \tau\begin{pmatrix} (1-\vartheta)s\Big(1-(1-\sigma)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +(1-\vartheta)(1-s)\Big(1-(1-\sigma)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +\vartheta s\Big(1-(1-\sigma)(1-\varrho)\delta\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \\ +\vartheta(1-s)\Big(1-(1-\sigma)(1-\varrho)\beta_f(1-b_\alpha)(1-\varepsilon\gamma)\Big)^n \end{pmatrix}$

With $\gamma = \gamma_0$ before the introduction of PrEP, and γ_1 after the introduction of PrEP;

$s = s_0$ before the introduction of PrEP and s_1 after the introduction of PrEP;

And $s_1 = s_0(1 + (\ \gamma_0 - \ \gamma_1))$.

1.2

Dynamic formulation of HIV risk

The static model was evolved into dynamical system through difference equation structure, taking the Bernoulli risk formulation (1.2) as the force of infection on FSW, and an equivalent Bernoulli risk formulation of HIV risk as the force of infection on the male partner population. Here, the male partner population, for the time period, h, are assumed to have C_f partners, with whom they have an average of n_f sex acts each. We assume an average probability of HIV transmission, β_m, per sexual contact with an HIV infected FSW partner. No male partners are assumed to be taking PrEP. Parameter ϑ_f is the proportion of HIV positive FSW that are on ART and $\sigma_m$is the average reduction in probability of HIV transmission to men, when the man himself has been circumcised.

The dynamic HIV compartmental model divides the population, of size *N*, into susceptible individuals S and HIV infected individuals, *I*. Instead of a static HIV prevalence, p, for each population, the dynamic model system allows prevalence to change over time as the proportion of HIV infected individuals, $\lambda = I/N$. The model is run from 1980 to 2035, with initial prevalence of HIV at the start of the epidemic in 1980 of p_{f_0}in FSW and p_{m_0} in male partners. PrEP is introduced for FSW in 2015 under the *Epidemic Equilibrium* (i.e. *steady state*) scenario, and retrospectively in 1995 under the *Increasing Epidemic* scenario where the HIV epidemics in FSW and their male partners are still increasing (i.e. *transient state*).

The dynamic model system assumes an underlying population mortality rate μ_f and μ_m in FSW and male partners respectively, as well as a rate of AIDS-related deaths of ξ_f and ξ_m in FSW and male partners respectively. The rate of recruitment into both populations are taken as the population growth rates θ_f and θ_m respectively.

As little is known about the rate of increase in condom consistency in these populations over time, change in condom consistency from the start of the HIV epidemic is approximated by a linear increase in consistency between 1980 and the year prior to the introduction of PrEP (2014 for the *Epidemic Equilibrium* analyses, and 1994 for the *Increasing Epidemic* analyses).

To account for changes in ART coverage over time, in the dynamic model, ART coverage is taken to be zero between 1980 and 2003. Linear scale up assumed from 2003, in line with the wide-scale

introduction in South Africa[5,6] in 2003, to levels in 2012 for male partners[7] and 2014 for FSW[8] (these being the latest available data for each population to parameterise the model up to the final point of fitting in 2014).

We account for changes in male circumcision levels in the context of the 2007 WHO and UNAIDS guidance on scale up voluntary male circumcision levels for HIV prevention[9] and the 2010 South African government introduction of their VMMC policy and programme.[7] Due to the limited data availability on circumcision levels in Hillbrow (or by proxy, Gauteng, the South African Province in which it lies), with national survey data only available for 2003[10] and 2012[7], we therefore assume that circumcision levels are constant at 2003 levels between 1980 and 2003, and that they increase linearly to 2012 levels and are constant thereafter (likewise as these are the latest available data to parameterise the model up to the final point of model fitting in 2014).

The equations used for the dynamical system formulation are given by:

Force of infection to FSW from male partners

$$\Pi_m = 1 - \left(1 + \lambda_m(\psi_f + \omega_f - 1)\right)^{C_m}$$

Where $\lambda_m = \frac{I_m}{N_m}$

2.1

Force of infection to male partners from FSW

$$\Pi_f = 1 - \left(1 + \lambda_f(\psi_m + \omega_m - 1)\right)^{C_f}$$

Where $\lambda_f = \frac{I_f}{N_f}$ and:

$$\psi_m = (1-\tau)\begin{pmatrix} \left(1-\vartheta_f\right)s\left(1-\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\left(1-\vartheta_f\right)(1-s)\left(1-\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f s\left(1-(1-\varrho)\delta\beta_m(1-\varepsilon\gamma)\right)^{n_f} \\ +\vartheta_f(1-s)\left(1-(1-\varrho)\beta_m(1-\varepsilon\gamma)\right)^{n_f} \end{pmatrix}$$

and $\omega_m = \tau \begin{pmatrix} (1-\vartheta_f)s\big(1-(1-\sigma_m)\delta\beta_m(1-\varepsilon\gamma)\big)^{n_f} \\ +(1-\vartheta_f)(1-s)\big(1-(1-\sigma_m)\beta_m(1-\varepsilon\gamma)\big)^{n_f} \\ +\vartheta_f s\big(1-(1-\sigma_m)(1-\varrho)\delta\beta_m(1-\varepsilon\gamma)\big)^{n_f} \\ +\vartheta_f(1-s)\big(1-(1-\sigma_m)(1-\varrho)\beta_m(1-\varepsilon\gamma)\big)^{n_f} \end{pmatrix}$

2.2

Population sizes

$N_m = S_m + I_m$

$N_f = S_f + I_f$

2.3

Balancing equation

$C_f = C_m N_f / N_m$

2.4

Difference Equations

$S_{f_{t+1}} = \theta_f N_{f_0} + S_{f_t} - \Pi_m S_{f_t} - \mu_f S_{f_t}$

$I_{f_{t+1}} = I_{f_t} + \Pi_m S_{f_t} - (\mu_f + \xi_f) I_{f_t}$

$S_{m_{t+1}} = \theta_m N_{m_0} + S_{m_t} - \Pi_f S_{m_t} - \mu_m S_{m_t}$

$I_{m_{t+1}} = I_{m_t} + \Pi_f S_{m_t} - (\mu_m + \xi_m) I_{m_t}$

2.5

Implementation context: FSW community in Hillbrow, South Africa, and PrEP

This comparison is undertaken at a time when PrEP has been demonstrated effective for populations at substantial risk of HIV.[11] However concerns around sub-optimal adherence[12,13] and behavioural disinhibition[14,15] have led to interest in understanding the trade-offs associated with PrEP implementation outside of trial settings.[16,17] Hillbrow is a pertinent setting for this assessment; a context with 72% HIV prevalence among FSW [8] and high prevalence among partner populations.[18,19]

PrEP has been rolled out for FSW in South Africa under the National Sex Worker HIV Plan (2016-2019),[20] however challenges in PrEP retention were observed in TaPS,[21] a 2015-2017 PrEP and early antiretroviral treatment (ART) demonstration project among the Hillbrow FSW community. Given the challenges FSW face in negotiating condom use[22] and the financial incentives for condomless sex with clients[23], this is a timely case study, which we hope will contribute to decision makers' understanding of the impact of reductions in condom use on PrEP effectiveness, should they be a program reality.

Additional analyses

Structural sensitivity analysis

To assess whether the inclusion of ART, circumcision and STIs in the models affects their conclusions, we conducted a model structural sensitivity analysis by rerunning the analyses, having removed all parameters relating to: the reduction in HIV transmission on ART and ART coverage; the reduction in HIV transmission in peno-vaginal sex when the male partner is circumcised and the proportion of the male partner population that is circumcised; and the multiplicative increase in per sex act in the probability of HIV transmission in the presence of an STI and the probability at least one person in the partnership has an STI.

Fully Endemic scenario

To assess whether there is a significant difference in the model comparisons when PrEP is implemented when the HIV epidemics have fully endemic in the populations, in comparison to when they first reach equilibrium, the analyses are repeated with PrEP introduced in 2030, when the epidemics are fully established in both FSW and partner populations.

Model parameterization

The data and data sources used in the parameterisation and fitting of the models are set out in **Table S1** below. Behavioural and epidemiological data are taken from Hillbrow, Johannesburg, where available, otherwise extrapolated from consistent high HIV burden contexts in South Africa.

Parameter	Symbol	Estimate	Low	High	References
Proportion of male partner population HIV infected	p_m	0.02	0.0	0.05	There are significant challenges in identifying prevalence in clients of sex workers. As such, it is approximated by prevalence in migrant workers, an established client group of FSW in sub-Saharan Africa.[24] **Year: 1980** At the start of the epidemic, males are assumed (owing to lack of data) to have very low prevalence of HIV, between the values stated
		0.259	0.203	0.325	**Year: 2000** Migrant workers, male, from KwaZulu-Natal, South Africa.[25] Low and high estimates are calculated as 95% CI from underlying data assuming binomially distributed.
		0.339	0.275	0.410	**Year: 2004** Non-residents (study proxy for migrant work), men, from KwaZulu-Natal, South Africa.[26]
Proportion of FSW population HIV infected	p_f	0.05	0.0	0.1	**Year: 1980**

Parameter	Symbol	Estimate	Low	High	References
					At the start of the epidemic, males are assumed (owing to lack of data) to have very low prevalence of HIV, between the values stated
		0.45	0.3891956	0.5123358	**Year: 1997** FSW, Johannesburg, South Africa.[27] Low and high estimates are calculated as 95% CI from underlying data assuming binomially distributed.
		0.718	0.565	0.812	**Year: 2014** FSW Johannesburg, South Africa.[8]
Initial condom consistency with partners	γ_0	0.05	0.0	0.1	**Year: 1980** At the start of the epidemic, condoms are assumed (owing to lack of data) to be used at very low levels, between the values stated.
		0.764 (with clients) 0.345 (non-paying partner)	0.902 (with clients) 0.548 (non-paying partner)	0.609 (with clients) 0.173 (non-paying partner)	**Year: 2014** FSW Johannesburg, South Africa.[8] Data used to inform the range of initial condom consistencies simulated in the analysis.
Probability at least one person in the partnership has an STI	s_0	0.21	0.15	0.3	Owing to limited data for this population, STI prevalence data is taken where available in relation to specific HIV-transmission increasing STIs[28], and otherwise in relation to STI prevalence in general:

Parameter	Symbol	Estimate	Low	High	References
					Estimate: Prevalence of Neisseria gonorrhoea in Hillbrow FSW.[29] Low Estimate: Prevalence of Chlamydia trachomatis & Neisseria gonorrhoea in Hillbrow FSW.[30] High Estimate: FSW STI prevalence, Durban.[31]
Proportion of HIV+ partner population on ART	ϑ_m	0.257	0.212	0.308	Proportion of South African males having accessed treatment, 2012.[7]
Proportion of HIV+ HRW women population on ART	ϑ_f	0.234	0.506	0.088	Current ART status, FSW, Johannesburg, South Africa, 2014.[8]
Number of generic male partners, per 3 month period	C_m	106	78	128	Sum of: Mean monthly reported number of clients per FSW, Hillbrow; multiplied by 3, i.e. 105 (78-126);[32] and Number of main sexual partners, FSW Hillbrow, i.e. 1 (0.37-2).[33]
Number of males' female partners, per 3 month period	C_f	4.5	2.97	6.75	Average number of sex partners for high risk men in control arm.[34] Low and high estimates are calculated as 95% CI from underlying data assuming binomially distributed.
Average number of sex acts – with generic male partners, per 3 month period	n_m	1.2	1.05	1.74	Weighted (by number of clients and number of main sexual partners stated in calculation of C_f) average of: - Number of sexual encounters per client, Hillbrow (1-1.2),[30] and

Parameter	Symbol	Estimate	Low	High	References
					- Mean monthly frequency of sex acts in main partnerships, Hillbrow, multiplied by 3: 24 (mid-point) (12-36).[32]
Average number of males' sex acts – with female partner, per 3 month period	n_f	6.3	4.5	9.0	Average frequency of sex acts in casual partnerships for people with high sexual activity, per month 2.1 (1.5 – 3.0), multiplied by 3.[30]
% male population circumcised	τ	0.252	0.159	0.376	**Year: 2003** Men 15-59 years, Gauteng Province.[10] Low and High Estimates are calculated as 95% CI from underlying data assuming binomially distributed.
		0.482	0.442	0.522	**Year: 2012** Adult males, Gauteng Province.[7]
Condom HIV risk reduction efficacy per sex act	ε	0.85	0.9	0.8	Midpoint:[35] (with consistent use),[36] (with consistent use)
Probability of HIV transmission, male to female, through peno-vaginal sex	β_f	0.0008	0.0006	0.0011	Per-act HIV-1 transmission probability, male to female[37]
Probability of HIV transmission, female to male, through peno-vaginal sex	β_m	0.0004	0.0001	0.0014	Per-act HIV-1 transmission probability, female to male[37]
Multiplicative increase in per sex act probability of HIV	δ	3.7	2	6	Combined study effectiveness estimate across STDs, and range spanning individual STD combined study effect estimates[38]

Parameter	Symbol	Estimate	Low	High	References
transmission in the presence of an STI					
Average reduction in probability HIV transmission on ART	ϱ	0.92	0.99	0.9	Estimate:[39] accounting for heterogeneity in sexual mixing and stage of infection, of all studies reviewed in systematic comparison.[40] Low and high: min and max of all studies.[40]
Average reduction in probability HIV transmission to males, when male partner has been circumcised	σ_m	0.6	0.66	0.44	Average,[41] low and high risk from CI in[42].
Average reduction in probability HIV transmission to females, when male partner has been circumcised	σ_f	0	0	0.2	Male circumcision; estimates of HIV infection in women.[41]
Number of unit time steps (duration) spent in PrEP programme/ cascade following uptake	h	3 months	N/A	N/A	Frequency of HIV testing (minimum of all regular testing requirements) WHO Implementation Tool (2017).[43]
Underlying population mortality rate per unit time step in females	μ_f	0.003788	0.003571	0.00625	1/ life expectancy at birth, females, divided by 4 (for 3 month time unit).[44]
Underlying population mortality rate per unit time step in males	μ_m	0.003968	0.003571	0.00625	1/ life expectancy at birth, females, divided by 4 (for 3 month time unit).[44]

Parameter	Symbol	Estimate	Low	High	References
Rate of AIDS deaths per unit time step, females	ξ_f	0.018775	0.012108	0.022353	As in,[45] from,[46] average time from HIV infection to death of 10.2 years. Multiplied by 4. Inverted and multiplied by (1- proportion of females on ART).
Rate of AIDS deaths per unit time step, males	ξ_m	0.018211	0.016985	0.019436	As in,[45] from, [46] average time from HIV infection to death of 10.2 years. Multiplied by 4. Inverted and multiplied by (1- proportion of males on ART).

Table S1: Parameters and data sources used in the parameterisation and fitting of the models.

Low and high estimates are 95% confidence intervals from the named sources, unless otherwise stated.

Supplementary Results

Model fits to data

The model fits to HIV prevalence corresponding to each level of initial condom consistency are shown below in Figure 1 for the *Epidemic Equilibrium* scenario, and for the *Increasing Epidemic* scenario in Figure 2.

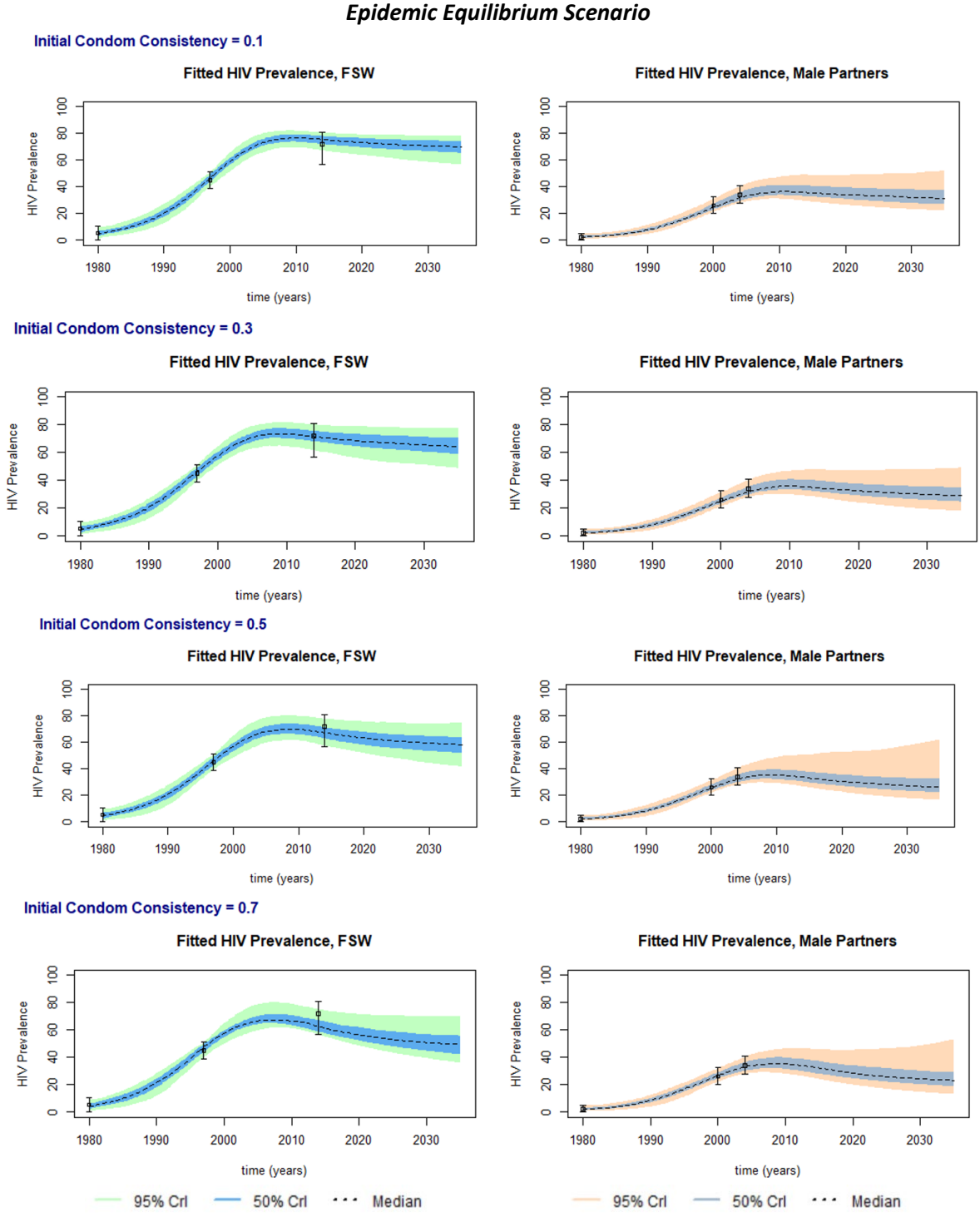

Figure S1: Plots of fits to FSW and male partner population HIV prevalence over time calculated through the dynamic model for the Epidemic Equilibrium scenario.

The plots are given distinctly for each level of initial condom consistency (in 2014) simulated, and in each case display the 95% and 50% credible intervals and median of all fits.

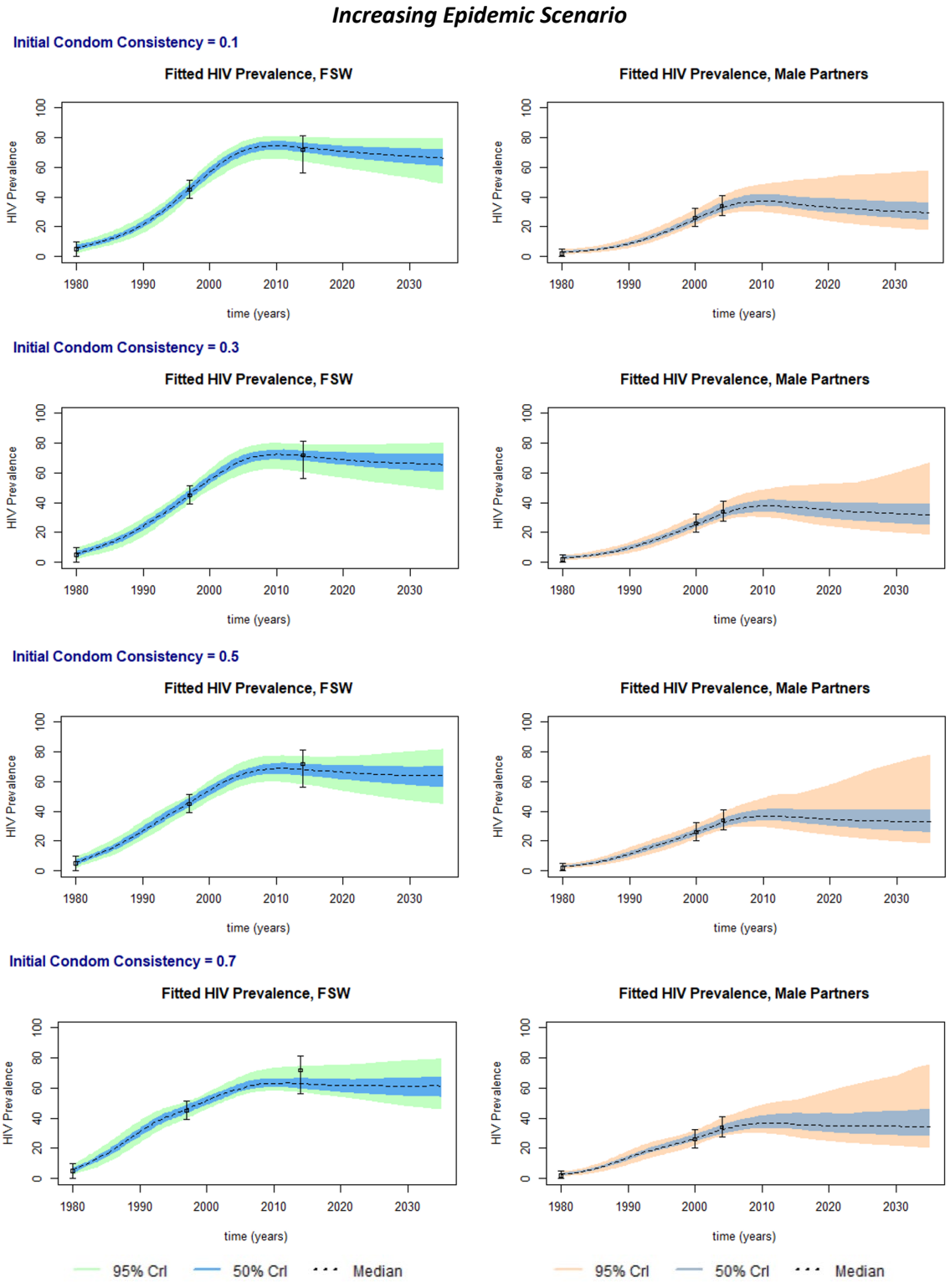

Figure S2: Plots of fits to FSW and male partner population HIV prevalence over time calculated through the dynamic model for the Increasing Epidemic scenario.

The plots are given distinctly for each level of initial condom consistency (in 1994) simulated, and in each case display the 95% and 50% credible intervals and median of all fits.

Model fits for additional analyses

The model fits to HIV prevalence corresponding to each level of initial condom consistency for the structural sensitivity analysis are shown below in Figure 1 for the *Epidemic Equilibrium* scenario, and for the *Increasing Epidemic* scenario in Figure 2.

Structural Sensitivity Analysis

Epidemic Equilibrium Scenario

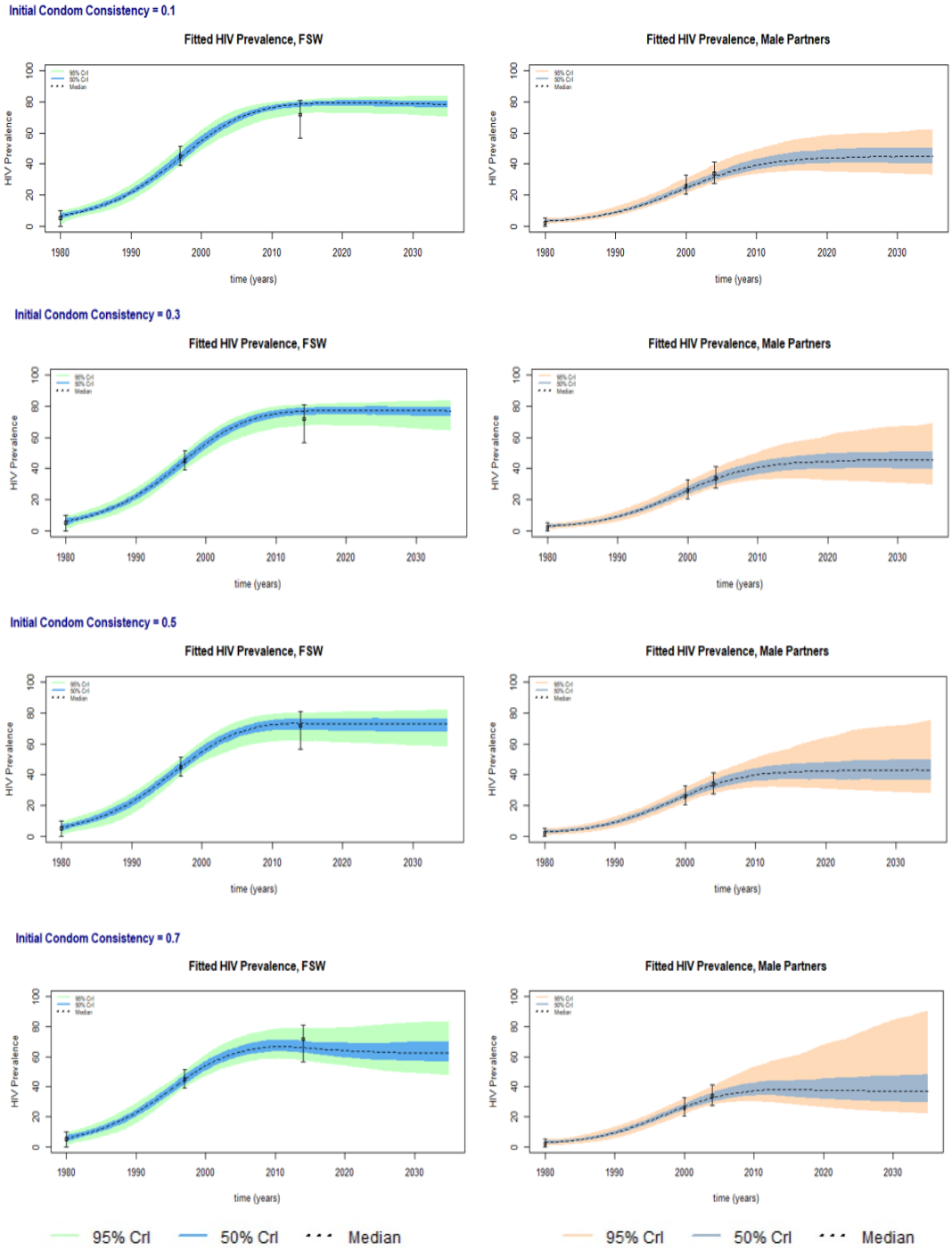

Figure S3: Plots of fits to FSW and male partner population HIV prevalence over time calculated through the dynamic model for the Epidemic Equilibrium scenario under the structural sensitivity analysis.

The plots are given distinctly for each level of initial condom consistency (in 2014) simulated, and in each case display the 95% and 50% credible intervals and median of all fits.

Structural Sensitivity Analysis

Increasing Epidemic Scenario

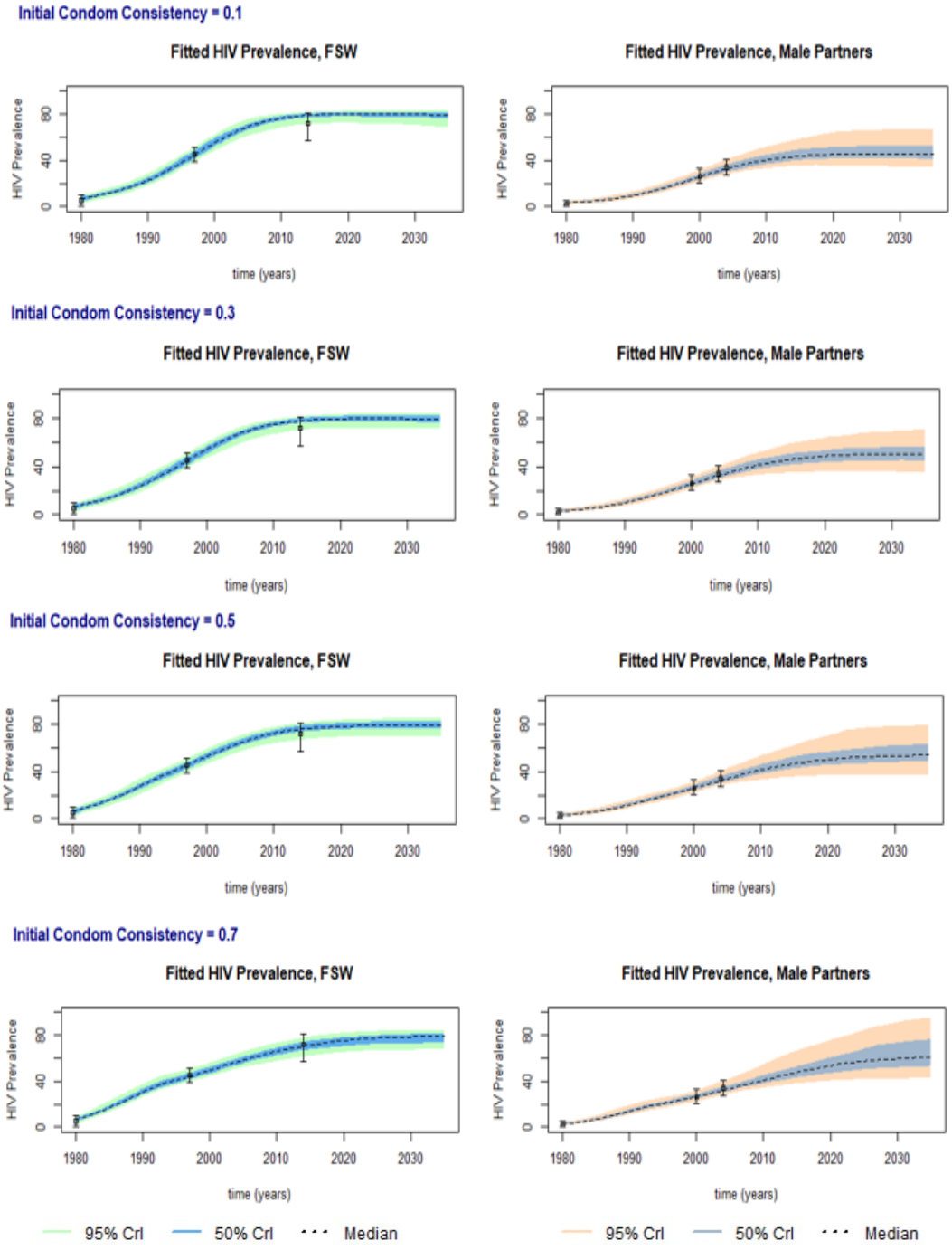

Figure S4: Plots of fits to FSW and male partner population HIV prevalence over time calculated through the dynamic model for the Increasing Epidemic scenario under the structural sensitivity analysis.
The plots are given distinctly for each level of initial condom consistency (in 1994) simulated, and in each case display the 95% and 50% credible intervals and median of all fits.

Fully Endemic Scenario

The model fits to HIV prevalence for the *Fully Endemic* analysis are the same as those for the *Epidemic Equilibrium* scenario – it is only PrEP that is implemented later in this analysis.

Boxplots for additional analyses

The 4x4 boxplots showing 1) the lowest level of condom consistency, and 2) the percentage reduction in condom consistency, tolerated following the introduction of PrEP for each of the scenarios evaluated are set out as follows:

- *Epidemic Equilibria* scenario in Figure S5 and Figure S6 respectively;
- *Increasing Epidemic* scenario in Figure S7 and Figure S8 respectively;
- *Structural sensitivity analysis - Epidemic Equilibrium* scenario in Figure S9 and Figure S10 respectively;
- *Structural sensitivity analysis – Increasing Epidemic* scenario in Figure S11 and Figure S12 respectively; and
- *Fully Endemic* scenario in Figure S13 and Figure S14 respectively.

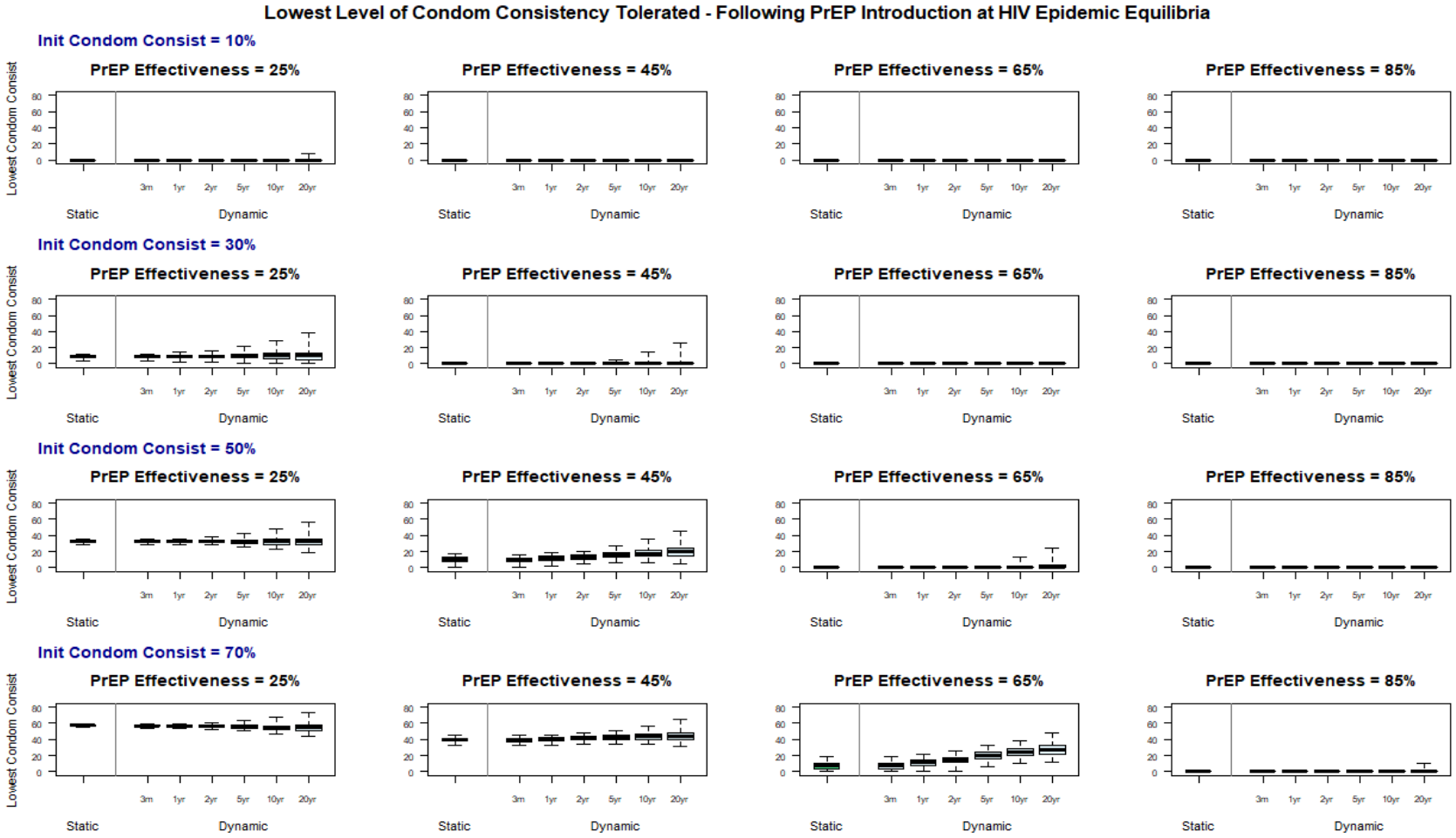

Figure S5: Boxplots comparing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest levels of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

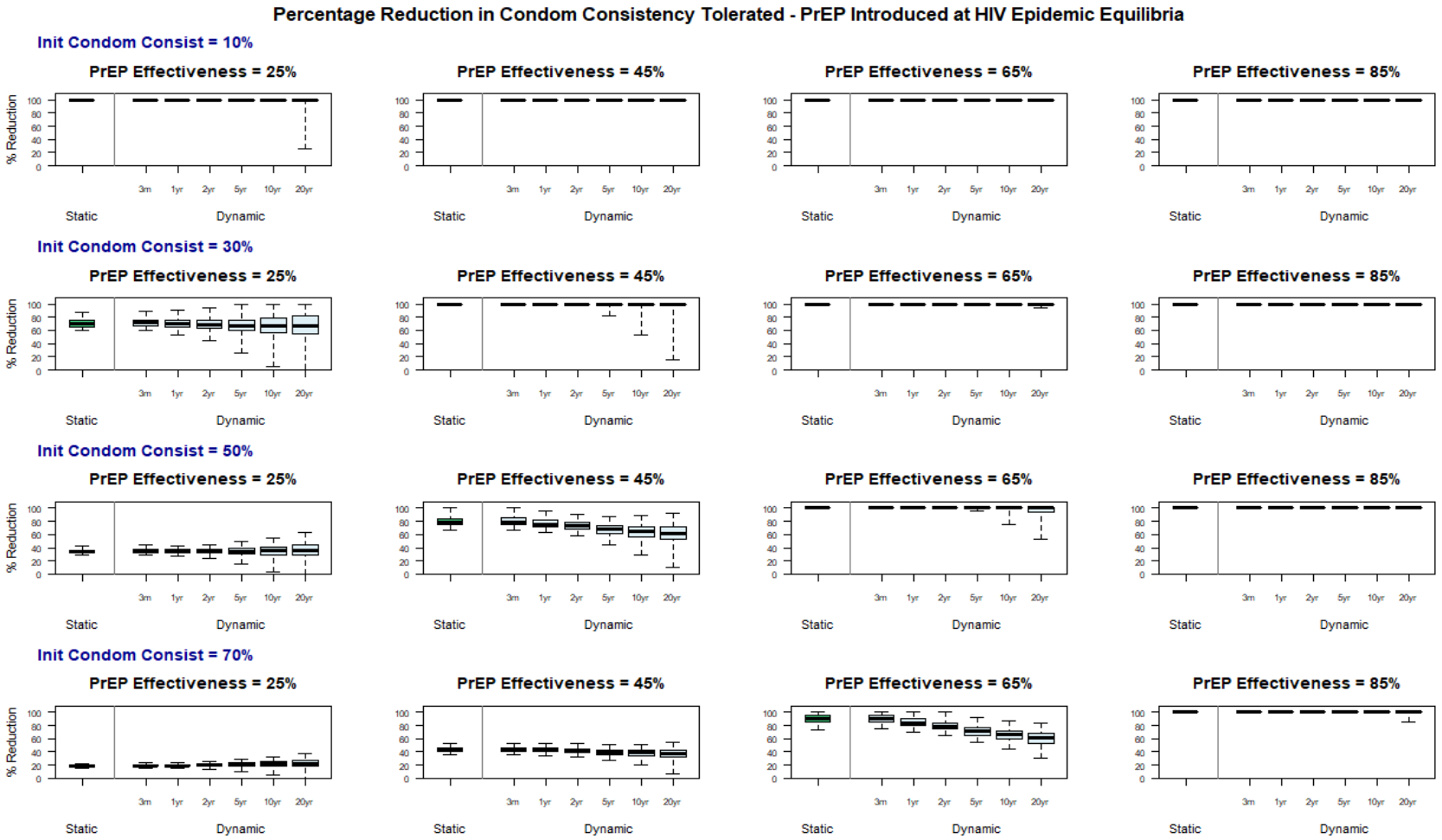

Figure S6: Boxplots comparing the percentage reduction in condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted percentage reductions in condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted percentage reductions in condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the percentage reduction in condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

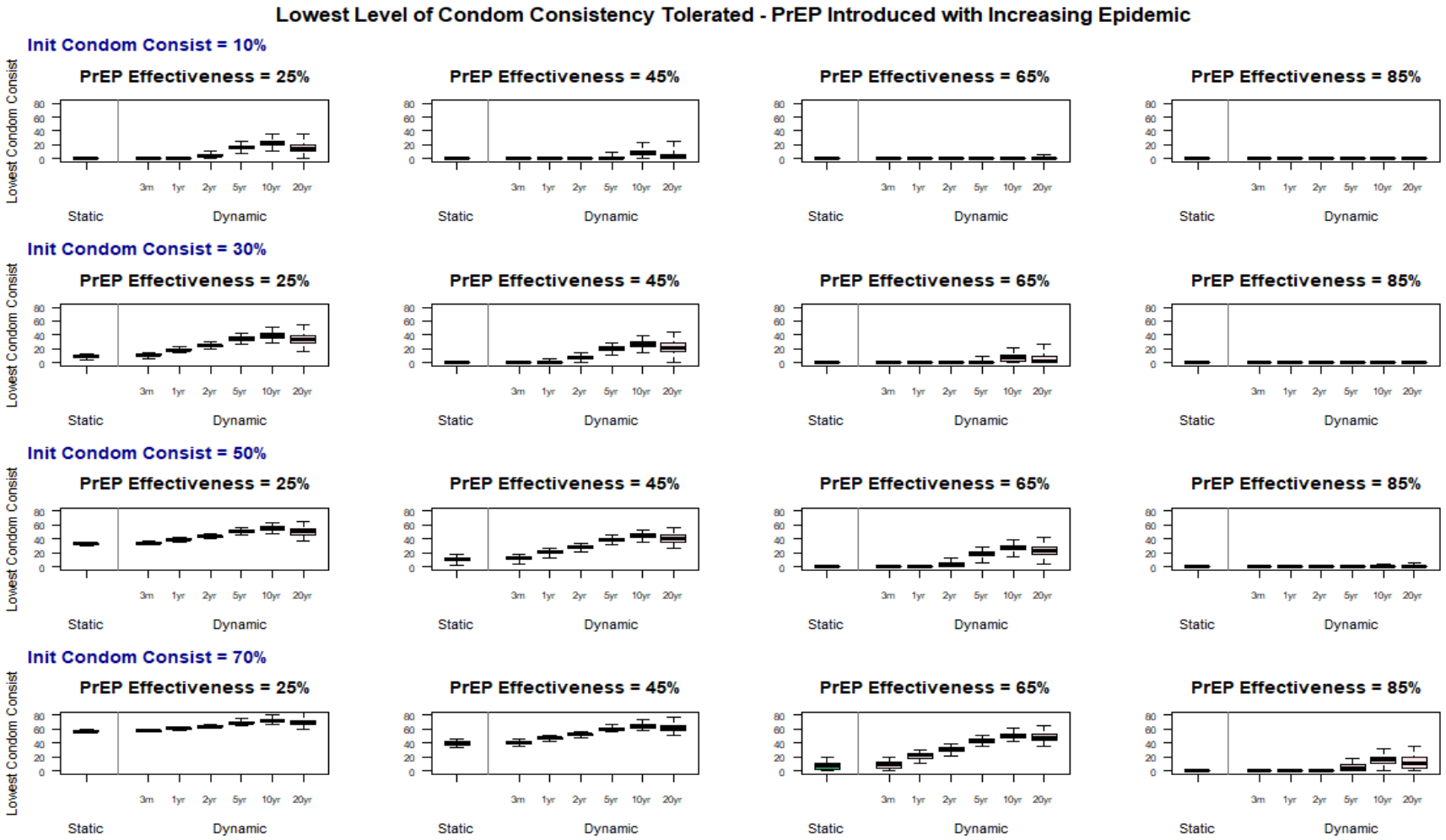

Figure S7: Boxplots comparing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest levels of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

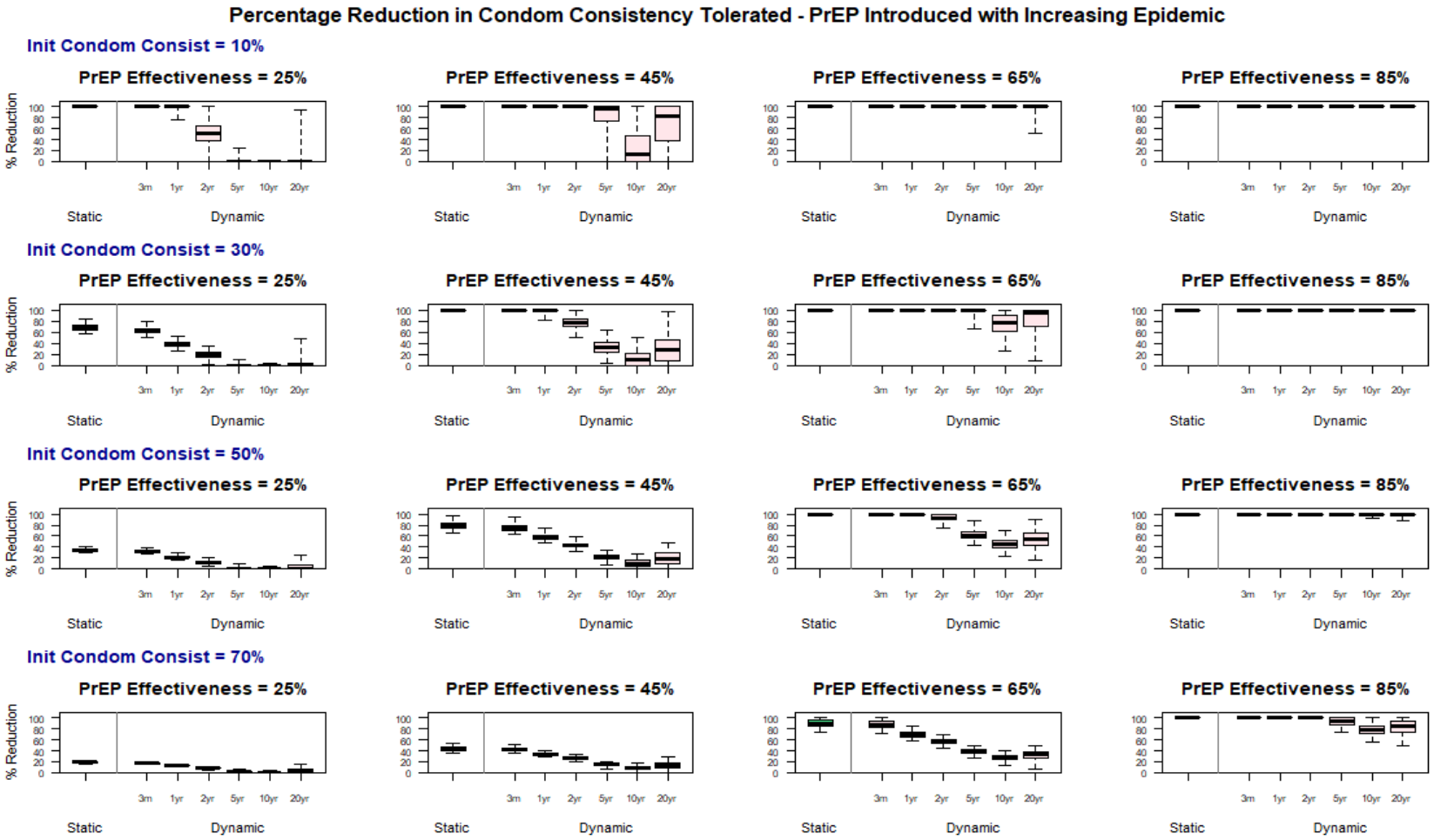

Figure S8: Boxplots comparing the percentage reduction in condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted percentage reductions in condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted percentage reductions in condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the percentage reduction in condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

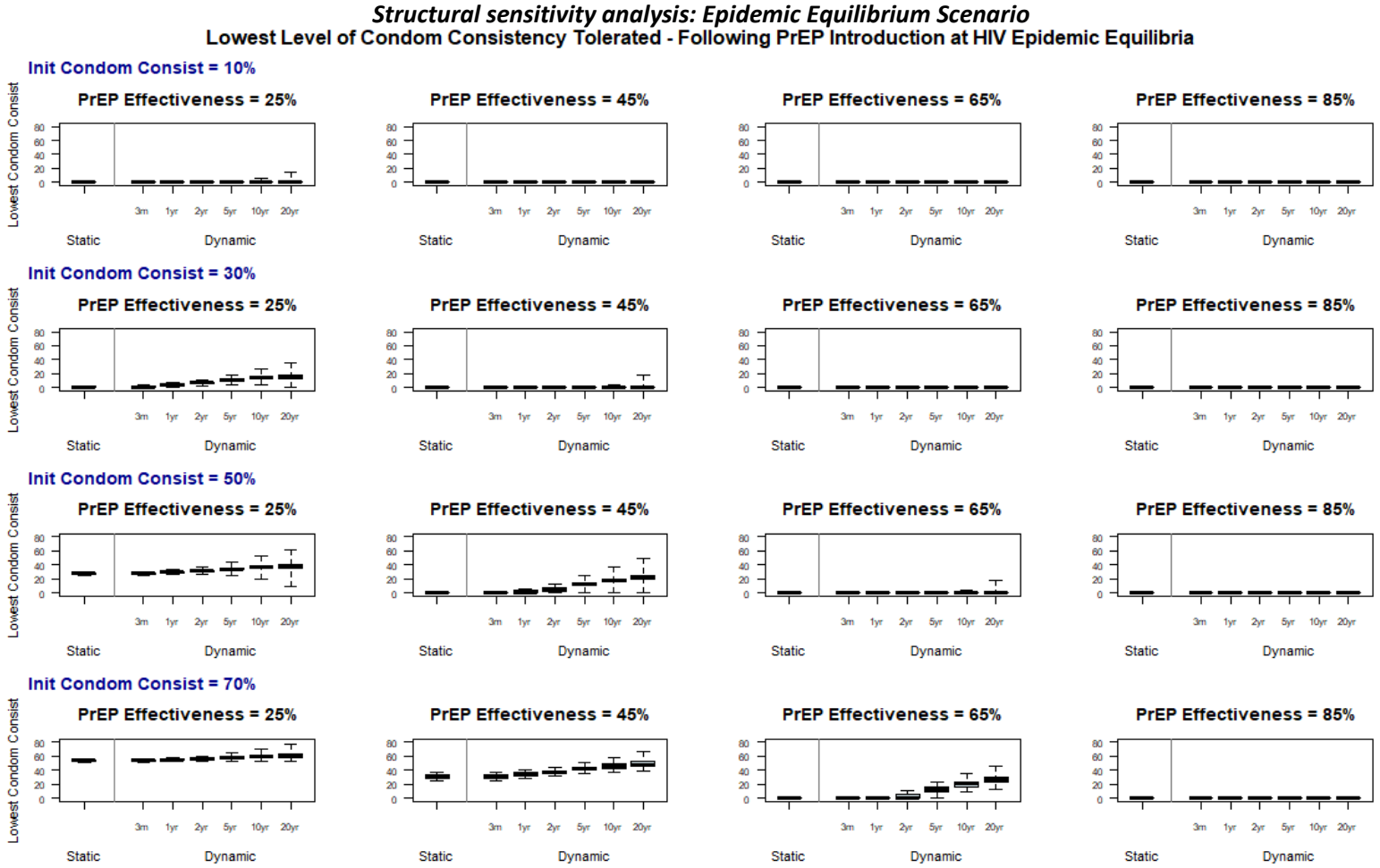

***Figure S9**: Boxplots comparing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium under the structural sensitivity analysis.*

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest level of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

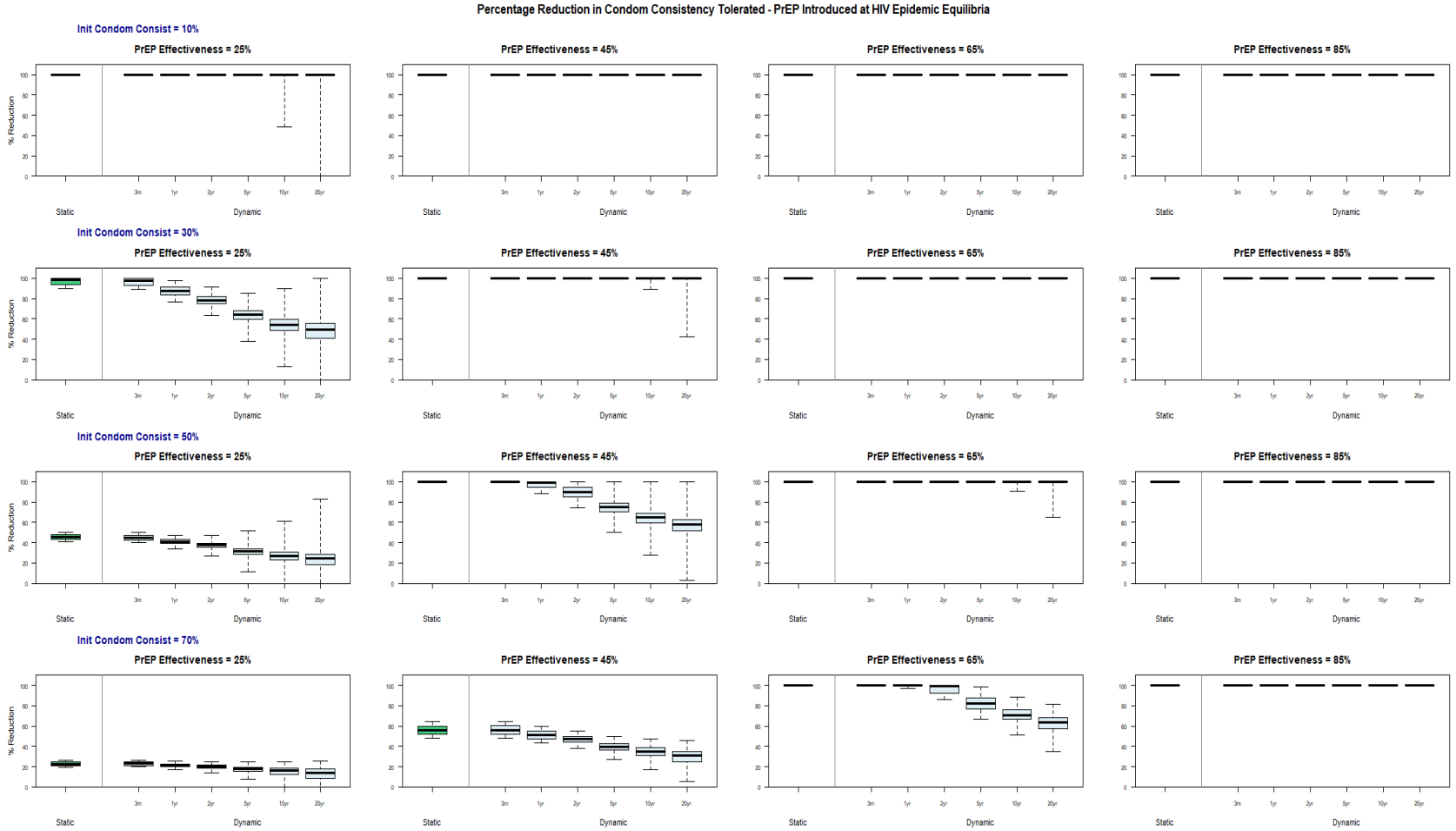

Figure S10: Boxplots comparing the percentage reduction in condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced at HIV Epidemic Equilibrium under the structural sensitivity analysis.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted percentage reductions in condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted percentage reductions in condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the percentage reduction in condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

Structural sensitivity analysis: Increasing Epidemic Scenario

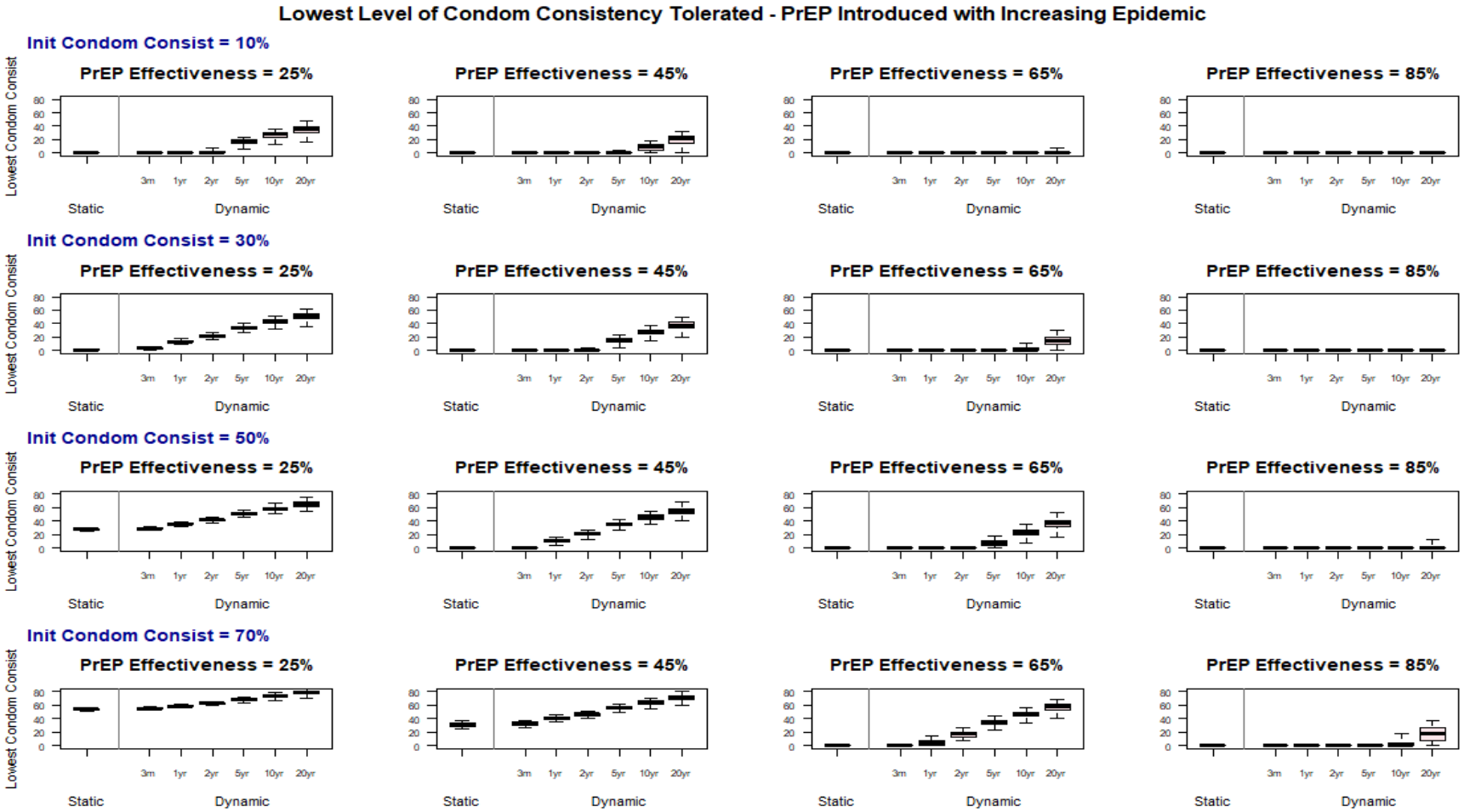

Figure S11: Boxplots comparing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic under the structural sensitivity analysis.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest level of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

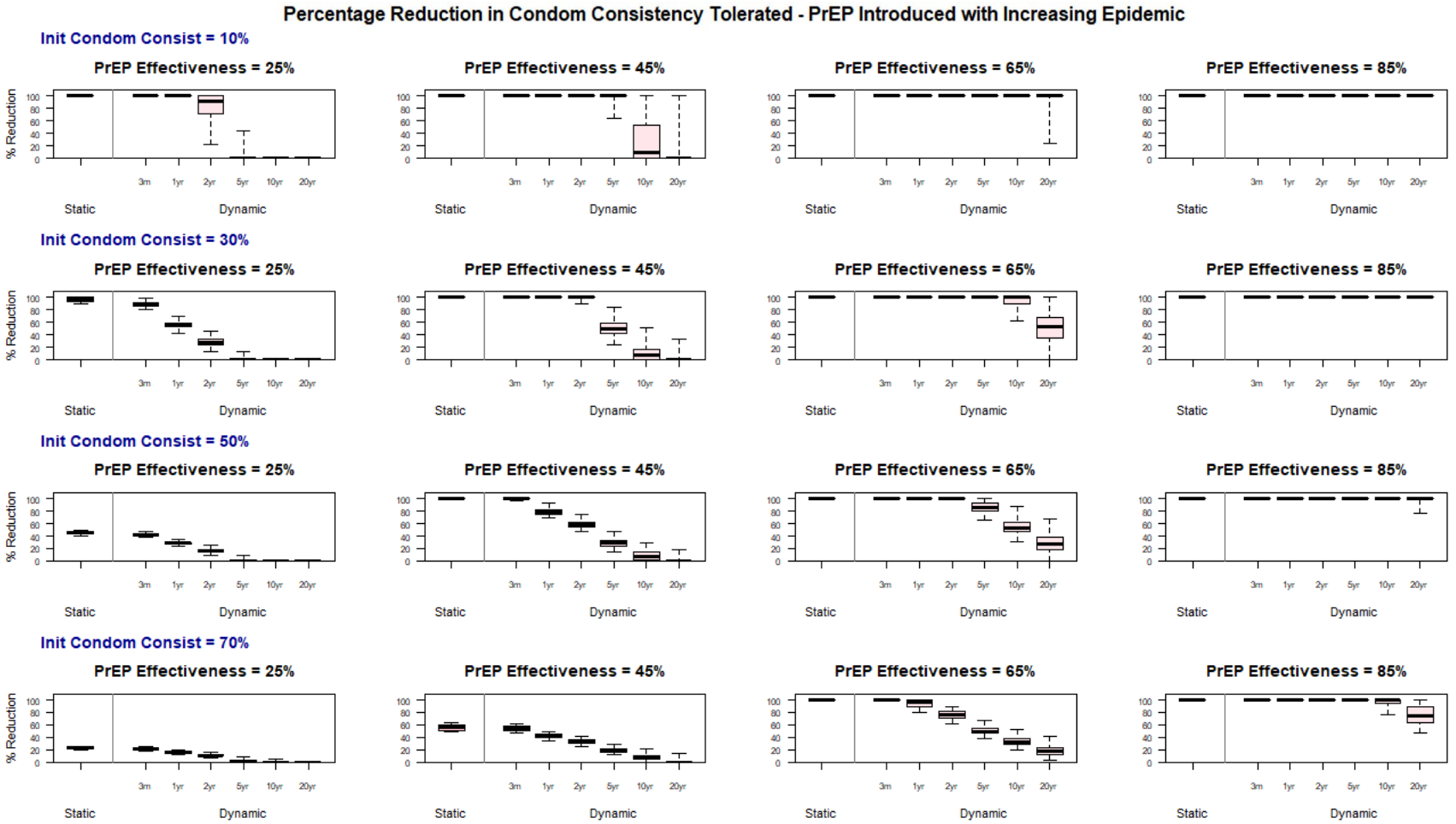

Figure S12: Boxplots comparing the percentage reduction in condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with Increasing Epidemic under the structural sensitivity analysis.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted percentage reductions in condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted percentage reductions in condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the percentage reduction in condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

Fully Endemic Scenario

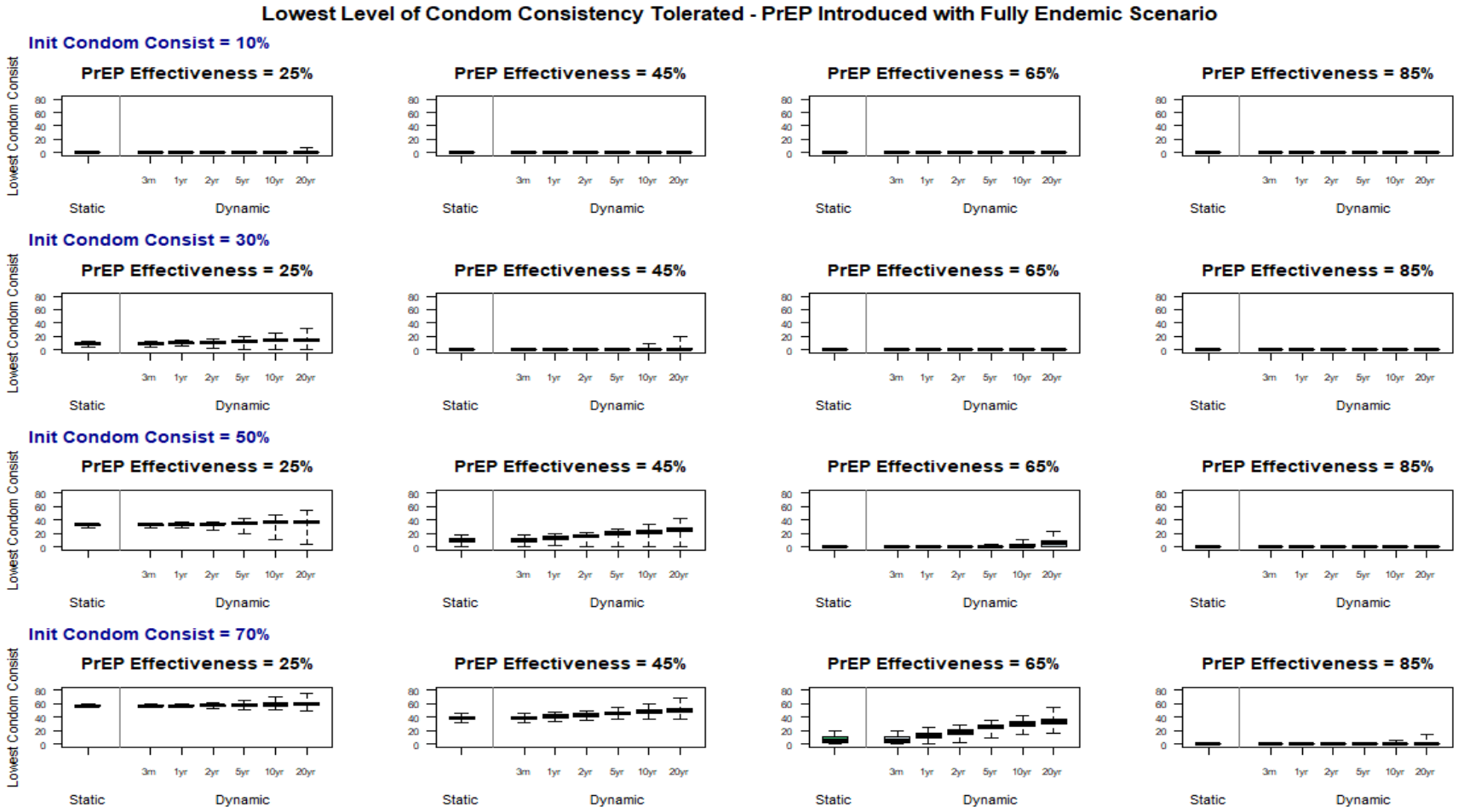

Figure S13: Boxplots comparing the lowest level of condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with the Fully Endemic scenario.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the lowest levels of condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the lowest levels of condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the lowest levels of condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

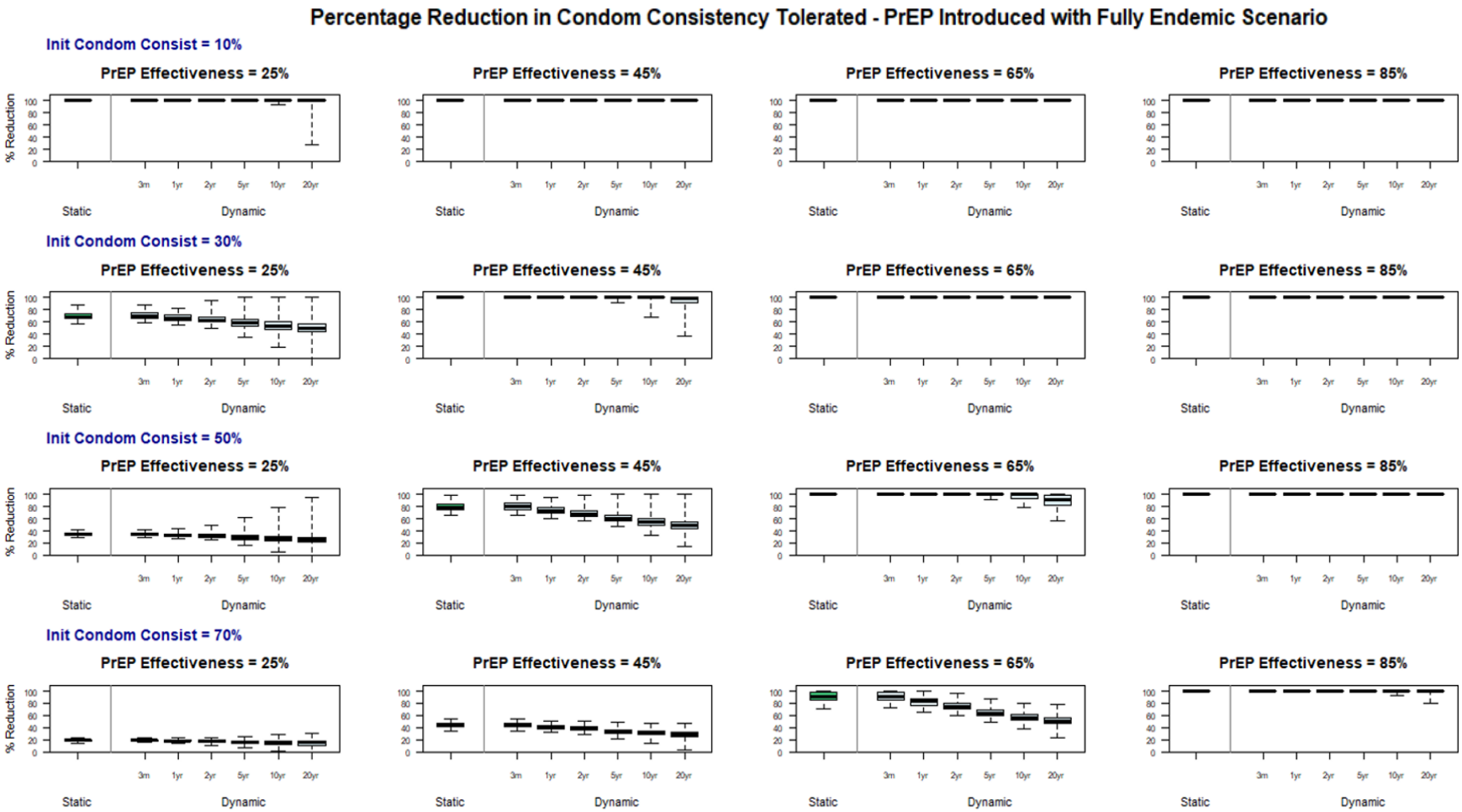

Figure S14: Boxplots comparing the percentage reduction in condom consistency tolerated on PrEP (for HIV risk not to increase) predicted through the static and dynamic models – PrEP introduced with the Fully Endemic scenario.

The results are shown distinctly for initial condom consistencies (at point of introduction of PrEP) of 10%, 30%, 50% and 70%, and simulated for levels of achieved PrEP use-effectiveness at HIV risk reduction of 25%, 45%, 65% and 85%. In the case of the static model, the predicted percentage reductions in condom consistency tolerated on PrEP are point estimates. In the case of the dynamic model, the predicted percentage reductions in condom consistency tolerated on PrEP are given after 3 months, 1 year, 2 years, 5 years, 10 years and 20 years on PrEP. The boxplots depict uncertainty in the percentage reduction in condom consistency tolerated, with the black line representing the median of all fits, the coloured section the interquartile range and the whiskers the maximum and minimum values.

Tables of Results

Percentage Reduction in Condom Consistency Tolerated: Tables of percentage change between static and dynamic model's outcomes

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the percentage change in condom consistency tolerated over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios are shown in Tables S2a and S2b respectively.

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static Model and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0.8 % , 0 %)
0.1	0.45	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0 % , 0 %)
0.1	0.65	0 % (0 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0 % , 0 %)
0.1	0.85	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (100 % , 0 %)	0 % (0.1 % , 0 %)
0.3	0.25	-1.9 % (-0.7 % , -1.4 %)	-0.1 % (2.8 % , -0.8 %)	2 % (9.2 % , -3.3 %)	4 % (23.5 % , -10.8 %)	3.6 % (100 % , -19.2 %)	4 % (67.2 % , -19.2 %)
0.3	0.45	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (29.2 % , 0 %)
0.3	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0 % , 0 %)
0.3	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0 % , 0 %)
0.5	0.25	-2.1 % (-2 % , -1.5 %)	-2.1 % (1.7 % , -1.5 %)	-2.4 % (10.7 % , -2.7 %)	-2.9 % (32 % , -15.5 %)	-4.4 % (100 % , -28.3 %)	-5.9 % (92 % , -38.9 %)
0.5	0.45	-0.8 % (-1.2 % , -0.8 %)	3.7 % (3.8 % , 5.2 %)	7.2 % (10.5 % , 8.5 %)	13.3 % (26.3 % , 13.1 %)	17.9 % (100 % , 11.8 %)	21.9 % (62.6 % , 11 %)
0.5	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (32.4 % , 0 %)
0.5	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0 % , 0 %)
0.7	0.25	-2.7 % (-1.9 % , -2.3 %)	-4.3 % (1.9 % , -3.7 %)	-8.7 % (7.5 % , -9.3 %)	-13.6 % (27.5 % , -24.7 %)	-19 % (100 % , -40.5 %)	-20.1 % (100 % , -56.7 %)
0.7	0.45	-1.2 % (-1.1 % , -1.4 %)	2.3 % (3.2 % , 2.4 %)	5.1 % (8.4 % , 5.4 %)	7.6 % (22.2 % , 5.8 %)	11.1 % (100 % , 4.8 %)	14.1 % (66.8 % , 1.2 %)
0.7	0.65	-0.7 % (-0.5 % , 0 %)	5.9 % (5.8 % , 1.2 %)	12.1 % (11.8 % , 8.1 %)	20.5 % (24.8 % , 15.9 %)	26.1 % (100 % , 20.5 %)	30.6 % (53.5 % , 21 %)
0.7	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (100 % , 0 %)	0 % (0.7 % , 0 %)

Table S2a: Epidemic Equilibrium Scenario: Percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static Model and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 % , 0 %)	0 % (4.3 % , 0 %)	48.7 % (87.5 % , 5.3 %)	100 % (100 % , 100 %)	100 % (100 % , 100 %)	100 % (100 % , 20.1 %)
0.1	0.45	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	4.5 % (69.6 % , 0 %)	87 % (100 % , 0 %)	18.4 % (100 % , 0 %)
0.1	0.65	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)
0.1	0.85	0.1 % (0.2 % , 0 %)	0.1 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)
0.3	0.25	8.8 % (9.3 % , 9 %)	43.8 % (50.6 % , 40.8 %)	73.1 % (89.8 % , 62.2 %)	100 % (100 % , 93.3 %)	100 % (100 % , 100 %)	100 % (100 % , 67.7 %)
0.3	0.45	0 % (0 % , 0 %)	0 % (9.5 % , 0 %)	22.2 % (41.1 % , 2.5 %)	66.8 % (89.2 % , 44 %)	90.1 % (100 % , 61.2 %)	71.1 % (100 % , 28.5 %)
0.3	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (21.1 % , 0 %)	22.8 % (63.1 % , 0 %)	5.7 % (66 % , 0 %)
0.3	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)
0.5	0.25	7.1 % (7.1 % , 7.8 %)	37.2 % (40.7 % , 34.4 %)	63.1 % (76.8 % , 55 %)	100 % (100 % , 82.9 %)	100 % (100 % , 90.5 %)	100 % (100 % , 50.3 %)
0.5	0.45	4.1 % (3.5 % , 4.4 %)	27.8 % (27.8 % , 27.6 %)	45.9 % (48.5 % , 44.2 %)	72.5 % (83.2 % , 65.2 %)	86.9 % (100 % , 73.5 %)	75.4 % (100 % , 54.6 %)
0.5	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	6.7 % (20.4 % , 0 %)	38.4 % (52.4 % , 21.3 %)	54.7 % (72.7 % , 35.2 %)	46.8 % (76.1 % , 15.8 %)
0.5	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (4.7 % , 0 %)
0.7	0.25	5.9 % (4.5 % , 5.6 %)	32.4 % (31.2 % , 28.7 %)	54.3 % (61.1 % , 47.2 %)	92.6 % (100 % , 76.4 %)	100 % (100 % , 90.3 %)	91 % (100 % , 47.2 %)
0.7	0.45	2.8 % (2.2 % , 3.1 %)	23.9 % (22.6 % , 22.7 %)	40.8 % (39.9 % , 38.6 %)	66.3 % (73.6 % , 60.3 %)	80 % (100 % , 70.5 %)	71.6 % (100 % , 52.4 %)
0.7	0.65	2.1 % (1.6 % , 0 %)	23.7 % (21.6 % , 16.4 %)	37.5 % (36.8 % , 31.9 %)	57.9 % (59.8 % , 53 %)	68.5 % (75.1 % , 61.9 %)	63.8 % (81.7 % , 52 %)
0.7	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	5.6 % (21 % , 0 %)	22.5 % (39.7 % , 2.5 %)	15.5 % (47.1 % , 0 %)

Table S2b: Increasing Epidemic Scenario: Percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S2a and S2b *respectively show for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic the percentage change between the static and dynamic models' prediction of the*

percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years. The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.

Additional analyses – Structural sensitivity analysis

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the percentage change in condom consistency tolerated over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios for the structural sensitivity analysis are shown in Tables S3a and S3b respectively.

Structural Sensitivity Analysis

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static Model and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (42.3%, 0%)
0.1	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)
0.1	0.65	0% (0%, 0%)	0% (0.1%, 0%)	0% (0.1%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)
0.1	0.85	0% (0.1%, 0%)	0% (0.1%, 0%)	0% (0.1%, 0%)	0% (0.1%, 0%)	0% (100%, 0%)	0% (0.1%, 0%)
0.3	0.25	0.8% (0.9%, 0%)	10.9% (11.6%, 4.1%)	20.1% (23.7%, 11.2%)	34.7% (45.3%, 22.5%)	44.5% (100%, 27.2%)	49.9% (82.6%, 26%)
0.3	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (13.4%, 0%)
0.3	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)
0.3	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)
0.5	0.25	0.4% (0.5%, 0.6%)	8.8% (10.7%, 7.6%)	16.8% (22.7%, 13.9%)	30.1% (49.8%, 23.5%)	39.6% (100%, 27.4%)	46.2% (100%, 28.2%)
0.5	0.45	0% (0%, 0%)	0.6% (10.1%, 0%)	10.5% (20%, 0.4%)	25.1% (37.9%, 14.7%)	35.1% (100%, 23.5%)	41.8% (70.8%, 29.1%)
0.5	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (7.1%, 0%)
0.5	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)
0.7	0.25	-0.9% (0%, 0.4%)	5.3% (8%, 5%)	11.9% (20.1%, 8.8%)	22% (47.7%, 13%)	30.4% (100%, 12.6%)	37.4% (100%, 10.3%)
0.7	0.45	-0.4% (0%, 0.6%)	7.7% (8.6%, 8.6%)	15.3% (17.4%, 15.6%)	28.4% (36.6%, 25%)	36.8% (100%, 30.9%)	43.8% (78.7%, 34.5%)
0.7	0.65	0% (0%, 0%)	0% (2.3%, 0%)	0.6% (13%, 0%)	17.4% (29.8%, 4.6%)	29% (100%, 15.2%)	36.6% (57.4%, 22.1%)
0.7	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (100%, 0%)	0% (0%, 0%)

Table S3a: Structural sensitivity analysis: Epidemic Equilibrium Scenario: Percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Structural Sensitivity Analysis

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static Model and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 % , 0 %)	0 % (0.1 % , 0 %)	9.2 % (51.6 % , 0 %)	100 % (100 % , 93.9 %)	100 % (100 % , 100 %)	100 % (100 % , 100 %)
0.1	0.45	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0 % , 0 %)	90.7 % (100 % , 0 %)	100 % (100 % , 51 %)
0.1	0.65	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (32.2 % , 0 %)
0.1	0.85	0.1 % (0.2 % , 0 %)	0.1 % (0.2 % , 0 %)	0.1 % (0.2 % , 0 %)	0.1 % (0.2 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)
0.3	0.25	9.1 % (9.9 % , 3.8 %)	43.3 % (48.7 % , 35.5 %)	71.6 % (81.8 % , 58.7 %)	100 % (100 % , 95.2 %)	100 % (100 % , 100 %)	100 % (100 % , 100 %)
0.3	0.45	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (3.4 % , 0 %)	50.4 % (68.9 % , 25.6 %)	91.8 % (100 % , 63.5 %)	100 % (100 % , 87.9 %)
0.3	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (27.8 % , 0 %)	47.1 % (90.6 % , 2.2 %)
0.3	0.85	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0.1 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)
0.5	0.25	7.1 % (8 % , 7.1 %)	37.3 % (42 % , 34.5 %)	64.2 % (73.8 % , 55.4 %)	100 % (100 % , 86.3 %)	100 % (100 % , 100 %)	100 % (100 % , 100 %)
0.5	0.45	0 % (3.1 % , 0 %)	21.1 % (30 % , 12.7 %)	41.7 % (50.7 % , 32.8 %)	71.8 % (82.6 % , 60.1 %)	92.7 % (100 % , 76.3 %)	100 % (100 % , 89 %)
0.5	0.65	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	13.6 % (30.7 % , 0 %)	46.5 % (64.4 % , 25.3 %)	72.3 % (94.3 % , 46.2 %)
0.5	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (6.1 % , 0 %)
0.7	0.25	5.7 % (6.1 % , 6.2 %)	30 % (32.8 % , 26.3 %)	53 % (60.6 % , 44.4 %)	92.6 % (100 % , 71.8 %)	100 % (100 % , 91.9 %)	100 % (100 % , 100 %)
0.7	0.45	3 % (3.3 % , 3.1 %)	23.8 % (24.9 % , 23.1 %)	40.8 % (43.1 % , 38 %)	66.3 % (73.2 % , 58 %)	85.8 % (98.6 % , 71.8 %)	100 % (100 % , 83.6 %)
0.7	0.65	0 % (0 % , 0 %)	4.4 % (18 % , 0 %)	24 % (35.6 % , 13.2 %)	50.3 % (60 % , 37.2 %)	67.6 % (77.4 % , 52.2 %)	82.7 % (95.9 % , 64.3 %)
0.7	0.85	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (16.9 % , 0 %)	25.5 % (47.4 % , 0 %)

Table S3b: Structural sensitivity analysis: Increasing Epidemic Scenario: Percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S3a and S3b *respectively show, for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic under the structural sensitivity analysis, the percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years. The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.*

Additional analyses - Fully Endemic scenario

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the percentage change in condom consistency tolerated over the time horizon for the additional scenario *Fully Endemic* (PrEP introduced in 2030) is shown in Table S4.

Fully Endemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static Model and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0.1 %, 0 %)	0 % (0.1 %, 0 %)	0 % (0.1 %, 0 %)	0 % (0.1 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0.1 %, 0 %)	0.1 % (0.1 %, 0 %)	0 % (0.2 %, 0 %)	0 % (0.1 %, 0 %)	0 % (100 %, 0 %)	0 % (0.1 %, 0 %)
0.3	0.25	-0.9 % (-1 %, -0.6 %)	3.5 % (4.2 %, 4.9 %)	8.2 % (10.3 %, 7.3 %)	15.8 % (24.6 %, 9.4 %)	22.1 % (100 %, 8.9 %)	26.8 % (53.3 %, 7.9 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	2.1 % (23 %, 0 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-0.6 % (-1 %, -0.7 %)	4.1 % (4 %, 3 %)	8.2 % (12 %, 5.7 %)	15.7 % (35.1 %, 4.7 %)	20.4 % (100 %, 1.2 %)	25.4 % (81.6 %, 0.5 %)
0.5	0.45	-0.4 % (-0.4 %, -0.5 %)	7.2 % (6.7 %, 6.8 %)	13.8 % (13.6 %, 13.4 %)	24.4 % (27 %, 22.1 %)	31.6 % (100 %, 25.5 %)	37.8 % (57.4 %, 28.3 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (3.6 %, 0 %)	0.3 % (100 %, 0 %)	9.7 % (28.8 %, 0 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	-1.1 % (-1.3 %, 0 %)	2.1 % (2.5 %, 2.3 %)	6.3 % (13.2 %, 2.3 %)	11.1 % (44.7 %, 0 %)	15.8 % (100 %, -6.4 %)	18.9 % (100 %, -10 %)
0.7	0.45	-0.9 % (-0.8 %, -0.2 %)	5.9 % (5.4 %, 6.7 %)	12.2 % (11.4 %, 12.1 %)	22.4 % (28.5 %, 19 %)	29.3 % (100 %, 23.5 %)	35.8 % (63.7 %, 24.4 %)
0.7	0.65	-0.5 % (-0.5 %, 0 %)	9.2 % (9.4 %, 1.3 %)	17.9 % (16.9 %, 10.5 %)	29.9 % (29.5 %, 22.8 %)	37.9 % (100 %, 29.3 %)	43.6 % (50.5 %, 34.7 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (12.6 %, 0 %)

Table S4: Percentage change between the static and dynamic models' prediction of the percentage change in condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years, under the Fully Endemic scenario.

The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.

Lowest Level of Condom Consistency Tolerated: Tables of absolute difference between static and dynamic model's outcomes

The absolute difference between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios are shown in Tables S5a and S5b respectively.

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	Absolute Difference between Initial Condom Consistency and Lowest Level of Condom Consistency on PrEP					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -0.1 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	0.4 % (0.3 %, 0.1 %)	0 % (0.2 %, -0.5 %)	-0.5 % (0.8 %, -1.7 %)	-0.9 % (2.7 %, -4.3 %)	-0.8 % (4.8 %, -7.5 %)	-0.9 % (4.8 %, -12.3 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -3.1 %)	0 % (0 %, -8.8 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	0.3 % (0.3 %, 0.3 %)	0.3 % (0.3 %, -0.3 %)	0.3 % (0.6 %, -1.6 %)	0.5 % (3.2 %, -4.8 %)	0.7 % (5.7 %, -8.5 %)	1 % (7.9 %, -13.8 %)
0.5	0.45	0.3 % (0.3 %, 0.4 %)	-1.5 % (-2.6 %, -1.3 %)	-2.8 % (-4.2 %, -3.6 %)	-5.2 % (-6.3 %, -9 %)	-7 % (-5.7 %, -14.1 %)	-8.5 % (-5.4 %, -21.5 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -6.5 %)	0 % (0 %, -16.2 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	0.3 % (0.4 %, 0.2 %)	0.5 % (0.6 %, -0.2 %)	1.1 % (1.5 %, -0.8 %)	1.7 % (3.8 %, -3.1 %)	2.4 % (6.2 %, -6.9 %)	2.6 % (8.6 %, -12.8 %)
0.7	0.45	0.4 % (0.5 %, 0.3 %)	-0.7 % (-0.9 %, -0.8 %)	-1.5 % (-1.9 %, -2.2 %)	-2.3 % (-2 %, -5.7 %)	-3.4 % (-1.7 %, -10.3 %)	-4.3 % (-0.4 %, -17.3 %)
0.7	0.65	0.4 % (0 %, 0.2 %)	-3.7 % (-0.8 %, -3.1 %)	-7.5 % (-5.7 %, -6.3 %)	-12.8 % (-11.1 %, -13.3 %)	-16.4 % (-14.4 %, -19.2 %)	-19.2 % (-14.7 %, -28.5 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -0.5 %)

Table S5a: Epidemic Equilibrium Scenario: Absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	Absolute Difference between Initial Condom Consistency and Lowest Level of Condom Consistency on PrEP					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, -0.4 %)	-4.9 % (-0.5 %, -8.8 %)	-16.6 % (-10.5 %, -22.4 %)	-22.4 % (-14.4 %, -30.6 %)	-15.2 % (-2 %, -28.8 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-0.4 % (0 %, -7 %)	-8.7 % (0 %, -17.4 %)	-1.8 % (0 %, -15.3 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	-1.9 % (-2.3 %, -1.6 %)	-9.1 % (-10.1 %, -8.9 %)	-15.2 % (-15.3 %, -15.9 %)	-24.9 % (-22.9 %, -27.5 %)	-30.1 % (-25.7 %, -35.3 %)	-24.2 % (-16.7 %, -35.8 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, -2.9 %)	-6.7 % (-0.8 %, -12.3 %)	-20 % (-13.2 %, -26.8 %)	-27 % (-18.4 %, -36.3 %)	-21.3 % (-8.5 %, -37.3 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -6.3 %)	-6.9 % (0 %, -18.9 %)	-1.7 % (0 %, -19.8 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-1.2 % (-1.6 %, -1 %)	-6.4 % (-6.8 %, -6 %)	-10.7 % (-10.9 %, -11.3 %)	-18.2 % (-16.5 %, -20.4 %)	-22.1 % (-18 %, -26.8 %)	-17.2 % (-10 %, -26.9 %)
0.5	0.45	-1.5 % (-2.1 %, -1.2 %)	-10.9 % (-12.9 %, -9.5 %)	-18 % (-20.7 %, -16.5 %)	-28.4 % (-30.5 %, -28.3 %)	-34.1 % (-34.4 %, -36.2 %)	-29.6 % (-25.6 %, -37.3 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-3.3 % (0 %, -10.2 %)	-19.2 % (-10.6 %, -26.2 %)	-27.4 % (-17.6 %, -36.4 %)	-23.4 % (-7.9 %, -38 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -2.4 %)
0.7	0.25	-0.8 % (-0.8 %, -0.5 %)	-4.3 % (-4.3 %, -3.4 %)	-7.2 % (-7.2 %, -6.7 %)	-12.2 % (-11.5 %, -13.3 %)	-15.3 % (-13.6 %, -18.1 %)	-12 % (-7.1 %, -19.6 %)
0.7	0.45	-0.9 % (-1.1 %, -0.6 %)	-7.3 % (-8.1 %, -5.7 %)	-12.4 % (-13.8 %, -10.1 %)	-20.2 % (-21.6 %, -18.7 %)	-24.4 % (-25.2 %, -25.4 %)	-21.8 % (-18.8 %, -27.2 %)
0.7	0.65	-1.3 % (0 %, -0.9 %)	-14.8 % (-11.5 %, -11.2 %)	-23.5 % (-22.3 %, -19.3 %)	-36.3 % (-37.1 %, -31.3 %)	-43 % (-43.3 %, -39.3 %)	-40.1 % (-36.4 %, -42.7 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-3.9 % (0 %, -14.7 %)	-15.8 % (-1.8 %, -27.8 %)	-10.8 % (0 %, -33 %)

Table S5b: Increasing Epidemic Scenario: Absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S5a and S5b *respectively show for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic the absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years. The values stated outside the brackets are the absolute difference between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the absolute difference between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.*

Additional analyses – Structural sensitivity analysis

The absolute difference between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios for the structural sensitivity analysis are shown in Tables S6a and S6b respectively.

Structural Sensitivity Analysis

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	Absolute Difference between Initial Condom Consistency and Lowest Level of Condom Consistency on PrEP					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -4.2 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	-0.2 % (0 %, -0.3 %)	-3.2 % (-1.2 %, -3.2 %)	-5.9 % (-3.4 %, -6.5 %)	-10.2 % (-6.8 %, -12.3 %)	-13.1 % (-8.2 %, -17.4 %)	-14.7 % (-7.8 %, -22.5 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -4 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-0.1 % (-0.1 %, -0.1 %)	-2 % (-1.8 %, -2.2 %)	-3.8 % (-3.4 %, -4.7 %)	-6.8 % (-5.8 %, -10.2 %)	-9 % (-6.8 %, -15.8 %)	-10.5 % (-7 %, -22.3 %)
0.5	0.45	0 % (0 %, 0 %)	-0.3 % (0 %, -5 %)	-5.2 % (-0.2 %, -10 %)	-12.5 % (-7.4 %, -18.9 %)	-17.5 % (-11.8 %, -27.7 %)	-20.9 % (-14.5 %, -35.4 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -3.5 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	0.1 % (-0.1 %, 0 %)	-0.9 % (-0.9 %, -1.1 %)	-1.9 % (-1.7 %, -2.7 %)	-3.5 % (-2.4 %, -6.6 %)	-4.8 % (-2.4 %, -12.6 %)	-6 % (-1.9 %, -19.3 %)
0.7	0.45	0.1 % (-0.3 %, 0 %)	-3 % (-3.9 %, -2.9 %)	-6 % (-7 %, -5.9 %)	-11.1 % (-11.2 %, -12.5 %)	-14.4 % (-13.9 %, -18.9 %)	-17.1 % (-15.5 %, -26.9 %)
0.7	0.65	0 % (0 %, 0 %)	0 % (0 %, -1.6 %)	-0.4 % (0 %, -9.1 %)	-12.2 % (-3.2 %, -20.9 %)	-20.3 % (-10.6 %, -31.4 %)	-25.6 % (-15.4 %, -40.2 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)

Table S6a: Structural sensitivity analysis: Epidemic Equilibrium Scenario: Absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Structural Sensitivity Analysis

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	Absolute Difference between Initial Condom Consistency and Lowest Level of Condom Consistency on PrEP					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-0.9 % (0 %, -5.2 %)	-17 % (-9.4 %, -21.5 %)	-28 % (-18.2 %, -33.9 %)	-36 % (-23.5 %, -44.4 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-9.1 % (0 %, -15.8 %)	-20.7 % (-5.1 %, -29.5 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -3.2 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	-2.7 % (-1.1 %, -2.7 %)	-12.7 % (-10.7 %, -13.2 %)	-21 % (-17.6 %, -22.3 %)	-33.4 % (-28.6 %, -36 %)	-42.4 % (-35.9 %, -47.2 %)	-49.7 % (-41 %, -57 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -1 %)	-15.1 % (-7.7 %, -20.7 %)	-27.5 % (-19 %, -35 %)	-37.4 % (-26.4 %, -48.2 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -8.4 %)	-14.1 % (-0.7 %, -27.2 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-1.6 % (-1.7 %, -1.6 %)	-8.4 % (-8.5 %, -8.7 %)	-14.4 % (-13.7 %, -15.2 %)	-24.2 % (-21.4 %, -26.3 %)	-31.3 % (-26.6 %, -34.6 %)	-37.9 % (-30.8 %, -42.9 %)
0.5	0.45	0 % (0 %, -1.5 %)	-10.6 % (-6.4 %, -15 %)	-20.8 % (-16.4 %, -25.4 %)	-35.9 % (-30 %, -41.3 %)	-46.4 % (-38.2 %, -53 %)	-55.4 % (-44.5 %, -63.5 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	-6.8 % (0 %, -15.3 %)	-23.2 % (-12.7 %, -32.2 %)	-36.2 % (-23.1 %, -47.2 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -3 %)
0.7	0.25	-0.9 % (-1.1 %, -0.8 %)	-4.9 % (-4.8 %, -4.5 %)	-8.6 % (-8 %, -8.3 %)	-14.9 % (-13 %, -15.3 %)	-20.3 % (-16.6 %, -21.8 %)	-25.5 % (-20 %, -29.6 %)
0.7	0.45	-1.2 % (-1.4 %, -1.2 %)	-9.4 % (-10.2 %, -8.5 %)	-16.2 % (-16.8 %, -14.7 %)	-26.2 % (-25.7 %, -24.9 %)	-33.9 % (-31.9 %, -33.5 %)	-41.7 % (-37.1 %, -42.3 %)
0.7	0.65	0 % (0 %, 0 %)	-3.1 % (0 %, -12.6 %)	-16.8 % (-9.2 %, -24.9 %)	-35.2 % (-26 %, -42 %)	-47.3 % (-36.5 %, -54.2 %)	-57.9 % (-45 %, -67.2 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -11.8 %)	-17.8 % (0 %, -33.2 %)

Table 6b: Structural sensitivity analysis: Increasing Epidemic Scenario: Absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S6a and S6b *respectively show, for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic under the structural sensitivity analysis, the absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years. The values stated outside the brackets are the absolute difference between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the absolute difference between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.*

Additional analyses - Fully Endemic scenario

The absolute difference between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated over the time horizon for the additional scenario *Fully Endemic* (PrEP introduced in 2030) is shown in Table S7.

Fully Endemic Scenario

Initial Condom Consistency	PrEP Effectiveness	Absolute Difference between Initial Condom Consistency and Lowest Level of Condom Consistency on PrEP					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	0.2 % (0.2 %, 0.1 %)	-0.7 % (-1.2 %, -0.8 %)	-1.7 % (-1.8 %, -1.9 %)	-3.2 % (-2.3 %, -4.5 %)	-4.5 % (-2.2 %, -6.8 %)	-5.5 % (-2 %, -9.7 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -3.4 %)	-0.6 % (0 %, -6.9 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	0.1 % (0.2 %, 0.1 %)	-0.6 % (-0.6 %, -0.6 %)	-1.4 % (-1.1 %, -1.9 %)	-2.7 % (-0.9 %, -5.3 %)	-3.4 % (-0.2 %, -8.3 %)	-4.3 % (-0.1 %, -12.3 %)
0.5	0.45	0.2 % (0.2 %, 0.2 %)	-2.8 % (-3.3 %, -2.3 %)	-5.4 % (-6.3 %, -4.7 %)	-9.6 % (-10.5 %, -9.3 %)	-12.5 % (-12 %, -14.1 %)	-14.9 % (-13.4 %, -19.7 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -1.8 %)	-0.1 % (0 %, -7.9 %)	-4.8 % (0 %, -14.4 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	0.2 % (0 %, 0.2 %)	-0.3 % (-0.3 %, -0.2 %)	-0.9 % (-0.3 %, -1.4 %)	-1.5 % (0 %, -5 %)	-2.1 % (0.9 %, -8.3 %)	-2.5 % (1.5 %, -11.8 %)
0.7	0.45	0.2 % (0.1 %, 0.2 %)	-1.8 % (-2.4 %, -1.4 %)	-3.8 % (-4.4 %, -2.9 %)	-7 % (-6.9 %, -7.3 %)	-9.1 % (-8.6 %, -11.5 %)	-11.1 % (-8.9 %, -16.4 %)
0.7	0.65	0.3 % (0 %, 0.2 %)	-5.9 % (-0.9 %, -5 %)	-11.4 % (-7.3 %, -9 %)	-19.1 % (-16 %, -15.6 %)	-24.2 % (-20.5 %, -20.9 %)	-27.9 % (-24.3 %, -26.7 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, -8.8 %)

Table S7: Absolute difference between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years, under the Fully Endemic scenario.

The values stated outside the brackets are the absolute difference between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the absolute difference between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.

Lowest Level of Condom Consistency Tolerated: Tables of percentage change between static and dynamic model's outcomes

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated in absolute terms over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios are shown in Tables S8a and S8b respectively.

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	4.4 % (-0.7 %, 0.9 %)	0 % (2.8 %, -4.3 %)	-5.6 % (9.2 %, -14.5 %)	-10 % (23.5 %, -36.8 %)	-8.9 % (41.1 %, -64.1 %)	-10 % (67.2 %, -105.1 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	0.9 % (-2 %, 0.9 %)	0.9 % (1.7 %, -0.9 %)	0.9 % (10.7 %, -4.6 %)	1.5 % (32 %, -13.7 %)	2.1 % (100 %, -24.3 %)	3 % (92 %, -39.4 %)
0.5	0.45	2.8 % (-1.2 %, 2.6 %)	-13.8 % (3.8 %, -8.3 %)	-25.7 % (10.5 %, -23.1 %)	-47.7 % (26.3 %, -57.7 %)	-64.2 % (100 %, -90.4 %)	-78 % (62.6 %, -137.8 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	0.5 % (-1.9 %, 0.3 %)	0.9 % (1.9 %, -0.3 %)	1.9 % (7.5 %, -1.4 %)	3 % (27.5 %, -5.3 %)	4.2 % (100 %, -11.7 %)	4.6 % (114.4 %, -21.8 %)
0.7	0.45	1 % (-1.1 %, 0.7 %)	-1.8 % (3.2 %, -1.8 %)	-3.8 % (8.4 %, -5 %)	-5.8 % (22.2 %, -12.9 %)	-8.5 % (100 %, -23.4 %)	-10.8 % (66.8 %, -39.2 %)
0.7	0.65	5.5 % (0 %, 1.2 %)	-50.7 % (5.8 %, -18.6 %)	-102.7 % (11.8 %, -37.7 %)	-175.3 % (24.8 %, -79.6 %)	-224.7 % (100 %, -115 %)	-263 % (53.5 %, -170.7 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)

Table S8a: Epidemic Equilibrium Scenario: Percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (87.5 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	-20.7 % (9.3 %, -13 %)	-98.9 % (50.6 %, -72.4 %)	-165.2 % (89.8 %, -129.3 %)	-270.7 % (100 %, -223.6 %)	-327.2 % (100 %, -287 %)	-263 % (100 %, -291.1 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (41.1 %, 0 %)	0 % (89.2 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-3.6 % (7.1 %, -2.8 %)	-19.4 % (40.7 %, -17 %)	-32.4 % (76.8 %, -32.1 %)	-55.2 % (100 %, -58 %)	-67 % (100 %, -76.1 %)	-52.1 % (100 %, -76.4 %)
0.5	0.45	-13.9 % (3.5 %, -7.5 %)	-100.9 % (27.8 %, -59.4 %)	-166.7 % (48.5 %, -103.1 %)	-263 % (83.2 %, -176.9 %)	-315.7 % (100 %, -226.3 %)	-274.1 % (100 %, -233.1 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (52.4 %, 0 %)	0 % (100 %, 0 %)	0 % (76.1 %, 0 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	-1.4 % (4.5 %, -0.8 %)	-7.6 % (31.2 %, -5.8 %)	-12.7 % (61.1 %, -11.4 %)	-21.5 % (100 %, -22.5 %)	-26.9 % (100 %, -30.7 %)	-21.1 % (100 %, -33.2 %)
0.7	0.45	-2.3 % (2.2 %, -1.3 %)	-18.5 % (22.6 %, -12.8 %)	-31.4 % (39.9 %, -22.6 %)	-51.1 % (73.6 %, -41.9 %)	-61.8 % (100 %, -57 %)	-55.2 % (100 %, -61 %)
0.7	0.65	-18.1 % (0 %, -5.1 %)	-205.6 % (21.6 %, -63.3 %)	-326.4 % (36.8 %, -109 %)	-504.2 % (59.8 %, -176.8 %)	-597.2 % (100 %, -222 %)	-556.9 % (81.7 %, -241.2 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (0 %, 0 %)

Table S8b: Increasing Epidemic Scenario: Percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S8a and S8b *respectively show for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic the percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated in absolute terms, when the dynamic model is run over a time horizon of 3 months to 20 years. The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the*

percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.

Additional analyses – Structural sensitivity analysis

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated in absolute terms over the time horizon for both the *Epidemic Equilibrium* and *Increasing Epidemic* scenarios for the structural sensitivity analysis are shown in Tables S9a andS 9b respectively.

Structural Sensitivity Analysis

Epidemic Equilibrium Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static and Dynamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.25	-33.3% (0%, -10.7%)	-533.3% (11.6%, -114.3%)	-983.3% (23.7%, -232.1%)	-1700% (45.3%, -439.3%)	-2183.3% (100%, -621.4%)	-2450% (82.6%, -803.6%)
0.3	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.5	0.25	-0.4% (0.5%, -0.3%)	-7.3% (10.7%, -7.5%)	-13.9% (22.7%, -15.9%)	-24.8% (49.8%, -34.6%)	-32.8% (100%, -53.6%)	-38.3% (109%, -75.6%)
0.5	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (20%, 0%)	0% (37.9%, 0%)	0% (100%, 0%)	0% (70.8%, 0%)
0.5	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.5	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.7	0.25	0.2% (0%, 0%)	-1.7% (8%, -2%)	-3.5% (20.1%, -4.8%)	-6.5% (47.7%, -11.8%)	-8.9% (100%, -22.5%)	-11.1% (139.2%, -34.4%)
0.7	0.45	0.3% (0%, 0%)	-9.7% (8.6%, -8.1%)	-19.4% (17.4%, -16.5%)	-35.8% (36.6%, -34.9%)	-46.5% (100%, -52.8%)	-55.2% (78.7%, -75.1%)
0.7	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (29.8%, 0%)	0% (100%, 0%)	0% (57.4%, 0%)
0.7	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)

Table S9a: Structural sensitivity analysis: Epidemic Equilibrium Scenario: Percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Structural Sensitivity Analysis

Increasing Epidemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static and Dyamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)
0.1	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)
0.1	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.1	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.3	0.25	-385.7 % (9.9 %, -96.4 %)	1814.3 % (48.7 %, -471.4 %	-3000 % (81.8 %, -796.4 %)	4771.4 % (100 %, -1285.7 %	6057.1 % (100 %, -1685.7 %	-7100 % (100 %, -2035.7 %)
0.3	0.45	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (68.9 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)
0.3	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (90.6 %, 0 %)
0.3	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.5	0.25	-5.8 % (8 %, -5.4 %)	-30.5 % (42 %, -29.6 %)	-52.4 % (73.8 %, -51.7 %)	-88 % (100 %, -89.5 %)	-113.8 % (100 %, -117.7 %)	-137.8 % (100 %, -145.9 %)
0.5	0.45	0 % (0 %, 0 %)	0 % (30 %, 0 %)	0 % (50.7 %, 0 %)	0 % (82.6 %, 0 %)	0 % (100 %, 0 %)	0 % (100 %, 0 %)
0.5	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (100 %, 0 %)	0 % (94.3 %, 0 %)
0.5	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)
0.7	0.25	-1.7 % (6.1 %, -1.4 %)	-9.1 % (32.8 %, -8 %)	-16 % (60.6 %, -14.8 %)	-27.6 % (100 %, -27.2 %)	-37.7 % (100 %, -38.8 %)	-47.3 % (100 %, -52.7 %)
0.7	0.45	-3.9 % (3.3 %, -3.3 %)	-30.8 % (24.9 %, -23.6 %)	-53.1 % (43.1 %, -40.8 %)	-85.9 % (73.2 %, -69.2 %)	-111.1 % (100 %, -93.1 %)	-136.7 % (100 %, -117.5 %)
0.7	0.65	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (35.6 %, 0 %)	0 % (60 %, 0 %)	0 % (100 %, 0 %)	0 % (95.9 %, 0 %)
0.7	0.85	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)	0 % (0 %, 0 %)

Table S9b: Structural sensitivity analysis: Increasing Epidemic Scenario: Percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years.

Tables S9a and S9b *respectively show, for the scenarios where PrEP is introduced at Epidemic Equilibrium and where PrEP is introduced with Increasing Epidemic under the structural sensitivity analysis, the percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated in absolute terms, when the dynamic model is run over a time horizon of 3 months to 20 years. The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.*

Additional analyses - Fully Endemic scenario

The percentage change between the median and 95% credible interval (CrI) of the static and dynamic models' predictions of the lowest level of condom consistency tolerated in absolute terms over the time horizon for the additional scenario *Fully Endemic* (PrEP introduced in 2030) is shown in Table 10.

Fully Endemic Scenario

Initial Condom Consistency	PrEP Effectiveness	% Change between Static and Dyamic Model after					
		3 months	1 year	2 years	5 years	10 years	20 years
0.1	0.25	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.1	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.25	2.1% (-1%, 0.8%)	-7.4% (4.2%, -6.7%)	-17.9% (10.3%, -16%)	-33.7% (24.6%, -37.8%)	-47.4% (100%, -57.1%)	-57.9% (53.3%, -81.5%)
0.3	0.45	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.3	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.5	0.25	0.3% (-1%, 0.3%)	-1.8% (4%, -1.7%)	-4.3% (12%, -5.4%)	-8.2% (35.1%, -15.1%)	-10.3% (100%, -23.7%)	-13.1% (81.6%, -35.1%)
0.5	0.45	1.9% (-0.4%, 1.3%)	-26.7% (6.7%, -14.6%)	-51.4% (13.6%, -29.9%)	-91.4% (27%, -59.2%)	-119% (100%, -89.8%)	-141.9% (57.4%, -125.5%)
0.5	0.65	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.5	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
0.7	0.25	0.4% (-1.3%, 0.3%)	-0.5% (2.5%, -0.3%)	-1.6% (13.2%, -2.4%)	-2.6% (44.7%, -8.5%)	-3.7% (100%, -14.1%)	-4.4% (106.3%, -20%)
0.7	0.45	0.5% (-0.8%, 0.5%)	-4.6% (5.4%, -3.2%)	-9.7% (11.4%, -6.6%)	-17.9% (28.5%, -16.5%)	-23.3% (100%, -26%)	-28.4% (63.7%, -37.1%)
0.7	0.65	4.9% (0%, 1.2%)	-96.7% (9.4%, -29.4%)	-186.9% (16.9%, -52.9%)	-313.1% (29.5%, -91.8%)	-396.7% (100%, -122.9%)	-457.4% (50.5%, -157.1%)
0.7	0.85	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)

Table S10: Percentage change between the static and dynamic models' prediction of the lowest level of condom consistency tolerated, when the dynamic model is run over a time horizon of 3 months to 20 years, under the Fully Endemic scenario.

The percentage change values stated outside the brackets are the percentage change between the median values predicted by the static and dynamic models, and the values in the left and right of the bracket are the percentage change between the lower and upper 95% credible intervals predicted by the static and dynamic models respectively.

Additional assessment of results

Comparison of static and dynamic model outcomes

Under the scenario that PrEP is introduced at HIV *Epidemic Equilibrium*, the static and dynamic models predict very closely at 3 months (<5% relative difference between medians, and <5% relative difference between model 95% credible intervals (CrIs) - see *Supplementary Materials Tables S2a and S2b)*, and predict fairly consistently up to a time horizon of 1 year (<10% relative difference between the median and 95% CrI predictions). After 5 years, the relative difference between the median model predictions is less than 25% (<35% relative difference between their 95% CrIs); and after 20 years the relative difference between the median model outcomes grows to up to 35% (up to 100% relative difference their 95% CrIs).

The model outcomes are more consistent over time at lower levels of initial condom consistency (≤30%), where the relative difference between median predictions is less than 5% (up to 70% relative difference between 95% CrIs) over the 20-year time horizon. Where both initial condom consistency is low (≤30%) and PrEP use-effectiveness is high (≥65%), there is no change between the models' median predictions (100% relative difference between their 95% CrIs from 10 years). The differences between the models are more pronounced over time where initial condom consistencies are higher (≥50%) and the levels of PrEP use-effectiveness achieved are lower (≤45%).

Under the *Increasing Epidemic* scenario, the comparison between static and dynamic models follow a similar trend to those under the *Epidemic Equilibrium* scenario, however the differences between the models are more pronounced over time. After 1 year the relative difference between the model medians is up to 45% and up to 55% between the 95% CrIs (in comparison to a relative difference of no more than 10% between the medians and 95% CrIs under the *Epidemic Equilibrium* scenario), and by 5 years, the relative difference between the models is up to 100% (in comparison to less than 25% between model medians and less than 35% between model 95% CrIs under the *Epidemic Equilibrium* scenario). After 20 years the differences between the models starts to decrease in response to the natural plateau and slight decline of the underlying HIV epidemics (*Supplementary Materials Table S2b)*.

Under the *Epidemic Equilibrium* scenario, at the lower and upper bounds of initial condom consistencies explored (10% and 70%) and where PrEP use-effectiveness is 85% (i.e. the maximum assumed use-effectiveness of condoms[35,36]), the minimum and maximum whiskers do not protrude from the interquartile ranges of the box plots, indicating reasonable consistency of results across the model fits. By contrast, under the *Increasing Epidemic* scenario, the minimum and maximum whiskers protrude from the interquartile ranges of the boxplots, other than where PrEP use-

effectiveness is 85% and initial condom consistency is low (≤30%), indicating increased variance in the results across model fits in comparison to the *Epidemic Equilibrium* scenario.

Additional analyses – structural sensitivity analysis

Removing the risk parameters relating to ART, circumcision and STIs from the models affects the difference between the percentage reduction in condom consistency tolerated predicted by the static and dynamic models in certain conditions. Under the *Epidemic Equilibrium* scenario, the notable differences can be seen for initial condom consistencies of 30% upwards and at lower levels of PrEP use-effectiveness (≤45%), where the differences between the two models' estimates of percentage reduction in condom consistency tolerated is greater over time (<35% relative difference between model medians and <45% between CrIs by 5 years, and <50% relative difference between medians and CrIs by 20 years) *(Supplementary Materials Figure S6 vs. Figure S10, and Table S2a vs. Table S3a)*. This is likely in response to differences in the underlying epidemic trajectories, which level out more quickly where these parameters are not included in the models (as the epidemic curves do not see the same slight dip after 2014 when male circumcision and ART are assumed to have reached their highest scale-up coverage), but slightly decrease under the base case. Accordingly, the slightly higher levels of underlying HIV prevalence in the former scenario result in increased HIV risk over time in the dynamic model in the cases where there is less protection (i.e. lower levels of PrEP and greater absolute drops in condom consistency).

Under the *Increasing Epidemic* scenario, the notable differences are more pronounced at higher levels of initial condom consistency (≥50%) and higher levels of PrEP use-effectiveness (≥65%) (<25% relative difference between model medians and CrIs by 5 years, and <30% relative difference between model medians and <35% between CrIs by 20 years for the *Increasing Epidemic* scenario) *(Supplementary Materials Figure S8 and Figure S11, and Table S2b vs. Table S3b)*. Similarly, this is likely in response to differences in the underlying epidemic trajectories, which continue to slightly increase over time after levelling out around 2010 where these parameters are not included in the models, but level out more evenly under the base case. For the same reasons, unlike under the base analysis, where after 20 years the differences between the models starts to decrease in response to the natural plateau of the underlying HIV epidemics, the same is not true where the specified risk parameters are removed from the equations, in which case the underlying epidemics instead slightly increase over time.

Additional analyses - Fully Endemic scenario

Introducing PrEP at 2030 when the underlying HIV epidemics are fully endemic in the populations, as opposed to in 2015 when they have just started to stabilise has little effect on the differences between the percentage reduction in condom consistency tolerated predicted by the static and dynamic models. The main differences are that at low levels of PrEP use-effectiveness (25%), the differences between the models are slightly greater under the *Fully Settled Epidemic* scenario (up to 25% difference between absolute medians), and whilst the interquartile ranges are narrower under the *Fully Settled Epidemic* scenario, the 95% CrIs are slightly wider under this scenario likely owing to greater uncertainty in epidemic pathways further out in time *(Supplementary Materials Figure S14, and Table S2a vs. Table S4).*

References to Appendix 3

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Appendix 4: Supplementary Materials to Research Paper 3

Supplementary Materials to: Time to scale-up PrEP beyond the highest-risk populations? Modelling insights from high-risk women in sub-Saharan Africa

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Supplementary Methods

Model Structure

We use a static Bernoulli formulation of HIV risk[1]. The sexual partners of high-risk women from population j are assumed to come from populations i in which the proportion HIV infected is p_i. We assume an average probability of HIV transmission, β_f, per sexual contact with an HIV infected male partner. High risk women are assumed to have C_i number of partners from each population a year, with whom they have an average of n_i sex acts a year each. Condoms are assumed to be used with partners from each population with consistency γ_{ij} and have an HIV risk reduction efficacy, ε, including slippage and breakage. Upon introduction, high-risk women from population j are assumed to adhere to PrEP at an average level α_j, which corresponds to a level of HIV risk reduction, θ_{α_j}. They are assumed to have 12-month program retention levels r_j. Sex acts are assumed to be peno-vaginal, the predominant pathway of HIV transmission to heterosexual women in sub-Saharan Africa.[2]

1.0 Individual level - Simple tools to help guide PrEP programme decision making

1.1 Assessment of HIV risk by risk factor

For the first analysis of HIV risk, we consider a simple model of HIV risk to a single high-risk woman with partners drawn from a single male population. HIV risk to an individual high-risk woman in the absence of PrEP is given by

$$\pi(0) = 1 - \left(p\left(1 - \beta_f(1 - \varepsilon\gamma)\right)^n + (1 - p)\right)^C, \tag{S1.1}$$

and on PrEP is

$$\pi(\theta_{\alpha_j}) = 1 - \left(p\left(1 - \beta_f\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma)\right)^n + (1 - p)\right)^C \tag{S1.2}$$

Using equations (S1.1) and (S1.2), HIV risk reduction on PrEP is given by

$$\pi(0) - \pi(\theta_{\alpha_j}) \tag{S1.3}$$

In order to parameterise the model to the spectrum of HIV risk faced by women in sub-Saharan Africa, equation (S1.1) was simulated across the parameter ranges set out in *Supporting Information: Methods – Table S2*, yielding 720,000 distinct parameter sets.

1.2 Simple rule to estimate relative cost-effectiveness

In estimating the relative cost-effectiveness among women at risk, we considered two high-risk women of different risk. One woman is drawn from a traditionally higher-risk population (e.g. female sex workers (FSW)) and the other from a relatively lower-risk female population (e.g. adolescent girls and young women aged 15-24 years (AGYW)), denoted $H$and L respectively. For simplicity, each high-risk woman is assumed to draw their partners from one population group.

Analysis was conducted over a one-year timeframe, as PrEP is intended for seasons of risk, and few PrEP demonstration programs have achieved significant retention in women in this context beyond the first 12 months.[3,4] Let π_H and π_L denote the respective HIV risk for each woman, with subscripts $H$and L denoting high and low risk groups Let $\$X_H$ and $\$X_L$be the 12-month unit costs of PrEP for each woman (the incremental cost of PrEP for a woman retained in a PrEP program over a 12-month period).

Then the cost of averting one HIV infection with PrEP per year is $\frac{\$X_H}{\pi_H(0)-\pi_H(\theta_{\alpha_H})}$ and $\frac{\$X_L}{\pi_L(0)-\pi_L(\theta_{\alpha_L})}$ respectively. PrEP will become equally cost-effective in the lower-risk group as it is in the higher-risk group where:

$$\frac{\$X_L}{\pi_L(0)-\pi_L(\theta_{\alpha_L})} = \frac{\$X_H}{\pi_H(0)-\pi_H(\theta_{\alpha_H})} \quad \text{(S1.4)}$$

Equation (S1.4) can be expressed as

$$\frac{\$X_L}{\$X_H} = \frac{\pi_L(0)-\pi_L(\theta_{\alpha_L})}{\pi_H(0)-\pi_H(\theta_{\alpha_H})} \quad \text{(S1.5)}$$

To derive a simple formulation of equation (S1.5) that is intuitive for policy makers and programmers in practical real-world settings, we simplify equations (S1.1) and (S1.2) using binomial theorem. Using the example of equation (S1.2), where $\beta(1-r\theta_\alpha)(1-\varepsilon\gamma) \ll 1$ we have:

$$\pi(\theta_{\alpha_j}) \approx 1 - \left(p\left(1 - n\beta_f\left(1 - r_j\theta_{\alpha_j}\right)(1-\varepsilon\gamma)\right) + (1-p)\right)^C$$

$$\approx 1 - \left(1 - pn\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma)\right)^C$$

for $pn\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma) \ll 1$,

$$\pi(\theta_{\alpha_j}) \approx Cpn\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma).$$

(S1.6)

In other words, the HIV risk reduction to an individual on PrEP can be approximated by the total number of sex acts per unit time multiplied by the partner HIV prevalence, the basic risk of HIV transmission through peno-vaginal sex (0.0006 - 0.0011[5]), the average proportion of sex acts not protected by condoms, and the use-effectiveness of PrEP. The use-effectiveness of PrEP is defined as the HIV-risk reduction through use of PrEP at a given level of adherence, for a population with a given average program retention level.

Thus the risk reduction in equation (S1.3) is approximately

$Cpn\beta(1 - \varepsilon\gamma) - Cpn\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma)$, and simplifies to

$$Cpn\beta(1 - \varepsilon\gamma)r_j\theta_{\alpha_j}.$$

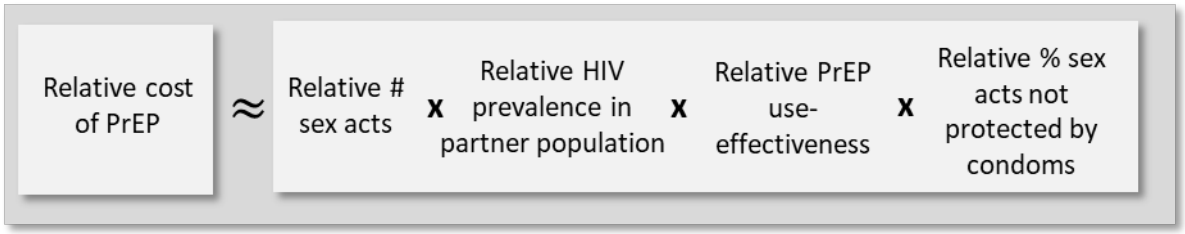
(S1.7)

Therefore, when $\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma) \ll 1$ and $pn\beta\left(1 - r_j\theta_{\alpha_j}\right)(1 - \varepsilon\gamma) \ll 1$,the condition for equal cost-effectiveness in equation (S1.5) between two populations with different risk levels becomes:

$$\frac{\$X_L}{\$X_H} = \frac{C_L n_L p_L (1-\varepsilon\gamma_L) r_L \theta_{\alpha_L}}{C_H n_H p_H (1-\varepsilon\gamma_H) r_H \theta_{\alpha_H}}$$

(S1.8)

The relationship on relative cost of PrEP is summarised as follows.



1.3 Relative risk reduction on PrEP

Using equation (S1.5) we calculate the relative risk reduction on PrEP between a higher- and lower-risk woman. To obtain a spectrum of HIV risk faced by both populations reflective of the sub-Saharan African settings, we simulated across the parameter ranges set out in *Supporting Information: Methods – Table S2*, yielding 7,920,000 distinct parameter sets.

2.0 Population level – country case studies

We modify the risk equations (S1.1) and (S1.2) to consider HIV risk and the scale-up of PrEP at a population rather than individual level.

The total population size of high-risk women of type j is N_j, in which the prevalence of HIV is p_j. The coverage of PrEP in the population is ω_j.

In the process of parameterising the model to specific high-risk women populations, we develop the risk equations to also account for population-specific STI levels, levels of viral load suppression due to ART in HIV positive partners and male circumcision.

The parameter s_{ij} is the probability that at least one person in the partnership between high risk woman from population j and partner from population i has an STI and δ is the multiplicative increase in per sex act probability of HIV transmission in the presence of an STI.

Parameter ϑ_i is the proportion of HIV+ partners from population i that are virally suppressed on ART and ϱ models the average reduction in the probability of HIV transmission due to viral suppression on ART. The parameter τ_i is the proportion of male partner population i that are circumcised and σ is the average reduction in probability HIV transmission to women, when the male partner has been circumcised.

Where high-risk women from population j have partners drawn from a single male population, their HIV risk for a 12-month period is in the absence of PrEP is given by (leaving the *j* denotation to improve readability):

$$\Pi(0) = 1 - \left(p(\psi_{(1-\tau),0} + \psi_{\tau,0}) + (1-p)\right)^C$$

Where:

$$\psi_{(1-\tau),0} = (1-\tau)\big((1-\vartheta)s(\,1-\delta\varsigma)^n + (1-\vartheta)(1-s)(\,1-\varsigma)^n + \vartheta s(\,1-(1-\varrho)\delta\varsigma)^n + \vartheta(1-s)(\,1-(1-\varrho)\varsigma)^n\big)$$

$$\psi_{\tau,0} = \tau\big((1-\vartheta)s(\,1-(1-\sigma)\delta\varsigma)^n + (1-\vartheta)(1-s)(\,1-(1-\sigma)\varsigma)^n + \vartheta s(\,1-(1-\sigma)(1-\varrho)\delta\varsigma)^n + \vartheta(1-s)(\,1-(1-\sigma)(1-\varrho)\varsigma)^n\big)$$

and $\varsigma = \beta_f(1-\varepsilon\gamma)$

(S2.1)

For women on PrEP we have

$$\Pi(r\theta_\alpha) = 1 - \big(p(\psi_{(1-\tau),r\theta_\alpha} + \psi_{\tau,\,r\theta_\alpha}) + (1-p)\big)^C$$

Where:

$$\psi_{(1-\tau),\,r\theta_\alpha} = (1-\tau)\big((1-\vartheta)s(\,1-\delta\kappa)^n + (1-\vartheta)(1-s)(\,1-\kappa)^n + \vartheta s(\,1-(1-\varrho)\delta\kappa)^n + \vartheta(1-s)(\,1-(1-\varrho)\kappa)^n\big)$$

$$\psi_{\tau,\,r\theta_\alpha} = \tau\big((1-\vartheta)s(\,1-(1-\sigma)\delta\kappa)^n + (1-\vartheta)(1-s)(\,1-(1-\sigma)\kappa)^n + \vartheta s(\,1-(1-\sigma)(1-\varrho)\delta\kappa)^n + \vartheta(1-s)(\,1-(1-\sigma)(1-\varrho)\kappa)^n\big)$$

and $\kappa = \beta_f(1-r\theta_\alpha)(1-\varepsilon\gamma)$

(S2.2)

Similarly, when high-risk women from population j have partners drawn from two male populations $i = 1, 2$, their HIV risk for a 12-month period is in the absence of PrEP is given by

$$\Pi(0) = 1 - \big(p_1(\psi^1_{(1-\tau),0} + \psi^1_{\tau,0}) + (1-p_1)\big)^{C_1}\big(p_2(\psi^2_{(1-\tau),0} + \psi^2_{\tau,0}) + (1-p_2)\big)^{C_2}$$

Where

$$\psi^1_{(1-\tau),0} = (1-\tau_1)\big((1-\vartheta_1)s_1(\,1-\delta\varsigma_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-\varsigma_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\varrho)\delta\varsigma_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\varrho)\varsigma_1)^{n_1}\big)$$

$$\psi^1_{\tau,0} = \tau_1\big((1-\vartheta_1)s_1(\,1-(1-\sigma)\delta\varsigma_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-(1-\sigma)\varsigma_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\sigma)(1-\varrho)\delta\varsigma_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\sigma)(1-\varrho)\varsigma_1)^{n_1}\big)$$

$\varsigma_1 = \beta_f(1-\varepsilon\gamma_1)$

and

$$\psi^2_{(1-\tau),0} = (1-\tau_2)\big((1-\vartheta_2)s_2(\,1-\delta\varsigma_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-\varsigma_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\varrho)\delta\varsigma_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\varrho)\varsigma_2)^{n_2}\big)$$

$$\psi^2_{\tau,0} = \tau_2\big((1-\vartheta_2)s_2(\,1-(1-\sigma)\delta\varsigma_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-(1-\sigma)\varsigma_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\sigma)(1-\varrho)\delta\varsigma_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\sigma)(1-\varrho)\varsigma_2)^{n_2}\big)$$

$$\varsigma_2 = \beta_f(1-\varepsilon\gamma_2)$$

(S2.3)

When enrolled on a PrEP program:

$$\Pi(r\theta_\alpha) = 1 - \big(p_1(\psi^1_{(1-\tau),\,r\theta_\alpha} + \psi^1_{\tau,\,r\theta_\alpha}) + (1-p_1)\big)^{C_1}\big(p_2(\psi^2_{(1-\tau),\,r\theta_\alpha} + \psi^2_{\tau,\,r\theta_\alpha}) + (1-p_2)\big)^{C_2}$$

Where

$$\psi^1_{(1-\tau),\,r\theta_\alpha} = (1-\tau_1)\big((1-\vartheta_1)s_1(\,1-\delta\kappa_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-\kappa_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\varrho)\delta\kappa_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\varrho)\kappa_1)^{n_1}\big)$$

$$\psi^1_{\tau,\,r\theta_\alpha} = \tau_1\big((1-\vartheta_1)s_1(\,1-(1-\sigma)\delta\kappa_1)^{n_1} + (1-\vartheta_1)(1-s_1)(\,1-(1-\sigma)\kappa_1)^{n_1} + \vartheta_1 s_1(\,1-(1-\sigma)(1-\varrho)\delta\kappa_1)^{n_1} + \vartheta_1(1-s_1)(\,1-(1-\sigma)(1-\varrho)\kappa_1)^{n_1}\big)$$

$$\kappa_1 = \beta_f(1-r\theta_\alpha)(1-\varepsilon\gamma_1)$$

And

$$\psi^2_{(1-\tau),\,r\theta_\alpha} = (1-\tau_2)\big((1-\vartheta_2)s_2(\,1-\delta\kappa_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-\kappa_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\varrho)\delta\kappa_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\varrho)\kappa_2)^{n_2}\big)$$

$$\psi^2_{\tau,\,r\theta_\alpha} = \tau_2\big((1-\vartheta_2)s_2(\,1-(1-\sigma)\delta\kappa_2)^{n_2} + (1-\vartheta_2)(1-s_2)(\,1-(1-\sigma)\kappa_2)^{n_2} + \vartheta_2 s_2(\,1-(1-\sigma)(1-\varrho)\delta\kappa_2)^{n_2} + \vartheta_2(1-s_2)(\,1-(1-\sigma)(1-\varrho)\kappa_2)^{n_2}\big)$$

$$\kappa_2 = \beta_f(1-r\theta_\alpha)(1-\varepsilon\gamma_2)$$

(S2.4)

All models were programmed in R version 3.3.2[6].

2.1 Country case studies

We apply the models to South Africa, Zimbabwe and Kenya, which are have generalised high prevalence HIV epidemics.[7–10] These countries were chosen as case studies as they span a range of

HIV burden levels in the region, they have each have adopted a national PrEP strategy,[11,12,13] and been at the forefront of PrEP roll-out in sub-Saharan Africa[14].

In each country, we consider four groups of women at high risk of HIV through heterosexual transmission[2,7,8,9]: $j = \{$FSW, adolescent girls and young women aged 15-24 years (AGYW), women 25-34 years and women 35-49 years$\}$.

FSW are assumed to have partners drawn from two populations: regular partners and clients. AGYW are assumed to have partners drawn from their own age group and also the 25-34 years age group, given that 17% and 14% women 15-19 years report relationships with men at least 10 years older in Zimbabwe[15] and Kenya[16] respectively, and 36% South African women 15-19 years report relationships with men at least 5 years older.[7] Women 25-34 years and women 35-49 years are assumed to have partners drawn from their own age groups.

Data ranges to parameterise the models of HIV risk for each high-risk female group were drawn from the latest available in the literature and fitted to the latest national estimates of HIV incidence by group (see *Supporting Information: Methods: Table S2*) using Latin Hypercube Sampling (R PSE Package[17]) to yield at least 200 sets of parameter fits for each high-risk woman population modelled.

2.2 Assessment of cost-effectiveness of scaling-up PrEP

Given the significantly higher individual HIV risk faced by FSW,[2] a priority group for PrEP roll-out in these settings,[11,12,13] we assumed FSW as the benchmark for assessment of cost-effectiveness.

Let $\$Y_j$ be the unit cost per high risk woman from population $j \neq FSW$ retained in a PrEP program for population j, with 12-month retention level r_j, and $\$Y_{FSW}$ the equivalent unit cost for a FSW PrEP program per FSW retained with 12-month retention level r_{FSW}.

Then the program's cost to avert 1 infection per year due to PrEP in each population is $\frac{\$Y_j}{\Pi_j(0)-\Pi_j(r_j\theta_{\alpha_j})}$ and $\frac{\$Y_{FSW}}{\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW}\theta_{\alpha_{FSW}})}$ respectively.

A PrEP program for high risk population $j \neq FSW$ will then be equally as cost-effective per infection averted due to PrEP, as it is for FSW where

$$\frac{\$Y_j}{\$Y_{FSW}} = \frac{\Pi_j(0)-\Pi_j(r_j\theta_{\alpha_j})}{\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW}\theta_{\alpha_{FSW}})}$$

(S2.5)

To determine the coverage, ω_j, of PrEP in high-risk woman population $j \neq FSW$ needed to achieve the same risk reduction as coverage ω_{FSW} in FSW, we have:

$$\omega_j N_j (1 - p_j) \left(\Pi_j(0) - \Pi_j(r_j \theta_{\alpha_j}) \right) = \omega_{FSW} N_{FSW} (1 - p_{FSW}) \left(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} \theta_{\alpha_{FSW}}) \right),$$

(S2.6)

when

$$\omega_j = \omega_{FSW} \frac{N_{FSW}(1-p_{FSW}) \left(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} \theta_{\alpha_{FSW}}) \right)}{N_j(1-p_j) \left(\Pi_j(0) - \Pi_j(r_j \theta_{\alpha_j}) \right)}.$$

(S2.7)

These levels of coverage would be at a relative total cost given by

$$\frac{\$Y_j \omega_j N_j (1-p_j)}{\$Y_{FSW} \omega_{FSW} N_{FSW} (1-p_{FSW})}$$

(S2.8)

If PrEP were scaled up at equal coverage in both populations, then the relative number of infections averted per year in high-risk woman population $j \neq FSW$ with respect to the FSW population would be:

$$\frac{N_j(1-p_j)(\Pi_j(0) - \Pi_j(r_j \theta_{\alpha_j}))}{N_{FSW}(1-p_{FSW})(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW} \theta_{\alpha_{FSW}}))}$$

(S2.9)

This is equivalent to the relative total maximum number of infections averted per year if PrEP programs were scaled up to all HIV negative women in each population.

For each $\$100k$ available for PrEP programming for each population, the estimated number of infections averted a year in each population would be:

In high-risk women $j \neq FSW$

$$\frac{\$100k}{\$Y_j} (\Pi_j(0) - \Pi_j(r_j \theta_{\alpha_j})),$$

and in FSW

$$\frac{\$100k}{\$Y_{FSW}}(\Pi_{FSW}(0) - \Pi_{FSW}(r_{FSW}\theta_{\alpha_{FSW}}))$$

(S2.10)

The proportion of the potential total number of infections that could be averted a year in each population with $\$100k$ is:

In high-risk women $j \neq FSW$

$$\frac{\$100k.(\Pi_j(0)-\Pi_j(r_j\theta_{\alpha_j}))}{\$Y_j.N_j(1-p_j).\Pi_j(0)},$$

and in FSW

$$\frac{\$100k.(\Pi_{FSW}(0)-\Pi_{FSW}(r_{FSW}\theta_{\alpha_{FSW}}))}{\$Y_{FSW}.N_{FSW}(1-p_{FSW}).\Pi_{FSW}(0)}$$

(S2.11)

Estimating costs of PrEP to each high-risk group of women

We estimated the costs of offering PrEP to each high-risk group of women. FSW were assumed to be offered PrEP through programmes with outreach and community mobilisation components. All other women were assumed to be offered PrEP through sexual and reproductive health services, with services for AGYW having larger counselling components. We reviewed cost data from demonstration projects and previous PrEP costing publications in Kenya[18,19] and South Africa.[3] We disaggregated cost estimates into service delivery and drug costs. For our calculations, we replaced reported drug costs by a range of USD57-80 per year. The lower bound is the internationally traded value of USD3.75 with a 25% top up of freight and distribution costs in country (15% shipping and handling charges, and 10% for drug distribution costs).[20] The high bound is the highest reported price for drugs in the demonstration projects - 30 days TDF/FTC at USD6.75. For Zimbabwe, in addition to drug costs, we transferred non-tradable components of South African estimates using purchasing power parities[21] following standard methods.[22] We adjusted all previously published costs to USD 2017.[23] The amounts and detailed assumptions underpinning the estimated unit costs for each high-risk women group by country are set out in Table S1 below.

Table of Estimated Unit Costs for High-Risk Women Populations in South Africa, Zimbabwe and Kenya

Country	Population	Unit cost (min - max)	Service delivery excl. drugs	Drugs only (min - max)	Comments
South Africa	FSW	190 – 210	130	57 - 80	Unit costs measured during a demonstration project in Johannesburg and Pretoria via FSW clinics. Costs reported by Eakle et al[3] included direct costs (eg, antiretrovirals, laboratory tests and consumables, labour and equipment) and indirect costs (eg, management, utilities, and transportation). We allocated outreach, demand creation and HCT costs to a unit cost of per person-year on PrEP as these were reported separately.
South Africa	AGYW (15-24y)	149 – 169	89	57 - 80	Unit costs estimated from local data and with input from several demonstration projects in South Africa. Costs reported by Meyer-Rath et al[24] included direct costs (eg, antiretrovirals, laboratory tests and consumables, labour and equipment), indirect costs (eg, management, utilities, and transportation), and outreach, demand creation and HCT costs. These estimates reflect the authors' estimation of costs among female adolescents.
South Africa	Women (25-34y)	128 – 148	68	57 - 80	Unit costs estimated from local data and with input from several demonstration projects in South Africa. Costs reported by Meyer-Rath et al[24] included direct costs (eg, antiretrovirals, laboratory tests and consumables, labour and equipment), indirect costs (eg, management, utilities, and transportation), and outreach, demand creation and HCT costs. These estimates reflect the authors' estimation of costs among young women.
South Africa	Women (35-49y)	87 – 107	27	57 - 80	Unit costs estimated from local data and with input from several demonstration projects in South Africa. Costs reported by Meyer-Rath et al[24] included direct costs (eg, antiretrovirals, laboratory tests and consumables, labour and equipment), indirect costs (eg, management, utilities, and transportation), and outreach, demand creation and HCT costs. These estimates reflect the authors estimation of costs among pregnant women - we assumed for this lowest risk population, the cost will be similar to those attending ANC.
Zimbabwe	FSW	293 – 317	237	57 - 80	Drug costs were kept constant and we adjusted service costs in South Africa using PPP index.[25]

Zimbabwe	AGYW (15-24y)	219 – 243	163	57 - 80	Drug costs were kept constant and we adjusted service costs in South Africa using PPP index.[25]
Zimbabwe	Women (25-34y)	181 - 204	124	57 - 80	Drug costs were kept constant and we adjusted service costs in South Africa using PPP index.[25]
Zimbabwe	Women (35-49y)	106 - 130	50	57 - 80	Drug costs were kept constant and we adjusted service costs in South Africa using PPP index.[25]
Kenya	FSW	399 - 423	343	57 - 80	Unit costs measured in preparation for a demonstration project in Nairobi via SWOP clinics (for FSW). Costs reported by Cremin et al[18] included direct costs (eg, antiretrovirals, laboratory tests and consumables, labour and equipment), related costs (eg, outreach and demand creation), and indirect costs (eg, management, utilities, and transportation).
Kenya	AGYW (15-24y)	358 - 382	302	57 - 80	Unit costs measured as part of a demonstration project aiming to integrate PrEP into routine maternal and child health and family planning clinics in western Kenya. Costs reported by Roberts et al[19] included fixed (start-up costs, such as microplanning and training, capital, overheads (e.g. building costs, transportation, and airtime) and administrative and supervisory personnel) or variable (drugs, clinical personnel direct service costs, laboratory testing, and other supplies). These estimates reflect the authors measurement of costs among the highest risk subpopulation in the general population.
Kenya	Women (25-34y)	294 - 318	238	57 - 80	Unit costs measured as part of a demonstration project aiming to integrate PrEP into routine maternal and child health and family planning clinics in western Kenya. Costs reported by Roberts et al[19] included fixed (start-up costs, such as microplanning and training, capital, overheads (e.g. building costs, transportation, and airtime) and administrative and supervisory personnel) or variable (drugs, clinical personnel direct service costs, laboratory testing, and other supplies). These estimates reflect the authors measurement of costs among all women.
Kenya	Women (35-49y)	185 - 209	129	57 - 80	Unit costs measured as part of a demonstration project aiming to integrate PrEP into routine maternal and child health and family planning clinics in western Kenya. Costs reported by Roberts et al[19] included fixed (start-up costs, such as microplanning and training, capital, overheads (e.g. building

		costs, transportation, and airtime) and administrative and supervisory personnel) or variable (drugs, clinical personnel direct service costs, laboratory testing, and other supplies). These estimates reflect the authors measurement of costs among all women excluding screening costs.

Table S1: Table of Estimated Unit Costs for High-Risk Women Populations in South Africa, Zimbabwe and Kenya.

The estimated unit costs for FSW, AGYW, women 25-34 years and women 35-49 years are shown disaggregated by the portion that is service delivery costs and the portion that is drug costs. The costs were calculated in line with the methodology set out in Supporting Information: Methods. The far right hand side column of the table sets out addition comments about specific assumptions made in calculating the data.

**For our calculations, we replaced reported drug costs by a range of USD57-80. The low bound is the internationally traded value of USD3.75 (https://www.theglobalfund.org/media/5813/ppm_arvreferencepricing_table_en.pdf) plus 25% top up of freight and distribution costs in country (15% shipping and handling charges, and 10% for drug distribution costs). The high bound is the highest reported price for drugs in the demonstration projects - 30 days TDF/FTC at USD6.75.*

***transferability of costs between countries followed standard guidelines (https://pdfs.semanticscholar.org/36ab/74fd24fb883db703c475364c34ad574a3f35.pdf)*

**** Purchasing Power Parities (PPP)*

Model calibration

The data used in the parameterisation and fitting of the models for all 3 country case studies shown in Table S2.

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
Epidemic parameters							
FSW: HIV incidence, per 100 person years	i_{FSW}	3.9 (2.2-5.6)	Nairobi, 2011[26] Nairobi, 2008[27] Estimate is mid-point. For context, 2.6 Mombasa, 2006[28]	5.87 (5.55-6.21)	2017 estimates[29]. 95% confidence intervals (CIs) estimated assuming binomially distributed, based on population size and proportion HIV-	7.2 (4.5-9.8)	CAPRISSA 002 2008[30]
AGYW: HIV incidence, per 100 person years	i_{AGYW}	0.28 (0.137 – 0.490)	UNAIDS 2018 Estimates[31]	0.53 (0.13, 0.93)	2016 estimates[32]	1.51 (1.31-1.71)	National estimates, 2017[33]
Women 25-34 years: HIV incidence, per 100 person years	i_{W25-34}	0.25 (0.120 – 0.431)	UNAIDS 2018 Estimates[31]	1.11 (0.41, 1.80)	2016 estimates[32]	1.045 (0.87-1.22)	2017 estimates[34]. Low and High are min and max across all ages within range.
Women 35-49 years: HIV incidence, per 100 person years	i_{W35-49}	0.16 (0.078– 0.282)	UNAIDS 2018 Estimates[31]	0.42 (0.00, 0.92)	2016 estimates[32]	0.665 (0.49-0.84)	2017 estimates[34]. Low and High are min and max across all ages within range.
FSW: Population size, in 1,000s of women	N_{FSW}	134	2013 size estimation[35]	45	2017 estimates[29]	138	2013 size estimation[36]
AGYW: Population size, in 1,000s of women	N_{AGYW}	4,067	2009 census[37]	1,304	2012 census[38]	4,901	2018 mid-year estimates[39]
Women 25-34 years: Population size, in 1,000s of women	N_{W25-34}	2,935	2009 census[37]	1,089	2012 census[38]	5,366	2018 mid-year estimates[39]

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
Women 34-49 years: Population size, in 1,000s of women	N_{W35-49}	2,374	2009 census[37]	817	2012 census[38]	5,354	2018 mid-year estimates[39]
Clients of FSW: HIV prevalence	p_c	0.165 (0.135-0.194)	Truck drivers, Kenya, 2005[40] Maximum county male prevalence (Siaya, males, 15-49 years), 2017[9] Estimate is mid-point.	0.273 (0.248, 0.295)	Long distance truck drivers, 2005[41]	0.339 (0.275 – 0.410)	Non-residents (study proxy for migrant work), men, from KwaZulu-Natal, South Africa, 2004.[42]
Men in general population 15-49 years: HIV prevalence	sp_{M15-49}	0.045 (0.0448-0.0451)	0.045 Males 15-49, 2017[9]. 0.044 (0.036-0.052) males 15-64 years, KAIS, 2012[43]. Use KAIS estimates as consistent with estimates used for individual age ranges below. No CI for 2017 estimate, but fits within CI of KAIS	0.107 (0.1066-0.1074)	2016 estimates[32] 95% CI estimated assuming binomially distributed, based on population size[38]	0.148 (0.133 – 0.165)	National estimates, 2017[7]
Men 15-24 years: HIV prevalence	p_{M15-24}	0.011 (0.005-0.018)	KAIS, 2012[43]	0.030 (0.0297-0.03030)	2016 estimates[32] 95% CI estimated assuming binomially distributed, based on population size[38]	0.039 (0.014 – 0.06)	AIDSInfo 2017[31]
Men 25-34 years: HIV prevalence	p_{M25-34}	0.054 (0.039-0.068)	KAIS, 2012[43]	0.060 (0.0595-0.0605)	2016 estimates[32] 95% CI estimated assuming	0.124-0.184	Min and max of 5-year age categories (full national results not yet

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
					binomially distributed, based on population size[38]		released). National estimates, 2017[33]
Men 35-49 years: HIV prevalence	p_{M35-49}	0.064 (0.051-0.076)	35 years+, KAIS, 2012[43]	0.237 (0.236-0.238)	2016 estimates[32] 95% CI estimated assuming binomially distributed, based on population size[38]	0.224-0.248	Min and max of 5-year age categories (full national results not yet released). National estimates, 2017[33]
FSW: HIV prevalence	p_{FSW}	0.293 (0.290,0.295)	2013 size estimation[35] 95% CI estimated assuming binomially distributed, based on population size	0.571 (0.566-0.576)	AIDSInfo 2017[31] 95% CI estimated assuming binomially distributed, based on population size[38]	0.689 (0.565-0.812)	FSW Johannesburg, South Africa, 2014.[44] Estimate is midpoint.0.10
AGYW: HIV prevalence	p_{AGYW}	0.03 (0.022-0.038)	KAIS, 2012[43]	0.059 (0.0586-0.0594)	2016 estimates[32]	0.102 (0.046–0.148)	AIDSInfo 2017[31]
Women 25-34 years: HIV prevalence	p_{W25-34}	0.073 (0.06-0.087)	KAIS, 2012[43]	0.182 (0.1813-0.1827)	2016 estimates[32]	0.275-0.347	Min and max of 5-year age categories (full national results not yet released). National estimates, 2017[33]
Women 35-49 years: HIV prevalence	p_{W35-49}	0.093 (0.083-0.113)	35 years+, KAIS, 2012[43]	0.282 (0.281-0.283)	2016 estimates[32]	0.303-0.394	Min and max of 5-year age categories (full national results not yet released). National estimates, 2017[33]
Behavioural parameters							
FSW: number of client partners/ year	C_{c_FSW}	320 (276-364)	Monthly liaisons x12, FSW at hotspots along	360 (234-486)	Across studies[46,47] Estimate is midpoint.	424 (312 – 504)	Mean monthly reported number of clients per FSW, multiplied by 12.[48]

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			Mombasa-Kampala highway, 2007[40] Median number in last 7 days x52 Nairobi, 2010[45] Estimate is midpoint.				
FSW: number of regular partners from male population 15-49 years/ year	C_{M15-49_FSW}	(1-4)	Nairobi, 2010[45] Point estimate not deducible as categorical data.	2.0 (0.74-4.0)	Imputed from South Africa, due to lack of data. Number of main sexual partners per 6 months, multiplied by 2.[49]	2.0 (0.74-4.0)	Number of main sexual partners per 6 months, multiplied by 2.[49]
FSW: number of sex acts per client/ year	n_{c_FSW}	1.59 (1-2.17)	FSW at hotspots along Mombasa-Kampala highway, 2007[40] Estimate is midpoint.	1 (1-1.2)	Imputed from South Africa, due to lack of data. Number of sexual encounters per client.[50]	1 (1-1.2)	Number of sexual encounters per client.[50]
FSW: number of sex acts with regular partners/ year	n_{M15-49_FSW}	96 (48-144)	Imputed from South Africa, due to lack of data.	96 (48-144)	Imputed from South Africa, due to lack of data.	96 (48-144)	Mean monthly frequency of sex acts in main partnerships, multiplied by 12.[48]
FSW: average condom consistency with clients	γ_{c_FSW}	0.773 (0.626-0.92)	Paying clients, FSW Nairobi, 2010[45] UNAIDS, 2017[31] Estimate is mid-point.	0.708 (0.455-0.961)	% reporting full adherence to condom use[51] 2017 estimates[29] Estimate is mid-point.	0.764 (0.609-0.902)	FSW Johannesburg, South Africa, 2014.[44]
FSW: average condom consistency with regular partners	γ_{M15-49_FSW}	0.463 (0.386-0.540)	Non-paying partner, Mombasa, 2007[52]	0.3375 (0.333-0.342)	Survey, 2011[53] Estimate is mid-point.	0.345 (0.173-0.548)	FSW Johannesburg, South Africa, with non-paying partner, 2014.[44]

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			Non-paying partner, Nairobi, 2010[45] Estimate is mid-point.				
FSW: probability at least 1 person in partnership has an STI – with clients	S_{c_FSW}	0.011 (0.004-0.021)	Prevalence of Neisseria gonorrhoea, FSW Nairobi, 2010[45]	0.019 (0.005-0.034)	Prevalence of Neisseria gonorrhoea, 2005[54]	0.21 (0.15-0.30)	Low: Prevalence of Chlamydia trachomatis & Neisseria gonorrhoea in Hillbrow FSW.[50] High: FSW STI prevalence, Durban.[30]
FSW: probability at least 1 person in partnership has an STI – with regular partners	S_{M15-49_FSW}	0.011 (0.004-0.021)	Prevalence of Neisseria gonorrhoea, FSW Nairobi, 2010[45]	0.019 (0.005-0.034)	Prevalence of Neisseria gonorrhoea, 2005[54]	0.21 (0.15-0.30)	Low: Prevalence of Chlamydia trachomatis & Neisseria gonorrhoea in Hillbrow FSW.[50] High: FSW STI prevalence, Durban.[30]
AGYW: number of male partners 15-24 years/ year	C_{M15-24_AGYW}	(0-4)	Estimated range, Women 15-24, 2014[16], accounting for the proportion who have never had sexual intercourse and mean lifetime partners. Point estimate not deducible as categorical data. A wider parameter	(0-4)	Estimated range, Women 15-24, 2015[15], accounting for the proportion who have never had sexual intercourse and mean lifetime partners. Point estimate not deducible as categorical data. A wider parameter	(0-4)	Estimated range, Women 15-24, 2016[55], accounting for the proportion who have never had sexual intercourse and mean lifetime partners. Point estimate not deducible as categorical data. A wider parameter range was considered in the fitting process (0-10).

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			range was considered in the fitting process (0-10).		range was considered in the fitting process (0-10).		
AGYW: number of male partners 25-34 years/ year	C_{M25-34_AGYW}	(0-4)	Estimated range, Women 15-24, 2014[16], accounting for the proportion of age-discordant relationship. Point estimate not deducible as categorical data. A wider parameter range was considered in the fitting process (0-10).	(0-4)	Estimated range, Women 15-24, 2015[15], accounting for the proportion of age-discordant relationship. Point estimate not deducible as categorical data. A wider parameter range was considered in the fitting process (0-10).	(0-4)	Estimated range, Women 15-24, 2016[55], accounting for the proportion of age-discordant relationships. Point estimate not deducible as categorical data. A wider parameter range was considered in the fitting process (0-10).
AGYW: number of sex acts male partners 15-24 years/ year	n_{M15-24_AGYW}	182 (156-208)	Imputed based on South Africa, due to lack of data	82 (156-208)	Imputed based on South Africa, due to lack of data	182 (156-208)	3-4 a week x 52, youth, with regular partner, 2000[56] Estimate is mid-point.
AGYW: number of sex acts male partners 24-34 years / year	n_{M25-34_AGYW}	48 (36-60)	Imputed based on South Africa, due to lack of data	48 (36-60)	Imputed based on South Africa, due to lack of data	48 (36-60)	3 sex acts a month, youth, non-spousal partner, 2000[56] 5 sex acts a month x12, married 18-20 year old, average number sex acts per short term partner formation, 2016[57] Estimate is mid-point

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
AGYW: average condom consistency with male partners 15-24 years	γ_{M15-24_AGYW}	0.355 (0.11-0.60)	Condom use at last sexual encounter with partner of unknown status[58] Condom use at last sexual intercourse, Women 15-24, 2014[16] Estimate is mid-point.	0.406 (0.213-0.599)	% who had intercourse in the past 12 months with a non-marital, non-cohabiting partner[15] 1-[Trial control arm, did not use condom at last sex, females,18-22 year olds[59]] Estimate is mid-point.	0.588 (0.498 - 0.677)	0.498, 0.677. Females, males. 15-24 years, condom use at last sex, 2017. [7] Estimate is mid-point.
AGYW: average condom consistency with male partners 25-34 years	γ_{M25-34_AGYW}	0.292 (0.11-0.474)	Condom use at last sexual encounter with partner of unknown status[58] Condom use at last transactional sex, Women 15-64 years, 2012[60] Estimate is mid-point.	0.299 (0.1-0.498)	Females aged <25, males aged 25+, 2005[61] Never married women, % who used condom at last sexual intercourse[15] Estimate is mid-point.	0.504 (0.473-0.534)	0.473 females 15-24 years, condom use last sex, those with more than 1 partner in the last year, 2017.[7] Estimate is mid-point.
AGYW: probability at least 1 person in partnership has an STI – with male partners 15-24 years	s_{M15-24_AGYW}	0.018 (0.002 – 0.062)	Gonorrhoea prevalence 15-24 year olds (combined study with Tanzania), 2010[62]	0.018 (0.01 – 0.029)	Gonorrhoea prevalence 15-24 year olds, 2001[62]	0.018 (0.008– 0.041)	Maximum of prevalence of gonorrhoea in 15-24 year old males and females
AGYW: probability at least 1 person in partnership has an STI – with male partners 25-34 years	s_{M25-34_AGYW}	0.009 (0.001 - 0.032)	Gonorrhoea prevalence 25-49 year olds (combined study	0.025 (0.018 – 0.036)	Gonorrhoea prevalence 25-49 year olds, 2001[62]	0.05 (0.022-0.04)	Gonorrhoea prevalence 25-49 year olds, 2010[62] (greater

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			with Tanzania), 2010[62]				than 15-24 years estimate above)
Women 25-34 years: number of male partners 25-34 years/ year	C_{M25-34_W25-3}	1.96 (0.92-3.0)	Lower bound as for Zimbabwe Estimated upper bound, Women 25-29, 30-39, accounting for mean lifetime partners, 2014[16] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).	1.96 (0.92-3.0)	Total partnerships in last 12 months reported by adult women, 2005[63] Estimated upper bound, Women 25-29, 30-39, accounting for mean lifetime partners, 2015[15] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).	2.02 (1.03–3.0)	Total partnerships in last 12 months reported by adult women, 2006[63] Estimated upper bound, Women 25-29 and 30-39, accounting for mean lifetime partners, 2016[55] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).
Women 25-34 years: number of sex acts male partners 24-34 years / year	n_{M25-34_W25-3}	93 (54-132)	Average number of sex acts per partner per year, before intervention, 1998, Kenya[64] Upper bound imputed from South Africa due to lack of data Estimate is mid-point.	96 (60-132)	Imputed from South Africa due to lack of data	96 (60-132)	Mean 5 sex acts a month x 12, 18-40 year old women, KwaZulu-Natal, 2010[65] 2.54 mean sex acts a week x52, women, 2007[66] Estimate is mid-point.
Women 25-34 years: average condom consistency with male partners 25-34 years	γ_{M25-34_W25-3}	0.183 (0.038-0.328)	Women 15-64 years, Married/	0.295 (0.07-0.520)	Females ages 25+, males aged 25+, 2005[61]	0.344 (0.324–0.366)	Condom use at last sex, 25-49 years, 2012[67]

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			Coinhabiting, 2012[60] Women 15-64 years, Casual/Other, 2012[60] Estimate is mid-point.		Condom use during last sexual intercourse, women reporting 2+ partners in last 12 months, max(25-29 year olds, 30-39 year olds)[15] Estimate is mid-point.		
Women 25-34 years: probability at least 1 person in partnership has an STI – with male partners 25-34 years	s_{M25-34_W25-3}	0.009 (0.001 - 0.032)	Gonorrhoea prevalence 25-49 year olds (combined study with Tanzania), 2010[62]	0.025 (0.018 – 0.036)	Gonorrhoea prevalence 25-49 year olds, 2001[62]	0.05 (0.022-0.04)	Gonorrhoea prevalence 25-49 year olds, 2010[62]
For model structural sensitivity analysis: Women 25-34 years: number of male partners 35-49 years/ year	C_{M35-49_W25-3}	50% of C_{M35-49_W35-49}	As below	50% of C_{M35-49_W35-49}	As below	50% of C_{M35-49_W35-49}	As below
For model structural sensitivity analysis: Women 25-34 years: number of sex acts male partners 35-49 years / year	n_{M35-49_W25-3}	n_{M35-49_W35-49}	As below	n_{M35-49_W35-49}	As below	n_{M35-49_W35-49}	As below
For model structural sensitivity analysis: Women 25-34 years: average condom consistency with male partners 35-49 years	γ_{M35-49_W25-3}	γ_{M25-34_W25-34} (same parameter value as γ_{M35-49_W35-49})	As above	γ_{M25-34_W25-34} (minimum of this and parameter value of γ_{M35-49_W35-49})	As above	γ_{M25-34_W25-34} (same parameter value as γ_{M35-49_W35-49})	As above

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
For model structural sensitivity analysis: Women 25-34 years: probability at least 1 person in partnership has an STI – with male partners 35-49 years	s_{M35-49_W25-3}	s_{M25-34_W25-34} (same parameter value as s_{M35-49_W35-49})	As above	s_{M25-34_W25-34} (same parameter value as s_{M35-49_W35-49})	As above	s_{M25-34_W25-34}(same parameter value as s_{M35-49_W35-49})	As above
Women 35-49 years: number of male partners 35-49 years/ year	C_{M35-49_W35-4}	1.96 (0.92-3.0)	Lower bound as for Zimbabwe Estimated upper bound, Women 30-39, 40-49, accounting for mean lifetime partners, 2014[16] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).	1.96 (0.92-3.0)	Total partnerships in last 12 months reported by adult women, 2005[63] (no data to calc 95% CI) Estimated upper bound for maximum women 30-30, 40-49, accounting for mean lifetime partners, 2015[15] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).	2.02 (1.03–3.0)	Total partnerships in last 12 months reported by adult women, 2006[63] Estimated upper bound, Women 30-39, 40-49, accounting for mean lifetime partners, 2016[55] Estimate is mid-point. A wider parameter range was considered in the fitting process (0-10).
Women 35-49 years: number of sex acts male partners 35-49 years / year	n_{M35-49_W35-4}	93 (54-132)	Average number of sex acts per partner per year, before intervention, 1998, Kenya[64] Upper bound imputed from	96 (60-132)	Imputed from South Africa due to lack of data	96 (60-132)	Mean 5 sex acts a month x 12, 18-40 year old women, KwaZulu-Natal, 2010[65] 2.54 mean sex acts a week x52, women, 2007[66] Estimate is mid-point.

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			South Africa due to lack of data Estimate is mid-point.				
Women 35-49 years: average condom consistency with male partners 35-49 years	γ_{M35-49_W35-4}	0.183 (0.038-0.328)	Women 15-64 years, Married/ Coinhabiting, 2012[60] Women 15-64 years, Casual/Other, 2012[60] Estimate is mid-point.	0.354 (0.07-0.638)	Females ages 25+, males aged 25+, 2005[61] Condom use during last sexual intercourse, women reporting 2+ partners in last 12 months, max(30-39year olds, 40-49) year olds[15] Estimate is mid-point.	0.344 (0.324–0.366)	Condom use at last sex, 25-49 years, 2012[67]
Women 35-49 years: probability at least 1 person in partnership has an STI – with male partners 35-49 years	s_{M35-49_W35-4}	0.009 (0.001 - 0.032)	Gonorrhoea prevalence 25-49 year olds (combined study with Tanzania), 2010[62]	0.025 (0.018 – 0.036)	Gonorrhoea prevalence 25-49 year olds, 2001[62]	0.05 (0.022-0.04)	Gonorrhoea prevalence 25-49 year olds, 2010[62]
Clients of FSW: proportion of HIV+ individuals virally supressed	ϑ_c	0.358 (0.3222-0.3938)	All ages, not disaggregated by sex (only data available), 2017[68]. Low and high values not reliably calculable binomially, as	0.489 (0.4401-0.5379)	2016 estimates[32]. Low and high values not reliably calculable binomially, as calculated based on ART cascade with unknown range at	0.508 (0.451 – 0.564)	Prevalence of viral load suppression, 15-49 years, 2017.[7] Estimate is mid-point

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			calculated based on ART cascade with unknown range at higher cascade levels, so taking low and high to be +/- 10% of point estimate Same for below viral suppression data.		higher cascade levels, so taking low and high to be +/- 10% of point estimate Same for below viral suppression data.		
Men in general population 15-49 years: proportion of HIV+ individuals virally supressed	ϑ_{M15-49}	0.358 (0.3222-0.3938)	All ages, not disaggregated by sex (only data available), 2017[68]	0.489 (0.4401-0.5379)	2016 estimates[32]	0.508 (0.451 – 0.564)	Prevalence of viral load suppression, 2017.[7] Estimate is mid-point
Men 15-24 years: proportion of HIV+ individuals virally supressed	ϑ_{M15-24}	0.358 (0.3222-0.3938)	All ages, not disaggregated by sex (only data available), 2017[68]	0.401 (0.3609-0.4411)	2016 estimates[32]	0.491 (0.4419-0.5401)	Prevalence of viral load suppression, 2017.[7] Low and high values not reliably calculable binomially, as calculated based on ART cascade with unknown range at higher cascade levels, so taking low and high to be +/-10% of point estimate. Same for below viral suppression data.
Men 25-34 years: proportion of HIV+ individuals virally supressed	ϑ_{M25-34}	0.358 (0.3222-0.3938)	All ages, not disaggregated by sex (only data available), 2017[68]	0.365 (0.3285-0.4015)	2016 estimates[32]	0.415 (0.3735-0.4565)	Prevalence of viral load suppression, 2017.[7]

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
Men 35-49 years: proportion of HIV+ individuals virally supressed	ϑ_{M35-49}	0.358 (0.3222-0.3938)	All ages, not disaggregated by sex (only data available), 2017[68]	0.562 (0.5058-0.6182)	2016 estimates[32]	0.522 (0.4698-0.5742)	Prevalence of viral load suppression, 35-44 years, 2017.[7]
Clients of FSW: proportion circumcised	τ_c	0.962 (0.9618-0.9621)	Males 15-49, 2014[16] 95% CI estimated assuming binomially distributed, based on population size[37]	0.143 (0.1426-0.1434)	Males 15-49, 2015[15] 95% CI estimated assuming binomially distributed, based on population size[38]	0.138 (0.1378-0.1382)	15-64 years, 2017.[7] 95% CI estimated assuming binomially distributed, based on population size[39]
Men in general population 15-49 years: proportion circumcised	τ_{M15-49}	0.962 (0.9618-0.9621)	Males 15-49, 2014[16] 95% CI estimated assuming binomially distributed, based on population size[37]	0.143 (0.1426-0.1434)	Males 15-49, 2015[15]	0.138 (0.1378-0.1382)	15-64 years, 2017.[7] 95% CI estimated assuming binomially distributed, based on population size[39]
Men 15-24 years: proportion circumcised	τ_{M15-49}	0.914 (0.9136-0.9144)	Males 15-24, 2014[16] 95% CI estimated assuming binomially distributed, based on population size[37]	0.188 (0.1873-0.18878)	Males 15-24, 2015[15]	0.702 (0.7014-0.7026)	2017.[7] 95% CI estimated assuming binomially distributed, based on population size[39]
Men 25-34 years: proportion circumcised	τ_{M25-34}	0.939 (0.934-0.946)	Males 25-29 and Males 30-39, 2014[16] Estimate is weighted average	0.107 (0.10-0.116)	Males 25-29 and Males 30-39, 2015[15] Estimate is weighted average	0.628 (0.6280-0.6284)	2017.[7] 95% CI estimated assuming binomially distributed, based on population size[39]
Men 35-49 years: proportion circumcised	τ_{M35-49}	0.931 (0.919-0.94)	Males 30-39 and Males 40-49, 2014[16]	0.111 (0.104-0.116)	Males 30-39 and Males 40-49, 2015[15]	0.626 (0.6255-0.6265)	35-44 years, 2017.[7] 95% CI estimated assuming binomially

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
			Estimate is weighted average				distributed, based on population size[39]
PrEP parameters							
FSW: average 12-month PrEP program retention	r_{FSW}					22%	TAPS[3]
FSW: average self-reported adherence	α_{FSW}					70-85%	TAPS[3]
FSW: HIV prevention-effective PrEP adherence	θ_{FSW}	Risk reduction of **0.79–0.99** ≥4 out 7 ($\geq 57\%$) reported daily doses of PrEP a week Risk reduction of **0.73–1.06** ≥6 out 7 ($\geq 86\%$) reported daily doses of PrEP a week For self-reported adherence of 70-85%, assume risk reduction range spanning range of both risk reduction estimates: 0.73-0.99			Partners Demonstration Project prevention-effective adherence analysis - females[69]		
Transmission Probabilities							
Per sex act probability of HIV transmission from a chronically infected female to a male partner	β_f	0.00085 (0.0006 - 0.0011)	Per-act HIV-1 transmission probability, male to female[5] Estimate is mid-point	As stated			
Average reduction in probability HIV transmission on ART	ϱ	0.945 (0.9 – 0.99)	Minimum and maximum across studies[70] Estimate is mid-point				
HIV risk-reduction efficacy of condoms	ε	0.85 (0.8 - 0.9)	With consistent use[71] and with consistent use[72] Estimate is mid-point				

Parameter	Symbol	Kenya		Zimbabwe		South Africa	
		Estimate (Low-High)	References	Estimate (Low-High)	References	Estimate (Low-High)	References
Multiplicative increase in per sex act probability of HIV transmission in the presence of an STI	δ	4 (2-6)	Combined study effectiveness estimate across STDs, and range spanning individual STD combined study effect estimates[73] Estimate is mid-point				
Average reduction in probability of HIV transmission to women, when the male partner has been circumcised	σ_f	0.1 (0–0.2)	Male circumcision; estimates of HIV infection in women.[74] Estimate is mid-point				

Table S2: Parameters and data sources used in the parameterisation and fitting of the models. *Point estimates are stated first with lower and upper bounds used in the latin hypercube fitting in brackets.*

Supplementary Results

Model calibration

The model fits to HIV incidence for each country and high-risk women population are shown in Figures S1-3.

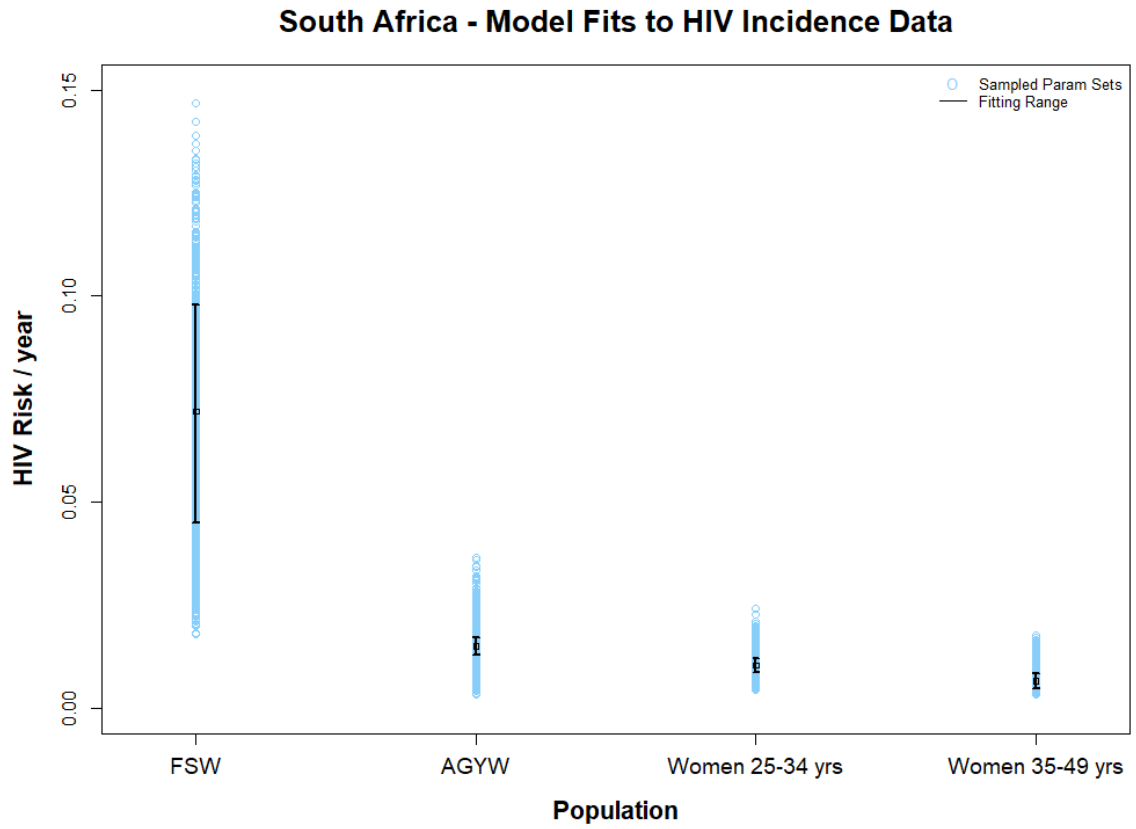


Figure S1: Model Fits to HIV Incidence Data for South Africa.
The model outcomes across the parameter ranges simulated through latin hypercube sampling are show in blue. The black book-ended lines show the 95% confidence intervals around national HIV incidence estimates (HIV risk per year), and the model outcomes that fit within this range are considered to be fits to data. The model outcomes and fitting ranges are shown distinctly for the four high-risk women populations: female sex workers (FSW), adolescent girls and young women aged 15-24 years (AGYW), women aged 25-34 years and women aged 35-49 years.

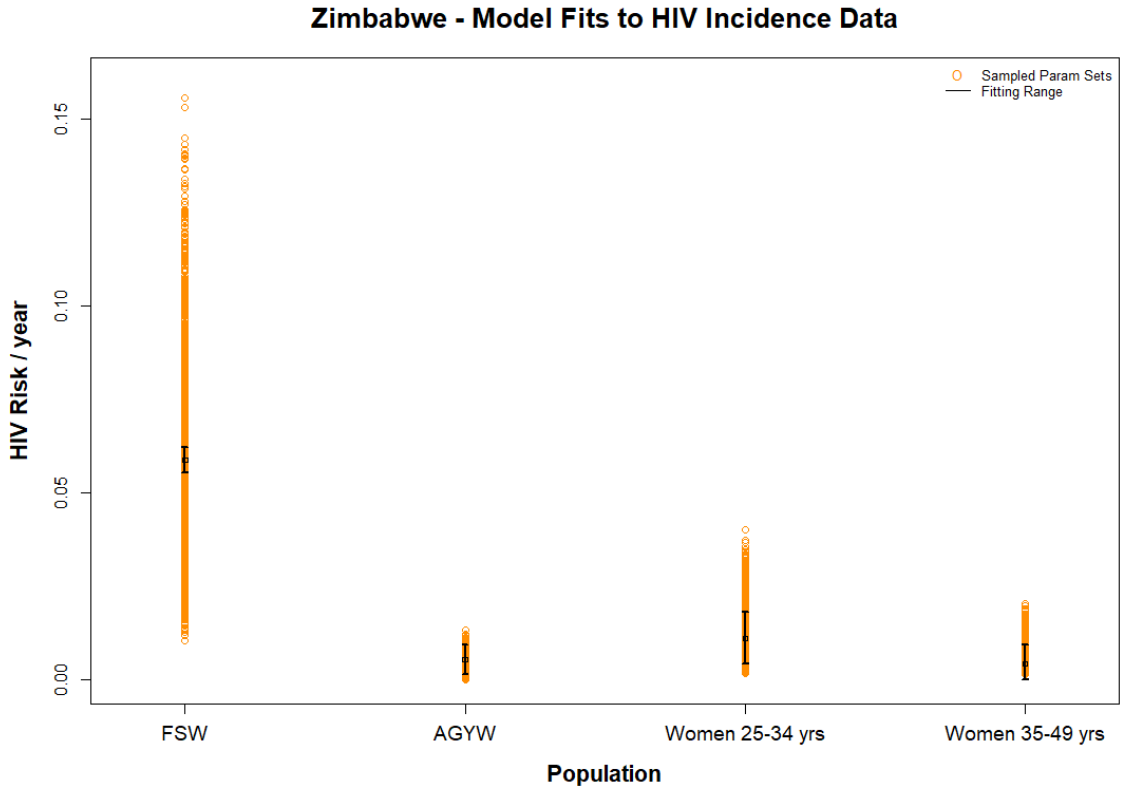


Figure S2: Model Fits to HIV Incidence Data for Zimbabwe.

The model outcomes across the parameter ranges simulated through latin hypercube sampling are show in orange. The black book-ended lines show the 95% confidence intervals around national HIV incidence estimates (HIV risk per year), and the model outcomes that fit within this range are considered to be fits to data. The model outcomes and fitting ranges are shown distinctly for the four high-risk women populations: female sex workers (FSW), adolescent girls and young women aged 15-24 years (AGYW), women aged 25-34 years and women aged 35-49 years.

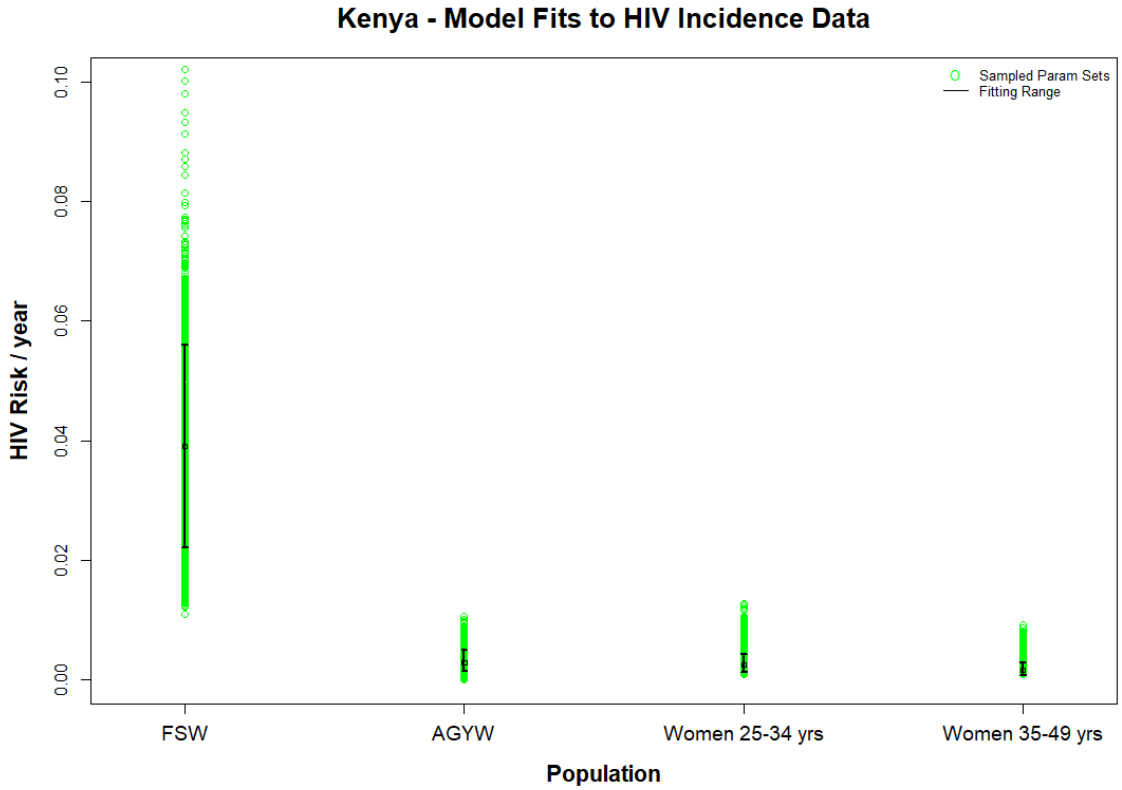


Figure S3: Model Fits to HIV Incidence Data for Kenya.
The model outcomes across the parameter ranges simulated through latin hypercube sampling are show in green. The black book-ended lines show the 95% confidence intervals around national HIV incidence estimates (HIV risk per year), and the model outcomes that fit within this range are considered to be fits to data. The model outcomes and fitting ranges are shown distinctly for the four high-risk women populations: female sex workers (FSW), adolescent girls and young women aged 15-24 years (AGYW), women aged 25-34 years and women aged 35-49 years.

Supplementary Results

Figure S4 illustrates the relative cost at which PrEP will be equally as cost-effective to scale-up in a lower-risk group as it will be in a high-risk group, in the case that HIV prevalence in the higher-risk women partner population is 20%. It is demonstrated in four scenarios: underlying HIV prevalence in the lower-risk women's partner population of 5%, 10%, 15% and 20%. This figure corresponds to *Figure 2* in the main text, which demonstrates that case that HIV prevalence in the higher-risk women's partner population is 40%.

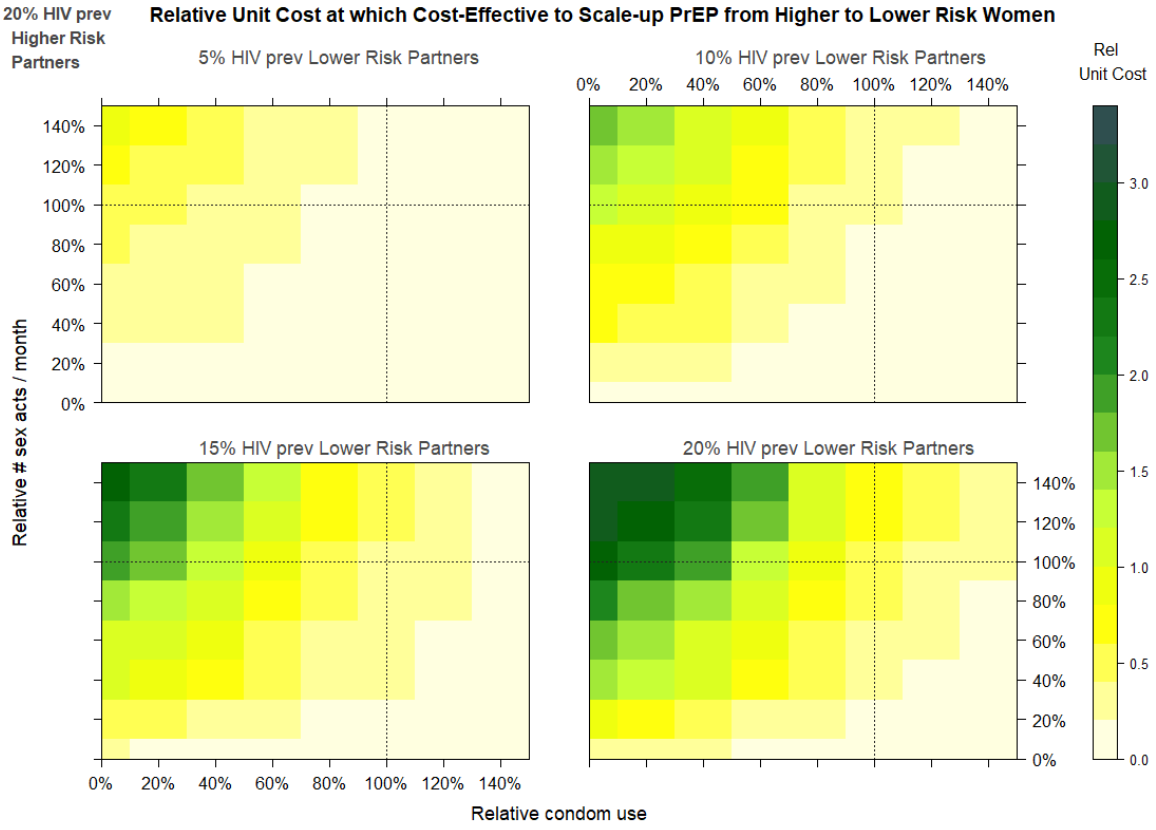


Figure S4: Relative unit cost at which it is cost-effective to scale-up PrEP from a higher- to lower-risk women group. *The heatmaps show the relative unit cost at which it is cost-effective to scale-up PrEP from a higher- to a lower-risk group. The relative unit cost at which PrEP is cost-effective is shown by the relative average condom use in the lower-risk group compared to the higher-risk group (x-axis), and the relative number of sex acts a month for women in the lower-risk group compared to the higher-risk group (y-axis). The unit cost of PrEP in the lower-risk group relative to the higher-risk group at which PrEP is equally cost-effective between the two groups is shown by colour, according to the colour key on the right-hand side of the graph. A colour within the yellow spectrum denotes that the relative unit cost of PrEP in the lower-risk group relative to the higher-risk group has to be less than 1 for it to be equally as cost cost-effective. A colour within the green spectrum denotes that the relative unit cost of PrEP in the lower-risk group relative to the higher-risk group will be greater than 1 for it to be equally as cost cost-effective. The 4 heatmaps correspond respectively (left to right, top to bottom) to underlying partner HIV prevalence of 5%, 10%, 15% and 20% in the lower-risk group's partner population and all of them corresponding to 20% HIV prevalence in the higher-risk women's partner population. The heatmaps are calculated using equation (S1.5) from the Supplementary Materials: Methods, assuming that women's partners are drawn from a single population each. The higher-risk group are assumed to have 12-month PrEP program retention levels of 22%[3] and adherence levels of 70-85% (corresponding to a risk reduction of 73-99%[69]). The PrEP program retention levels for the lower-risk group were simulated between +/- 25% the retention of the higher-risk group.[4] For those lower-risk women retained in the PrEP program, it was assumed that PrEP adherence was the same as the higher-risk group.*

Comparison of the Maximum Unit Costs of PrEP in Lower-Risk Groups Relative to Unit Costs FSW to be Equally as Cost-Effective, with Estimates of Current Relative Unit Costs

		High Risk Women Population		
Country	**Unit Cost Relative to FSWs**	**AGYW**	**Women 25-34 years**	**Women 35-49 years**
South Africa	Maximum Relative Unit Cost to be Cost-Effective	23.3 % (13.3 % , 36.8 %)	16.2 % (9.1 % , 26 %)	10.5 % (5.7 % , 18 %)
	Estimated Current Relative Unit Cost	79.6 % (72.4 % , 86.7 %)	68.7 % (62.7 % , 75.8 %)	48.3 % (42.4 % , 54.7 %)
	Difference (relative to FSW Unit Cost)	-56.2 % (-69.2 % , -40.4 %)	-52.2 % (-62.5 % , -41.4 %)	-37.6 % (-45.8 % , -28.7 %)
	Difference (relative to own Unit Cost)	-70.8 % (-83.4 % , -53.2 %)	-76.2 % (-87.0 % , -62.6 %)	-78.4 % (-88.1 % , -61.8 %)
Zimbabwe	Maximum Relative Unit Cost to be Cost-Effective	7.1 % (2.7 % , 14.9 %)	17.7 % (7.1 % , 31.2 %)	11 % (5.5 % , 17.2 %)
	Estimated Current Relative Unit Cost	75.6 % (70.8 % , 80.8 %)	63 % (58 % , 67.7 %)	38.8 % (34.1 % , 42.7 %)
	Difference (relative to FSW Unit Cost)	-67.7 % (-75.1 % , -60.1 %)	-44.6 % (-58.3 % , -31.1 %)	-28.1 % (-35.3 % , -18.7 %)
	Difference (relative to own Unit Cost)	-90.4 % (-96.5 % , -80.6 %)	-71.8 % (-88.9 % , -50.8 %)	-72 % (-86.1 % , -53.6 %)
Kenya	Maximum Relative Unit Cost to be Cost-Effective	8.1 % (3.9 % , 18.5 %)	9.1 % (3.6 % , 17.7 %)	6.4 % (3.1 % , 11.6 %)
	Estimated Current Relative Unit Cost	90.3 % (86.2 % , 94.8 %)	74.9 % (71.1 % , 78.4 %)	48.1 % (45.1 % , 51.6 %)
	Difference (relative to FSW Unit Cost)	-81.5 % (-89 % , -71 %)	-66 % (-73.4 % , -57.5 %)	-41.7 % (-46.4 % , -36.2 %)
	Difference (relative to own Unit Cost)	-91 % (-95.7 % , -79.6 %)	-88 % (-95.3 % , -76.6 %)	-86.7 % (-93.7 % , -75.4 %)

Table S3: Comparison of the Maximum Unit Costs of PrEP in Lower-Risk Groups Relative to Unit Costs FSW to be Equally as Cost-Effective, with Estimates of Current Relative Unit Costs. *The table shows the maximum relative unit costs of PrEP in AGYW, women 25-34 years and women 35-49 years relative to the unit costs of PrEP for FSW, for PrEP to be equally as cost-effective (calculated using equation S1.5 in Supplementary Materials: Methods). It compares this to the estimated current relative unit costs between the populations, calculated using the data set out in Table S2. The table shows the difference between these two estimates (relative to the FSW unit cost of PrEP). It also shows what this difference represents relative to the group's (i.e. AGYW, women 25-34 years or women 35-49 years) own unit cost, which is equivalent to the % the unit cost would have to drop for PrEP to be equally as cost-effective as for FSW. The comparisons are shown separately for South Africa, Zimbabwe and Kenya. The values shown in the table outside the brackets are the median values, and the values shown in the brackets are the 95% credible intervals (CrIs).*

Table S4 sets out the estimated number of infections that could be averted a year due to PrEP in each high-risk women population group, in each country, for every $100,000 available for PrEP programming, at the PrEP unit costs stated in Table S2. These data correspond to Figure 4 in the main text.

For each $100k available for PrEP programming a year, the number of HIV infections that could be averted due to PrEP

	High Risk Women Population			
Country	FSW	AGYW	Women 25-34 years	Women 35-49 years
South Africa	5.7 (3.8 , 8.8)	1.7 (1.1 , 2.4)	1.3 (0.9 , 2)	1.2 (0.8 , 2)
Zimbabwe	3.4 (2.9 , 4.1)	0.3 (0.1 , 0.7)	1 (0.4 , 1.8)	0.9 (0.5 , 1.6)
Kenya	1.5 (0.9 , 2.4)	0.1 (0.1 , 0.3)	0.2 (0.1 , 0.3)	0.2 (0.1 , 0.3)

Table S4: Median and 95% credible intervals (95% CrIs) of the relative number of infections that could be averted a year due to PrEP for each $100k available for PrEP programming.
The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the number of HIV infections that could be averted a year due to PrEP, for each $100k available for PrEP programming, for FSW, AGYW, women 25-34 years or women 35-49 years. The relative number of infections that could be averted is calculated using equation S2.10 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] The unit costs of PrEP for each high-risk woman group are as stated in Table S2. AGYW is used as shorthand for adolescent girls and young women 15-24 years.

In South Africa, $100,000 could avert a median 5.7 infections a year or 0.2% (95% CrI: 0.1%, 0.4%) of the total infections a year due to PrEP in FSW; median 1.7 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of the total infections a year in AGYW; mediaan 1.3 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 25-34 years; and median 1.2 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 35-49 years. This highlights, that to maximise cost-effectiveness on an individual basis, PrEP would be scaled-up first in FSW, then AGYW, then women 35-49 years, then women 25-34 years.

In Zimbabwe, $100,000 could avert a median 3.4 infections a year or 0.3% (95% CrI: 0.3%, 0.4%) of the total infections a year due to PrEP in FSW; median 0.3 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of the total infections a year in AGYW; median 1.0 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 25-34 years; and median 0.9 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 35-49 years. This highlights, that to maximise cost-effectiveness on an individual basis, PrEP would be scaled-up first in FSW, then women 25-34 years, then women 35-49 years, then AGYW.

In Kenya, $100,000 could avert a median 1.5 infections a year or <0.1% (95% CrI: <0.1%, 0.1%) of the total infections a year due to PrEP in FSW; median 0.1 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of the total infections a year in AGYW; median 0.2 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 25-34 years; and median 0.2 infections a year or <0.1% (95% CrI: <0.1%, <0.1%) of total infections a year in women 35-49 years. This highlights, that to maximise cost-effectiveness on an individual basis, PrEP would be scaled-up first in FSW, then women 25-34 years and women 35-49 years, and then AGYW.

Figure S5 shows, the proportion of the total number of HIV infections that could be averted a year for each $100k available for PrEP programming.. The corresponding data to the figure are set out in Table S5 below.

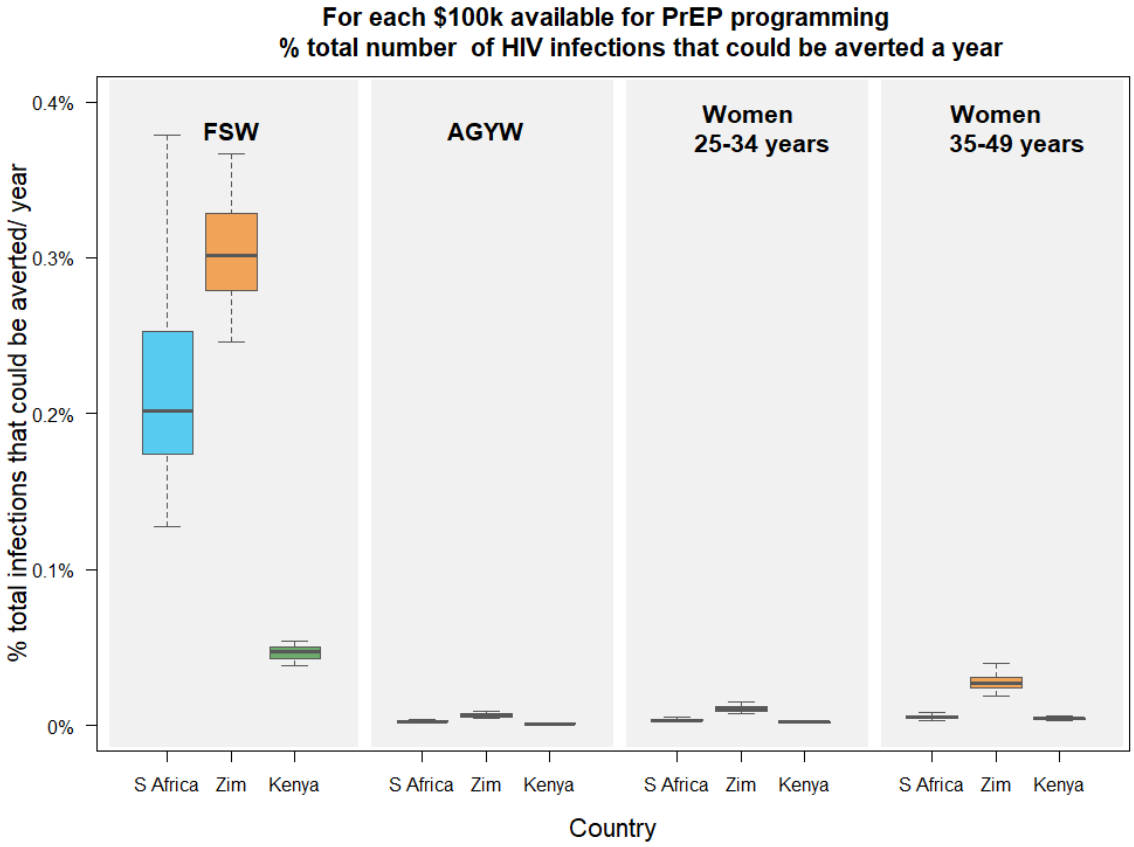


Figure S5: Boxplot showing for each $100k available for PrEP programming, the proportion of the total number of HIV infections that could be averted a year with these funds.

The boxplot shows for each $100k available for PrEP programming, the proportion of infections that could be averted a year with these funds for each of HIV negative FSW, AGYW, women 25-34 years or women 35-49 years. The proportion of total infections that could be averted a year are shown, grouped left to right, for FSW, AGYW, women 25-34 years and women 35-49 years. Within each age grouping, the results are show by country, left to right, for South Africa (in blue), Zimbabwe (in orange) and Kenya (in blue). The proportion of total infections that could be averted a year are calculated using equation S2.11 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] The abbreviations used in the graph are as follows: AGYW denotes adolescent girls and young women 15-24 years, S Africa denotes South Africa and Zim denotes Zimbabwe.

For each $100k available for PrEP programming,
the proportion of HIV infections that could be averted a year

	High Risk Women Population			
Country	FSW	AGYW	Women 25-34 years	Women 35-49 years
South Africa	0.2 % (0.1 % , 0.4 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)
Zimbabwe	0.3 % (0.3 % , 0.4 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)
Kenya	0 % (0 % , 0.1 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)	0 % (0 % , 0 %)

Table S5: Median and 95% credible intervals (95% CrIs) of the proportion of the total number of HIV infections that could be averted a year with each $100k available for PrEP programming.

Figure S6 sets out the number of HIV negative individuals in each high-risk woman population that would need to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW. The corresponding data to the figure are set out in Table S6.

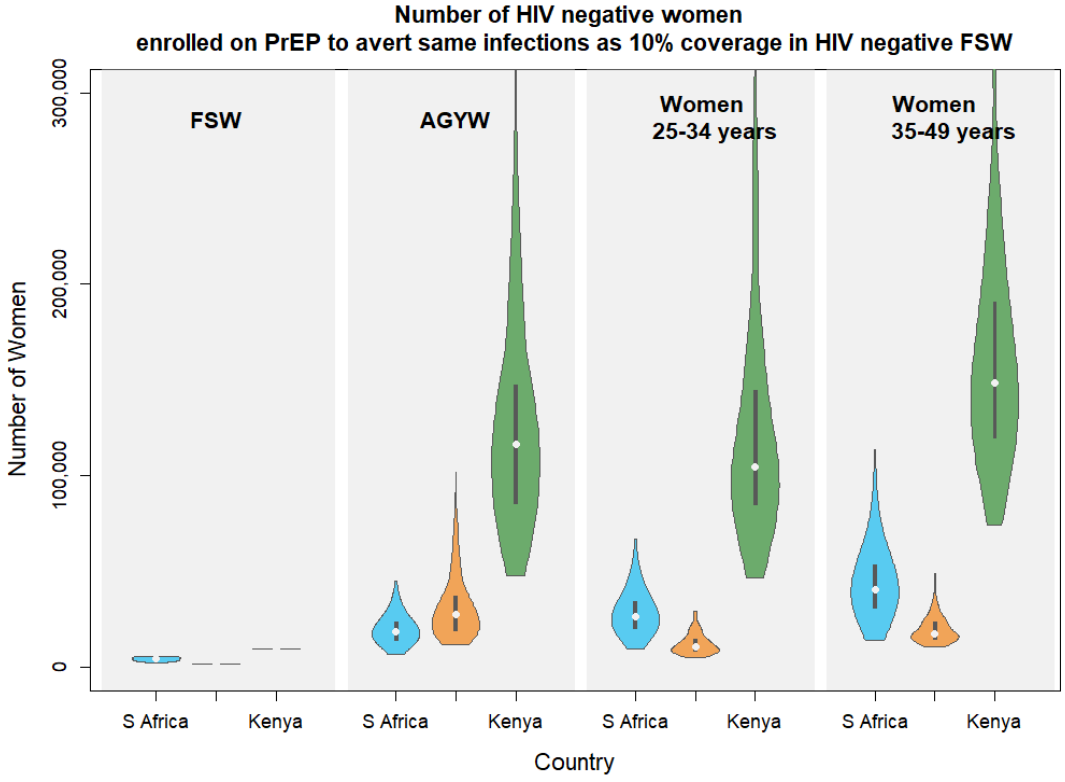


Figure S6: Number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW.
The violin plot shows number of HIV negative AGYW, women 25-34 years or women 35-49 years in the population that would have to be enrolled in a PrEP program in order to achieve the same number of infections averted over 12 months as with 10% of the HIV negative FSW population enrolled in a PrEP program. As a comparison, the number of women represented by 10% of HIV negative FSW is shown in the far left hand side block of the figure. The number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW is then grouped left to right, for AGYW, women 25-34 years or women 35-49 years. Within each age grouping, the results are show by country, left to right, for South Africa (in blue), Zimbabwe (in orange) and Kenya (in blue). In the violin plots, the white dots represent the median values, the thick black vertical lines represent the interquartile range, the vertical length of the violin represents the range of values and the width of the violin represents the frequency with which those values occur. Where two horizontal grey lines are shown instead of a violin, it indicates that the range of

values is limited in variation. The number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections averted as 10% PrEP program coverage in HIV negative FSW is calculated using equation S2.7 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] The abbreviations used in the graph are as follows: AGYW denotes adolescent girls and young women 15-24 years, S Africa denotes South Africa and Zim denotes Zimbabwe.

Number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW

	High Risk Women Population			
Country	FSW (comparator)	AGYW	Women 25-34 years	Women 35-49 years
South Africa	4359 (2774, 5914)	18531 (9594, 37052)	31798 (16411, 65199)	52240 (26287 , 111053)
Zimbabwe	1933 (1910, 1953)	27496 (12962, 72904)	14933 (8535, 37453)	36978 (23578, 73838)
Kenya	9477 (9449, 9513)	116565 (51258, 246376)	151830 (78163, 380590)	274531 (149378, 567706)

Table S6: Median and 95% credible interval (CrIs) of the number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW.
The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the number of HIV negative AGYW, women 25-34 years or women 35-49 years in the population that would have to be enrolled in a PrEP program in order to achieve the same number of infections averted over 12 months as with 10% of the HIV negative FSW population enrolled in a PrEP program. As a comparison, the median and 95% CrIs of the numbers of women represented by 10% of HIV negative FSW is shown in the far left column of the table. The median and 95% CrIs of the numbers of HIV negative women needed to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW is then grouped left to right in the 2nd to 4th columns of the table, for AGYW, women 25-34 years or women 35-49 years respectively. Within each age grouping, the results are show by country, for South Africa, Zimbabwe and Kenya in rows 1 to 3 respectively. The number of HIV negative women needed to be enrolled on PrEP to avert the same number of infections averted as 10% PrEP program coverage in HIV negative FSW is calculated using equation S2.7 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3]

Figure S7 shows PrEP program coverage in HIV negative individuals in each high-risk woman population that would need to be enrolled on PrEP to avert the same number of infections as 10% PrEP program coverage in HIV negative FSW. The corresponding data are shown in Table S7 below.

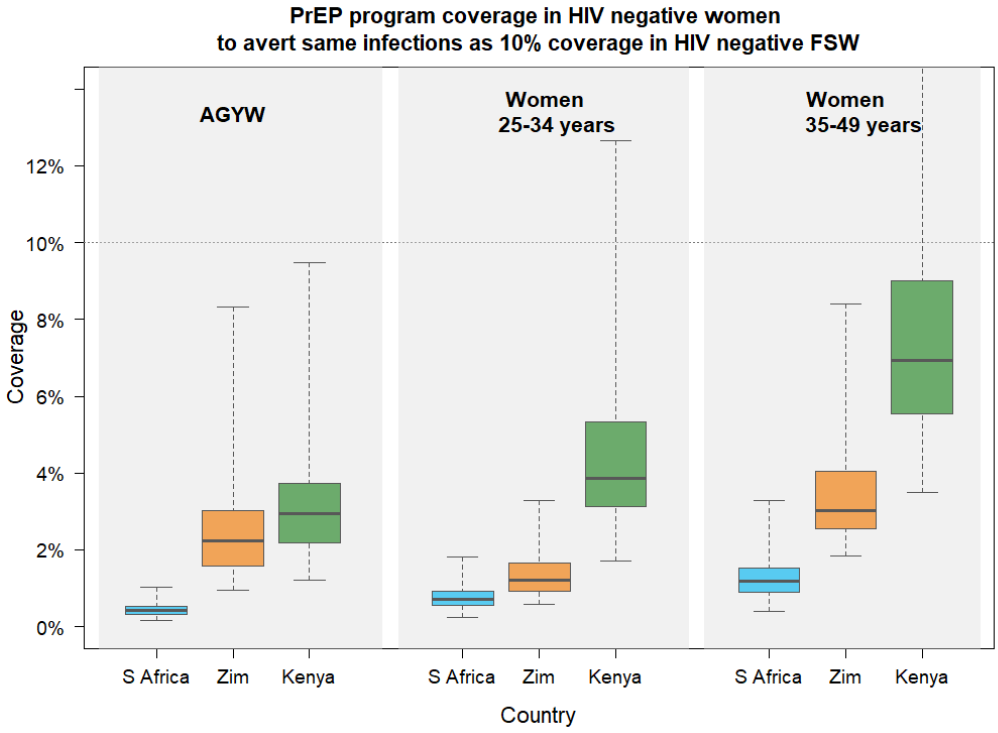


Figure S7: Boxplot of the PrEP program coverage in HIV negative women needed to avert the same number of HIV infections as 10% coverage in HIV negative FSW.

The boxplot shows the PrEP program coverage in HIV negative AGYW, women 25-34 years or women 35-49 years to avert the same number of infections as 10% program coverage in HIV negative FSW. The PrEP program coverage levels are shown, grouped left to right, for AGYW, women 25-34 years or women 35-49 years. Within each age grouping, the results are show by country, left to right, for South Africa (in blue), Zimbabwe (in orange) and Kenya (in blue). The coverage levels are calculated using equation S2.7 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] The abbreviations used in the graph are as follows: AGYW denotes adolescent girls and young women 15-24 years, S Africa denotes South Africa and Zim denotes Zimbabwe.

PrEP program coverage in HIV negative women to avert the same number of infections as 10% coverage in HIV negative FSW

	High Risk Women Population		
Country	AGYW	Women 25-34	Women 35-49 years
South Africa	0.4 % (0.2 % , 0.8 %)	0.7 % (0.4 % , 1.4 %)	1.2 % (0.6 % , 2.5 %)
Zimbabwe	2.2 % (1.1 % , 5.9 %)	1.2 % (0.7 % , 3.1 %)	3 % (1.9 % , 6 %)
Kenya	2.9 % (1.3 % , 6.3 %)	3.8 % (2 % , 9.7 %)	6.9 % (3.8 % , 14.4 %)

Table S7: Median and 95% credible intervals (95% CrIs) of the PrEP program coverage in HIV negative women to avert the same number of infections as with 10% PrEP program coverage in HIV negative FSW.

The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the PrEP program coverage in AGYW, women 25-34 years or women 35-49 years to achieve the same number of infections a year as 10% PrEP program coverage in HIV negative FSW. The PrEP program coverage is calculated using equation S2.7 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] AGYW is used as shorthand for adolescent girls and young women 15-24 years.

Table S8 shows the relative number of infections that could be averted a year with PrEP at equal coverage levels in AGYW, women 25-34 years and women 35-49 years as in FSW. These data correspond to Figure 5 in the main text.

Relative number of infections that could be averted a year on PrEP with equal program coverage as in FSW

	High Risk Women Population		
Country	AGYW	Women 25-34 years	Women 35-49 years
South Africa	24 (12 , 45)	14 (7 , 27)	8 (4 , 17)
Zimbabwe	4 (2 , 9)	8 (3 , 14)	3 (2 , 5)
Kenya	3 (2 , 8)	3 (1 , 5)	1 (1 , 3)

Table S8: Median and 95% credible intervals (95% CrIs) of the relative number of infections that could be averted a year on PrEP with equal program coverage as in FSW.
The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the relative number of infections that could be averted a year on PrEP in AGYW, women 25-34 years or women 35-49 years relative to the number that could be averted in FSW with equal PrEP program coverage. The relative number of infections that could be averted is calculated using equation S2.9 from Supplementary Materials and assumes that 12-month PrEP program retention in AGYW, women 25-34 years or women 35-49 years is within +/-25% of retention levels for FSW, taken to be 22%, in line with the results of the TAPS demonstration project.[3] AGYW is used as shorthand for adolescent girls and young women 15-24 years.

Sensitivity analysis

25% less PrEP-adherence-related HIV risk reduction across all women groups

Table S9 shows the percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all women groups. These results are a comparison of the results set out in Table S3 (top row for each country) with what the results would be if the same analysis were repeated with 25% less PrEP-adherence-related HIV risk reduction across all women groups.

% Change in Maximum Unit Cost at which PrEP is equally as Cost-Effective as for FSW, with 25% reduced HIV risk-reduction across all Groups

	High Risk Women Population		
Country	AGYW	Women 25-34	Women 35-49 years
South Africa	0.001% (0.000%, 0.003%)	-0.002% (-0.002%, 0.000%)	0.000% (-0.002%, 0.000%)
Zimbabwe	0.001% (-0.002%, 0.002%)	-0.002% (-0.001%, 0.001%)	-0.001% (-0.002%, -0.001%)
Kenya	0.000% (0.000%, 0.001%)	0.001% (0.000%, 0.002%)	0.000% (0.000%, 0.000%)

Table S9: Percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all women groups.
The table shows the percentage change in the maximum relative unit costs of PrEP in AGYW, women 25-34 years and women 35-49 years relative to the unit costs of PrEP for FSW, for PrEP to be equally as cost-effective (calculated using equation S1.5 in Supplementary Materials: Methods), if the PrEP-adherence-associated HIV risk reduction were reduced by

25% compared to the baseline analysis presented in Table S3 (top row for each country). The comparisons are shown separately for South Africa, Zimbabwe and Kenya. AGYW is used as shorthand for adolescent girls and young women 15-24 years. The values shown in the table outside the brackets are the median values, and the values shown in the brackets are the 95% credible intervals (CrIs). All values are shown rounded to the nearest 3 decimal places.

Table S10 sets out the percentage change in the in the relative number of infections averted a year on PrEP with equal coverage as with FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all women groups. These results are a comparison of the results set out in Table S8 with what the results would be if the same analysis were repeated with 25% less PrEP-adherence-related HIV risk reduction across all women groups.

% Change in Relative Number of Infections Averted a Year on PrEP with equal coverage as with FSW,
with 25% reduced PrEP-adherence-related HIV-risk reduction across Groups

	High Risk Women Population		
Country	AGYW	Women 25-34 years	Women 35-49 years
South Africa	0.000 % (-0.001% , 0.000 %)	-0.001 % (-0.001% , -0.001%)	-0.001 % (-0.001 % , 0.000 %)
Zimbabwe	0.000% (-0.001 % , 0.002 %)	-0.002% (-0.001 % , 0.001%)	-0.001% (-0.002 % , -0.001 %)
Kenya	0.000% (0.000% , 0.001 %)	0.001% (0.000% , 0.002%)	0.000% (0.000 % , 0.000 %)

Table S10: Percentage change in the relative number of infections averted a year on PrEP with equal coverage as with FSW, with 25% reduced PrEP-adherence-related HIV-risk reduction across groups.
The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the percentage change in the relative number of infections that could be averted a year on PrEP in AGYW, women 25-34 years or women 35-49 years relative to the number that could be averted in FSW with equal PrEP program coverage, if the PrEP-adherence-associated HIV risk reduction were reduced by 25% compared to the baseline analysis presented in Table S8. For the underlying analyses, the relative number of infections that could be averted is calculated using equation S2.9 from Supplementary Materials. AGYW is used as shorthand for adolescent girls and young women 15-24 years. All values are shown rounded to the nearest 3 decimal places.

<u>25% less PrEP-adherence-related HIV risk reduction across all non-FSW women groups</u>

Table S11 sets out the percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all non-FSW women groups (i.e. AGYW, women 25-34 years and women 35-49 years). These results are a comparison of the results set out in Table S3 (top row for each country) with what the results would be if the same analysis were repeated with 25% less PrEP-adherence-related HIV risk reduction across all non-FSW women groups.

% Change in Maximum Unit Cost at which PrEP is equally as Cost-Effective as for FSW, with 25% reduced HIV risk-reduction across all non-FSW women groups

	High Risk Women Population		
Country	AGYW	Women 25-34	Women 35-49 years
South Africa	0.253 % (0.252 %, 0.252 %)	0.253 % (0.252 %, 0.252%)	0.252 % (0.251%, 0.251%)
Zimbabwe	0.254 % (0.253 %, 0.253 %)	0.253 % (0.253% ,0.254%)	0.252 % (0.252%,0.252%)
Kenya	0.258 % (0.260 %, 0.256 %)	0.257 % (0.257%,0.258%)	0.256 % (0.255%,0.258%)

Table S11: Percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all non-FSW women groups (i.e. AGYW, women 25-34 years and women 35-49 years).

The table shows the percentage change in the maximum relative unit costs of PrEP in AGYW, women 25-34 years and women 35-49 years relative to the unit costs of PrEP for FSW, for PrEP to be equally as cost-effective (calculated using equation S1.5 in Supplementary Materials: Methods), if the PrEP-adherence-associated HIV risk reduction were reduced by 25% for all non-FSW women groups compared to the baseline analysis presented in Table S3 (top row for each country). The comparisons are shown separately for South Africa, Zimbabwe and Kenya. AGYW is used as shorthand for adolescent girls and young women 15-24 years. The values shown in the table outside the brackets are the median values, and the values shown in the brackets are the 95% credible intervals (CrIs). All values are shown rounded to the nearest 3 decimal places.

Table S12 sets out the percentage change in the in the relative number of infections averted a year on PrEP with equal coverage as with FSW, if 25% less PrEP-adherence-related HIV risk reduction were assumed across all non-FSW women groups (i.e. AGYW, women 25-34 years and women 35-49 years). These results are a comparison of the results set out in Table S8 with what the results would be if the same analysis were repeated with 25% less PrEP-adherence-related HIV risk reduction across all non-FSW women groups.

% Change in Relative Number of Infections Averted a Year on PrEP with equal coverage as with FSW,
with 25% reduced PrEP-adherence-related HIV-risk reduction across all non-FSW women groups

	High Risk Women Population		
Country	AGYW	Women 25-34 years	Women 35-49 years
South Africa	0.252 % (0.250 % , 0.252 %)	0.251 % (0.252 % , 0.252 %)	0.252 % (0.251 % , 0.251 %)
Zimbabwe	0.253 % (0.254 % , 0.254 %)	0.253 % (0.253 % , 0.254 %)	0.252 % (0.252 % , 0.253 %)
Kenya	0.257 % (0.260 % , 0.256 %)	0.26 % (0.257 % , 0.258 %)	0.256 % (0.255 % , 0.258 %)

Table S12: Percentage change in the relative number of infections averted a year on PrEP with equal coverage as with FSW, with 25% reduced PrEP-adherence-related HIV-risk reduction across all non-FSW women groups (i.e. AGYW, women 25-34 years and women 35-49 years).

The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the percentage change in the relative number of infections that could be averted a year on PrEP in AGYW, women 25-34 years or women 35-49 years relative to the number that could be averted in FSW with equal PrEP program coverage, if the PrEP-adherence-associated HIV risk reduction were reduced by 25% for all non-FSW women groups compared to the baseline analysis presented in Table S8. For the underlying analyses, the relative number of infections that could be averted is calculated using equation S2.9 from Supplementary Materials. AGYW is used as shorthand for adolescent girls and young women 15-24 years. All values are shown rounded to the nearest 3 decimal places.

Structural sensitivity analysis: women 25-34 years have partners from males 35-49 years, in addition to 25-34 years

Table S13 sets out the percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, under the structural sensitivity analysis exploring the case that women 25-34 years draw partners from males 35-49 years, in addition to 25-34 years. These results are a comparison of the results set out in Table S3 (top row for each country) with what the results would be if the same analysis were repeated with women 25-34 years drawing partners from males 35-49 years, in addition to 25-34 years (assumed to be the only partner population, in Table S3). Whilst the structural sensitivity analysis directly affects the model outcomes for women 25-34 years, it also indirectly affects the mean and 95% CrI outcomes for FSW, AGYW and women 35-49 year through changes to the number of underlying fitted parameter sets across all women groups.

% Change in Maximum Unit Cost at which PrEP is equally as Cost-Effective as for FSW, with women 25-34 years having partners drawn from 2 populations

	High Risk Women Population		
Country	AGYW	Women 25-34	Women 35-49 years
South Africa	-0.017 % (-0.063%, 0.017%)	-0.091% (-0.157%, -0.089%)	0.016% (-0.009%, 0.060%)
Zimbabwe	0.003% (0.015%, 0.018%)	-0.299% (-0.476%, -0.081%)	0.075% (-0.015%, 0.128%)
Kenya	0.020% (-0.004%, 0.000%)	-0.205% (-0.596%, 0.023%)	0.038% (0.030%, 0.059%)

Table S13: Percentage change in the maximum unit cost at which PrEP will be equally cost-effective in other high-risk women groups (AGYW, women 25-34 years and women 35-49 years) as in FSW, under the structural sensitivity analysis exploring the case that women 25-34 years draw partners from males 35-49 years, in addition to 25-34 years.
The table shows the percentage change in the maximum relative unit costs of PrEP in AGYW, women 25-34 years and women 35-49 years relative to the unit costs of PrEP for FSW, for PrEP to be equally as cost-effective (calculated using equation S1.5 in Supplementary Materials: Methods), if women 25-34 years are assumed to draw partners from males 35-49 years, in addition to 25-34 years, compared to the baseline analysis presented in Table S3 (top row for each country). The comparisons are shown separately for South Africa, Zimbabwe and Kenya. AGYW is used as shorthand for adolescent girls and young women 15-24 years. The values shown in the table outside the brackets are the median values, and the values shown in the brackets are the 95% credible intervals (CrIs). All values are shown rounded to the nearest 3 decimal places.

Table S14 sets out the percentage change in the in the relative number of infections averted a year on PrEP with equal coverage as with FSW, if women 25-34 years are assumed to draw partners from males 35-49 years, in addition to 25-34 years. These results are a comparison of the results set out in Table S8 with what the results would be if the same analysis were repeated with women 25-34 years drawing partners from males 35-49 years, in addition to 25-34 years (assumed to be the only partner population, in Table S8). Whilst the structural sensitivity analysis directly affects the model outcomes for women 25-34 years, it also indirectly affects the mean and 95% CrI outcomes for FSW, AGYW and women 35-49 year through changes to the number of underlying fitted parameter sets across all women groups.

	% Change in Relative Number of Infections Averted a Year on PrEP with equal coverage as with FSW, with women 25-34 years having partners drawn from 2 populations		
	High Risk Women Population		
Country	AGYW	Women 25-34 years	Women 35-49 years
South Africa	0.044 % (-0.091 %, -0.03 %)	-0.024 % (-0.176 % , -0.12 %)	0.039 % (-0.054 %, 0.061 %)
Zimbabwe	0.001 % (0.008 %, 0.015 %)	-0.297 % (-0.483 %, -0.087 %)	0.064 % (-0.018 %, 0.125 %)
Kenya	0.023 % (-0.004 %, -0.002 %)	-0.223 % (-0.593 %, 0.023 %)	0.048 % (0.042 % , 0.074 %)

Table S14: Percentage change in the relative number of infections averted a year on PrEP with equal coverage as with FSW, under the structural sensitivity analysis exploring the case that women 25-34 years draw partners from males 35-49 years, in addition to 25-34 years.

The table shows the median (value outside the brackets) and 95% CrIs (inside the brackets) of the percentage change in the relative number of infections that could be averted a year on PrEP in AGYW, women 25-34 years or women 35-49 years relative to the number that could be averted in FSW with equal PrEP program coverage, if women 25-34 years are assumed to draw partners from males 35-49 years, in addition to 25-34 years, compared to the baseline analysis presented in Table S8. For the underlying analyses, the relative number of infections that could be averted is calculated using equation S2.9 from Supplementary Materials. AGYW is used as shorthand for adolescent girls and young women 15-24 years. All values are shown rounded to the nearest 3 decimal places.

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Appendix 5: Commentary on Risk Compensation

Risk compensation and STI incidence in PrEP programmes: Latest evidence and research gaps

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Pre-exposure prophylaxis (PrEP) for HIV prevention is recommended by the WHO as part of a comprehensive HIV prevention package for those at substantial risk of HIV infection[1]. PrEP is effective at preventing HIV acquisition, demonstrated by high efficacy in placebo-controlled trials and demonstration projects, and increased PrEP coverage is associated with substantial decreases in population-level HIV incidence among men who have sex with men (MSM) in high-income settings[2-4]. Although PrEP is effective in preventing HIV infection, reduced condom use or other increases in sexual risk taking risk may increase STI transmission, especially in populations with low PrEP adherence, an increase in STIs may play an important role in affecting HIV transmission dynamics.

Before PrEP was widely available, some urged caution in recommending it because of the potential for *risk compensation*. As cyclists ride faster when made to wear helmets[5], so might PrEP users increase condomless sex or sexual partners, increasing the risk of other sexually transmitted infections (STIs)[6, 7]. As defined elsewhere[1], risk compensation refers to an increase in risk-related behaviours, because an intervention reduces perceptions of risk among individuals or a population.

Self-reported condom use and STIs did not change in placebo-controlled PrEP studies[3, 8]. However, in some open-label studies where users knew they were taking highly effective PrEP, PrEP use was associated with increases in condomless sex and, most importantly, STIs[9]. One observational study showed evidence of community-level risk compensation, where MSM *not* using PrEP also reduced condom use as PrEP coverage increased[10]. Importantly, six presentations at the 22nd International AIDS Conference in Amsterdam (Table 1) provide further evidence of risk compensation.

HIV prevention is at a crossroads. The potential effects of increasing STI incidence must be understood alongside the HIV benefits of PrEP, especially with suboptimal adherence or antibiotic-resistant STIs. We make an urgent call for more evidence on the potential effect of individual and community-level risk compensation on HIV and STI transmission among all groups where PrEP is available, alongside proportionate and context-specific programming and communication to mitigate risk compensation.

First, we do not understand how PrEP will affect epidemic dynamics well enough to make informed trade-offs between disease burdens from HIV and STIs. Models have not always predicted HIV epidemics accurately to-date[11], and more data are needed to fully understand the long-term impact of PrEP in a variety of real-world settings, in order to improve incorrect assumptions which reduce modeller and policymaker confidence in their projections. Yet modelling is an important component of the health technology appraisal process, and will be critical to understand how PrEP's impact is affected by risk compensation and resulting changes in STI dynamics[12]. There are currently few behavioural data to parameterise PrEP models, for example risk compensation may cluster among

people with different risk factors (e.g. multiple partners or seroconcordance) which are not accurately reflected in sexual mixing assumptions. PrEP guidelines also require regular STI testing which could increase early diagnosis and treatment, potentially counteracting or even surpassing the effect of any increases in risky sexual behaviour.

Second, the majority of evidence on risk compensation exists among MSM groups in high-income countries. Yet PrEP is now a key part of HIV prevention programmes among other high-risk groups, for example adolescent girls and young women in sub-Saharan Africa. We have little evidence on risk compensation or PrEP adherence among these groups. The burden of STI acquisition is also much higher among women of reproductive age, where chlamydia and gonorrhoea can cause a range of reproductive morbidity and display increasing antibiotic resistance. Therefore, the generalisability of risk compensation evidence and its implications outside high-income MSM groups is very limited.

Third, more evidence is needed on the effect of community-level risk compensation; in particular sexual behaviours among non-PrEP users in the context of PrEP availability, and early treatment for people living with HIV (PLHIV). Risk compensation is unlikely to undermine the HIV prevention benefits of PrEP among adherent PrEP users. However, small behavioural changes among non-users may reduce PrEP's overall epidemiological benefit. To model this, it is important to quantify the extent to which PLHIV are likely to have undetectable viral loads and/or STIs, particularly in low and middle-income countries where data is scarce.

Fourth, more research is needed on how users understand PrEP as a complement or substitute for alternate prevention strategies. Although guidelines recommend that PrEP users be counselled to use condoms, these are inconsistent since eligibility criteria for PrEP include reporting inconsistent condom use. Different, effective alternatives may therefore be needed to prevent STIs alongside PrEP, as condoms may be hard to promote among people who are primarily concerned with HIV prevention. The extent to which PrEP is used as a substitute to condoms, is likely to vary between populations and contexts. It is critical that we understand behavioural and structural approaches that support the provision of combination prevention services and tailored prevention packages.

Finally, where intermittent PrEP is provided, evidence is needed to understand behaviours before, during, and between episodes of use. Since intermittent PrEP regimens depend partly on user risk perception, it is important to understand how the choice to use PrEP is made, and how time on PrEP impacts risk behaviours during and potentially after PrEP use. Importantly, risk perceptions are rarely measured but inferred from behaviour change without knowing why behaviours changed – more work on measuring risk changing risk perceptions is needed.

PrEP has an important role in HIV prevention, and uncertainty in its effect on risk compensation and STI incidence should not prevent provision to those at high risk. Nonetheless, in order to support effective PrEP programming, researchers and practitioners need reliable and robust behavioural evidence from all populations to evaluate its true risks and benefits in order to evaluate its true risks and benefits.

Declaration of interest statement: No interests to declare

Authors	Title	Study Population, Location	Evidence type	Findings related to risk compensation
Rendina et al. http://programme.aids2018.org/ Abstract/Abstract/8121	Changes in rectal STI incidence and behavioral HIV risk before, during, and after PrEP in a national sample of gay and bisexual men in the United States	MSM, multiple sites, United States of America	Behavioural indicators, STI incidence	• No change in odds of rectal STI during PrEP use or after discontinuation compared to before uptake • Compared to before PrEP use: ○ 156% increase in condomless anal sex with casual partners ○ 410% increase in receptive condomless anal sex with serodiscordant male partners while on PrEP, but average of <1 act per person
De Wit et al. http://programme.aids2018.org/ Abstract/Abstract/10801	Attitudes regarding HIV, PrEP and condom use jointly predict risk compensation among men who have sex with men - findings from the VicPrEP implementation project, Melbourne	MSM, Melbourne, Australia	Behavioural indicators	• Frequency of condom use for anal sex with causal partners decreased significantly over one year follow up • Median condom protected acts in last three months reduced from 3 to 2
Traeger et al. http://programme.aids2018.org/ Abstract/Abstract/3905	Changes, patterns and predictors of sexually transmitted infections in gay and bisexual men using PrEP; interim analysis from the PrEPX demonstration study	MSM, Melbourne, Australia	Behavioural indicators, STI incidence	• STI incidence (chlamydia, gonorrhea, syphilis, and rectal pharyngeal or urethral infections) increased after PrEP use compared to before (IRR: 1.42 95%CI: 1.29-1.56)

Molina et al. http://programme.aids2018.org/ Abstract/Abstract/13278	Incidence of HIV-infection in the ANRS Prevenir Study in the Paris Region with Daily or On Demand PrEP with TDF/FTC	MSM, Paris, France	Behavioural indicators	• Indicative (not statistically tested) evidence of behavioural risk compensation (condomless sex at last intercourse, number of condomless acts in previous 4 weeks)
Prestage et al. http://programme.aids2018.org/ Abstract/Abstract/8042	A longitudinal analysis of the impact of PrEP on sexual behaviour and drug use among Australian gay and bisexual men	MSM, multiple sites, Australia	Behavioural indicators	• Among PrEP users significant increase in: ○ Condomless anal sex (78% increase) ○ number of partners in previous six months (100% increase) ○ Proportion reporting group sex (96% increase)
Morris et al. http://programme.aids2018.org/ Abstract/Abstract/11478	High HIV PrEP adherence is associated with syphilis incidence	MSM, California, United States of America		• The incidence rate of syphilis was over 3 times higher among those highly adherent (≥1246 fmol/punch, consistent with 7 doses per week or near perfect dosing) to TFV-DP at week 12 and week 48, compared to those not highly adherent at week 12 and 48

Table 1: Studies presented at AIDS 2018 Amsterdam containing evidence on risk compensation

References to Appendix 5

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