

REEXAMINING ASSUMPTIONS IN COMPARTMENTAL MODELS OF
HETEROSEXUAL HIV TRANSMISSION APPLIED TO ESWATINI



by

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Abstract

Compartmental HIV transmission models help guide global, national, and local epidemic responses via detailed projections, hypothetical scenarios, and mechanistic inference. While such models must make simplifying assumptions due to time and data constraints, prior work has shown that these assumptions can sometimes bias model outputs. In this thesis, I re-examine common assumptions used in compartmental HIV transmission models, and explore their potential influence on key model outputs. I focus on disproportionate risk among female sex workers, within the high-prevalence HIV epidemic of Eswatini.

First, I systematically review how differential risk has been captured in prior models exploring HIV treatment scale-up across Sub-Saharan Africa. Among 94 studies, I find that only 2/5 explicitly included sex work, and only 1/4 considered differences in treatment access across risk groups. Next, I design, parameterize, and calibrate a model of heterosexual HIV transmission in Eswatini. The model features 4 partnership types and 8 risk groups, including higher/lower risk female sex workers and their clients. While parameterizing the model, I develop several new adjustments for common sources of bias in sexual behaviour data. I also critically review existing “force of infection equation” approaches, used to model HIV transmission via sexual partnerships within compartmental models, with respect to their implicit assumptions, data needs, strengths, and limitations. Drawing on this review, I develop a new approach — the *Effective Partnerships Adjustment* — which can overcome some of the key limitations of existing approaches. Comparing the new and existing approaches in the Eswatini model, I show that some existing approaches might be systematically overestimating the impact of prevention in longer partnerships, and underestimating the impact of prevention in shorter partnerships. Finally, I apply the Eswatini model to further explore scenarios with different HIV treatment scale-up across risk groups. I find that the prevention impacts of treatment could be substantially reduced if higher risk groups are “left behind”.

Taken together, these results suggest that existing compartmental HIV transmission models may underestimate the importance of prioritizing resources to populations at highest risk of HIV acquisition and/or transmission, including female sex workers, even within a high prevalence epidemic such as Eswatini.

slow is smooth

smooth is fast

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Finally, I would like to reflect and comment on my positionality with respect to HIV research and practice. My lived experience is shaped by many dimensions of privilege, including being white, male, cisgender, heterosexual, and English-speaking. I was born and raised in a highly supportive upper middle class Canadian family, and I have had numerous opportunities to travel, learn, and follow my interests. I recognize that my lived experiences are, in fact, quite distant from those that afford a deeper understanding of the HIV epidemic, in Eswatini and elsewhere. I have never been to Eswatini and only travelled to Sub-Saharan Africa once, for two months in 2015 as part of the Engineering World Health Summer Institute in Rwanda. I have never delivered health services, though I am fortunate to work with many who have.

Nevertheless I am inspired by people living with HIV, families, friends, brave leaders and advocates of marginalized communities, healthcare providers and public health professionals who have been fighting for decades against HIV. I believe that these efforts can end the HIV epidemic in our lifetime, provided they remain responsive to emergent risks and persistent prevention gaps. I believe that these risks and gaps can be difficult to identify and are easily overlooked, but that they often derive from intersecting upstream inequities. I believe that quantitative data about these inequities cannot be understood without qualitative insights, and that the benefits of addressing these inequities extend beyond biomedical definitions of wellness. Thus, while my thesis highlights the importance of HIV prevention for female sex workers and their clients in Eswatini, I perceive this work as part of broader efforts to maintain health equity at the fore of the HIV epidemic response.

Contributions

Chapter 1. I was the sole author, with guidance and feedback from Sharmistha Mishra.

Chapter 2. Sharmistha Mishra and I conceptualized the study and developed the search strategy. I performed the search, extracted the data, conducted the analysis, and generated the results. I drafted the main text and appendix, with edits from Sharmistha Mishra. Sharmistha Mishra, Rupert Kaul, and I reviewed the results and contributed to revisions.

Chapter 3. Sharmistha Mishra and I conceptualized and designed the model structure. Huiting Ma, Linwei Wang, Stefan Baral, Carly Comins, and Sheree Schwartz provided feedback on the model design. I led model parameterization and calibration, including review of published data, design and implementation of bias adjustments, and original analysis of FSW survey data. Huiting Ma, Linwei Wang, Rupert Kaul, and Sharmistha Mishra supported these aspects with biostatistical and epidemiological expertise. Bheki Sithole, Sindy Matse, Zandile Mnisi, Laura Muzart, Stefan Baral, Carly Comins, Sheree Schwartz, Amrita Rao, Nikita Viswasam, Oluwasolape Olawore, and Sosthenes Ketende provided feedback on parameters and calibration targets for Eswatini and FSW specifically. Michael Escobar and Sharmistha Mishra supported design of model calibration, and interpretation of calibration results. I implemented the model and generated the results. I drafted the main text and appendix, with edits from Sharmistha Mishra.

Chapter 4. Sharmistha Mishra and I conceptualized the review of prior approaches. I led the review and designed the experiments. I developed the new approach, implemented all approaches and experiments in the model from Chapter 3, and generated the results, with guidance and feedback from Sharmistha Mishra. Sharmistha Mishra and I interpreted the results, and I drafted the main text and appendix, with edits from Sharmistha Mishra.

Chapter 5. Sharmistha Mishra and I conceptualized the study and designed the experiments, with input from Stefan Baral, Sheree Schwartz, Huiting Ma, and Linwei Wang. I implemented the experiments in the model from Chapter 3, and generated the results, with guidance and feedback from Sharmistha Mishra and Michael Escobar. Sharmistha Mishra, Stefan Baral, Rupert Kaul, Michael Escobar, Linwei Wang, Bheki Sithole, and I interpreted the results. I drafted the main text and appendix, with edits from Sharmistha Mishra.

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Table 1: Acronyms

Acronym	Definition
AGYW	adolescent girls and young women
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
BAB	beta approximation of binomial distribution
BPH	between-partnership heterogeneity
CD4	cluster of differentiation 4 (lymphocyte type)
DCM	deterministic compartmental model
FSW	female sex worker
FTFI	face-to-face interview
GUD	genital ulcer disease
HIV	human immunodeficiency virus
LTFU	lost to follow-up
MSM	men who have sex with men
p12m	past 12 months
PLHIV	people living with HIV
PrEP	pre-exposure prophylaxis
PTC	post-transmission contacts
RDS	respondent-driven sampling
SSA	Sub-Saharan Africa
STI	sexually transmitted infection
TPAF	transmission population attributable fraction
VMMC	voluntary medical male circumcision
VLS	viral load suppression
WPH	within-partnership heterogeneity
WHO	World Health Organization
95% CI	95% confidence interval

Chapter 1

Introduction

Human immunodeficiency virus (HIV) is the causative agent of acquired immune deficiency syndrome (AIDS) and a leading cause of morbidity and mortality [1, 2]. Mathematical modelling of HIV transmission supports the policy and programmatic response to the HIV epidemic in numerous ways. Examples of model applications include projecting the potential impact of interventions [3] and generating fundamental insights about transmission dynamics [4]. These models aim to mechanistically represent the populations, behaviours, probabilities, and interventions involved in transmission [5]. Yet, mathematical models must make simplifying assumptions for tractability of design, implementation, and interpretation, and given the often limited quantity and quality of data [5, 6]. Previous work has shown that certain modelling assumptions can influence model-based answers to particular research questions [4, 6–10], with possible implications for how HIV resources are prioritized using model-based evidence.

It is generally impossible to rank modelling assumptions from “most important” to “least important” overall, across the broad range of contexts and applications. However, rigorous modelling analysis will include a context/application-specific examination of assumptions, which may offer generalizable insights [11]. To this end, this thesis explores the epidemiological drivers of heterosexual HIV transmission in Eswatini, and examines modelling assumptions related to sexual partnership dynamics and unmet HIV prevention needs within sex work. The focus on Eswatini is motivated by both high HIV prevalence and recent exemplary scale-up of universal HIV treatment.

The remainder of this chapter introduces key concepts in HIV, including: infection, epidemiology, treatment, and prevention; followed by key concepts in mathematical modelling of HIV transmission, including: types of models, applications, fundamental principles, and challenges in choosing assumptions.

Table 1.1: Estimated probability of HIV transmission per 10,000 exposures

Exposure	Risk ^a	(95% CI)
Blood transfusion	9250	(8900, 9610)
Needle sharing	63	(41, 92)
Receptive anal sex	138	(102, 186)
Insertive anal sex	11	(4, 28)
Receptive vaginal sex	8	(6, 11)
Insertive vaginal sex	4	(1, 14)
Oral sex	—	(0, 4)
Mother-to-child	2260	(1700, 2900)

Adapted from [17]; ^a per 10,000 exposures

1.1 HIV

An estimated 38 million people are living with HIV globally, with 1.5 million new infections annually [12]. As discussed below, HIV often disproportionately affects specific populations due to intersecting social, economic, and biological vulnerabilities [13, 14]. Advances in prevention and treatment continue to reduce the rate of new infections and increase the quality and quantity of life among people living with HIV (PLHIV) [15]. However, application of these tools must remain responsive to the unique needs of different populations in order to rapidly and equitably end the epidemic [15].

1.1.1 Infection & Natural History

HIV infection involves three key steps: entry of the virus into target cells (mainly cells bearing the CD4 receptor, especially T lymphocytes); reverse transcription and integration of viral RNA into host cell DNA; and cellular production of HIV proteins to yield mature virions [1, 16]. Transmission of HIV then requires direct contact of infected bodily fluids with mucosal tissue, blood, or broken skin, and transmission risk is mediated by the degree of viral exposure to target cells [16]. Table 1.1 (adapted from [17]) summarizes the average probability of transmission for different unprotected exposures, though transmission risk varies substantially with numerous factors [18].

Following infection, HIV spreads rapidly through the lymphoid system and becomes detectable in the blood within 10 days [16]. During the subsequent acute phase (<1–2 months), individuals may experience nonspecific symptoms as plasma viral loads increase and circulating CD4 T cells decrease [1, 16, 19]. These trends are then reversed by an adaptive immune response, which temporarily suppresses infection, marking the transition from acute to chronic phase [1, 16]. Untreated asymptomatic chronic infection typically lasts multiple years, as HIV evades clearance and CD4 T cells are progressively depleted [16]. Progressive depletion of CD4 T cells then coincides with increasing risk of other infections — i.e., immune deficiency, eventually reaching the clinical criteria for AIDS [20] — and with re-increasing viral load [1, 16]. HIV infection also increases the risk of other diseases and mortality, with multiple hypothesized mechanisms [21].

1.1.2 Epidemiology of HIV

While global adult HIV prevalence is estimated at 0.7%, national estimates range from <0.1 to 28% [12]. Sub-Saharan Africa (SSA) bears the largest burden, with an estimated two-thirds of all current infections and over half of all new infections [12]. Whereas transmission is often concentrated among specific key populations (see below), widespread transmission beyond key populations is more common in SSA, especially in East and Southern Africa [12, 22]. As such, national epidemics have historically been classified as “concentrated”, “generalized”, or “mixed” based on overall HIV prevalence; however, the utility of this classification has been questioned because it fails to reflect local drivers of transmission, which can/should be used to guide epidemic response [23–25].

1.1.2.1 Key Populations & Female Sex Workers

Several key populations at highest risk of HIV acquisition have been identified, including sex workers, men who have sex with men, transgender people, prisoners, and people who inject drugs [13, 14, 26–31]. This list is not exhaustive, and other populations at higher HIV risk — particularly in SSA — include highly mobile populations, young women, and those engaged in transactional sex [32–37]. HIV disproportionately affects these populations due to intersections of behavioural risks, stigma, criminalization, violence, and poverty [13]. For example, women may enter sex work out of food/economic insecurity [29]. Then, criminalization of sex work leaves women vulnerable to sexual violence (including by police) and arrest for carrying condoms, or condom confiscation [29, 30]. Moreover, women selling sex may be reluctant to engage in HIV treatment and/or prevention services due to criminalization and experiences of stigma and discrimination [38, 39].

The odds of HIV infection among female sex workers (FSW) vs. women aged 15–49 was estimated as 13.5 globally, using data from 2007–11, and 12.4 in SSA specifically [28]. Higher numbers of sexual partners increases risk directly via more potential exposures, but also via co-transmission of other sexually transmitted infections (STIs) [29]. Some clients may also pay more for condomless and/or anal sex, or perpetrate sexual violence [29, 30]. Women, especially young women, also have increased biological susceptibility to HIV due to physical and immunological genital differences [40]. These vulnerabilities can be amplified through multiple structural factors noted above, as well as patriarchal attitudes [29, 30].

The contribution of transmission among key populations and via sex work is often suggested to be small in “generalized” epidemics [41, 42]. However, such conclusions typically rely on biased household-based face-to-face survey data [43, 44], generic behavioural assumptions [42], and simplistic methodology which fails to account for onward transmission [45]. By contrast, mathematical transmission models can capture the large indirect benefits of interventions prioritizing key populations [45, 46] and such models often show that these prioritized interventions are most cost effective [47–49].

Understanding and meeting the unique needs of different key populations is thus a core pillar of HIV response, which often overlaps with broader equity goals [30, 50, 51]. However, data collection and service delivery for key populations typically requires distinct approaches from the population overall due to the same factors that underpin vulnerabilities [13, 52]. For example, the sizes of key populations are likely substantially underestimated in household-based surveys, but could be estimated via respondent-driven or location-based sampling [44, 52, 53]. Moreover, key populations’ needs are rarely homogeneous within or between contexts. Rather, emerging evidence indicates that differentiated service delivery —

i.e., increasing options and convenience for accessing treatment and prevention services — is critical for maximizing coverage and impact [54–56]. For example, a recent trial among South African FSW identified benefits of decentralized HIV treatment access via a mobile van, including: reduced travel costs (direct costs, and opportunity costs of time away from work), fewer administrative barriers (e.g., proof of residence), and confidentiality (with respect to both HIV status and sex work) [57]. Community empowerment and direct engagement with community members for service planning can also improve treatment and prevention outcomes among FSW and key populations in general [58].

1.1.3 Epidemic Response

HIV infection has been stigmatized since the beginning of the epidemic, and the epidemic response — including efforts to raise awareness and funding for HIV research and services — is rooted in activism against stigma and towards equity [59]. By now, over US\$ 20 billion is available globally each year to fight HIV, with approximately 60% of funds provided by domestic and private sources (e.g., ministries of health), and 40% by international organizations [60], including: PEPFAR (the President’s Emergency Plan for AIDS Relief), the Global Fund (to Fight AIDS, Tuberculosis and Malaria), and UNAIDS (Joint United Nations Programme on HIV and AIDS). These funds support numerous prevention and treatment tools [15], which are ideally prioritized according to epidemic drivers and cost effectiveness. Understanding these drivers and estimating intervention impacts is rarely simple, but can be supported by implementation science and mathematical modelling [61–65].

1.1.3.1 Prevention

The earliest efforts to prevent sexual transmission of HIV focused on condom distribution and promotion, behaviour change, voluntary counselling and testing (VCT), and treatment of other sexually transmitted infections (STIs) [66, 67]. Condoms continue to be a key tool in prevention, including following HIV diagnosis [68]. By contrast, the effectiveness of population-level behaviour change interventions, such as to reduce numbers of sexual partners, remains unclear [69]. Current behavioural interventions mainly focus on education to empower informed decision making [70]. In many cases, the feasibility of individual-level behaviour change is constrained by structural factors, including economic and political stability, gender equality, and criminalization [71]. The role of structural factors were recognized early on [72], and efforts to understand and address these factors continue to inform novel prevention strategies [27, 71, 73]. Voluntary medical male circumcision (VMMC) is also protective [74], and has been recommended in some contexts since 2007 [75]. More recent advancements in antiretroviral therapy (ART), especially multi-drug combinations, have opened up new avenues of prevention, including pre- and post-exposure prophylaxis (PEP, PrEP), as well as “treatment as prevention” [76]. While treatment of people living with HIV offers many benefits (see § 1.1.3.2 below), prioritizing ART scale-up for preventing HIV may pull focus and funds away from more cost-effective prevention strategies, especially strategies which meet the needs of key populations [61, 64, 77].

1.1.3.2 Treatment

The goal of HIV *cure* remains illusive due to reverse transcription of viral DNA into host cell genomes and subsequent latency (viral inactivity), which establishes a persistent reservoir comprising 0.01–1% of CD4 T cells [78]. This reservoir is then maintained against clearance mechanisms via viral replication and clonal expansion of latently infected cells [1, 78]. Therefore, the goal of HIV *treatment* has been to suppress viral replication, and thereby restore normal immunologic function, including mitigation of non-infectious disease pathways (e.g., chronic inflammation) [16, 21, 79].

Numerous antiretroviral agents are now available, which have multiple mechanisms of interrupting viral replication [1, 20]. Standard therapy includes three agents in combination — also known as: combination ART (cART), highly active ART (HAART), or now simply ART — to reduce the risk of treatment failure and/or resistance mutations [20]. Since turnover of free virus in blood occurs rapidly (mean generation time estimated as 2.6 days) [80], ART initially reduces blood viral loads rapidly [1, 81]. Subsequent reductions are more gradual, and time to “undetectable” viral load (defined here as < 80 viral RNA copies per mL of blood)¹ is estimated as median 3.1 [IQR: 2.8, 5.5] months [82]. Recovery of CD4 T cells is even slower, and complete recovery to baseline levels is rare [1, 83].

Treatment Eligibility & Benefits. Initial ART eligibility criteria (especially for resource-constrained settings) were focused on PLHIV with advanced disease (defined by CD4 T cell counts per mL of blood and/or clinical staging) [84], for whom ART is most beneficial [1, 85].² However, studies have since highlighted health benefits of earlier ART initiation [87–90], and WHO has progressively expanded recommended eligibility criteria, culminating in the 2016 “treat all” recommendation [20, 84, 91, 92]. Expanding eligibility has coincided with growing recognition of additional benefits of ART for preventing transmission, as demonstrated in several trials of serodiscordant couples [93–95]. This recognition, along with model-based predictions [3, 96], then motivated several large-scale studies of “treatment as prevention” designed to estimate the population-level incidence reduction achievable via ART scale-up [97–99]. The results of these trials were mostly inconclusive, prompting renewed calls to understand and address “who is left behind”, and other persistent drivers of transmission [15, 64, 100, 101]. Improving ART coverage for individual-level and partnership-level benefits nevertheless remains a distinct goal [102].

Treatment Cascade. The HIV treatment cascade is conceptualized as key steps along the pathway to viral suppression. Although more detailed steps can help identify specific service gaps [103], the most basic cascade is defined as 3 steps: HIV diagnosis, ART initiation, and viral suppression [104]. These steps then form the basis of UNAIDS targets: 90-90-90 by 2020 [104] and 95-95-95 by 2030 [102], corresponding to the percentage of people living with HIV who know their HIV status, of whom, the percentage who are on ART, of whom, the percentage who have undetectable viral load. National progress towards these goals is highly prioritized and commonly reported [12], although differences across risk groups — and the potential implications of these differences for “treatment as prevention” — are increasingly highlighted [100, 105, 106].

¹ Definitions of “undetectable” viral load can range from < 50 to < 1000 copies/mL.

² The cost of ART per person-year continues to vary widely, from less than \$100 for generic WHO-recommended first-line regimens to approximately \$30,000 for patented combinations in the USA [86].

1.2 Eswatini HIV Epidemic

Eswatini³ is a small landlocked country bordering South Africa and Mozambique, with approximately 1.2 million total population (630,000 aged 15–49) as of 2021 [107]. Since approximately 2004, Eswatini has had the highest HIV prevalence in the world (among ages 15–49), estimated to be 28% in 2021 [12, 107]. Even within this context, burden of HIV among FSW remains even higher, estimated around 60% in 2011 and 2021 [108, 109]. Yet, Eswatini was also recently among the first countries in SSA to achieve the UNAIDS 95-95-95 ART cascade goals [12, 102]. Thus, Eswatini represents a unique context in which to explore various modelling assumptions about: relative drivers of transmission in a high-prevalence epidemic — including unmet needs of FSW — and the potential prevention impacts of ART — including rapid, yet evidently achievable, scale-up. This section provides general and HIV-specific context about HIV, including a summary of the major data sources.

1.2.1 Society & Politics

Eswatini is divided into four regions: Hhohho, Lubombo, Manzini, and Shiselweni, each comprising several tinkhundla (administrative subdivisions), which in turn comprise several imiphakatsi (chiefdoms). The country gained independence from British colonial rule in 1968, and remains the last absolute monarchy in Africa under King Mswati III (1986–present), son of King Sobhuza II (1921–1982) [110]. Political parties have been officially banned since 1973, and the monarchy retains powers to dissolve parliament, veto bills, and appoint most politicians [111]. Lavish expenditures by the royal family have been criticized [110, 112], and some authors have argued that cultural traditions and institutions have been appropriated to entrench and legitimize royal power [112, 113]. Socioeconomic inequality remains high [107, 112, 114], although economic growth and human development indicators were above the SSA average prior to the HIV epidemic [115]. While freedoms of expression remain severely restricted [110, 112], trade unions act as proxies for political parties, and calls for democratic reform have recently grown [110–112, 116].

Patriarchal norms are strong in Eswatini and domestic violence is common [113, 117–120]. Husbands often earn and control most/all household income, and women have reported prioritizing “honour in marriage and performance of being a good wife” [120]. Married women must usually consult with a “therapy management group”, comprising her husband and kin from both sides of the family, before seeking healthcare; the group may in fact make decisions fully on her behalf [120]. Such barriers can cause substantial delays in accessing HIV treatment [120]. Gender-based food and/or economic insecurity also motivate transactional sex and sex work across SSA [29].

Key populations are criminalized in Eswatini, including anybody buying or selling sex, engaging in same-sex sex acts, or possessing drugs [121]. As noted in § 1.1.2.1, such laws have substantial implications for the ability of population-level data and services to reach key populations [13]. Despite the recognized importance of meeting these populations’ prevention needs [122], specific services were not prioritized for this purpose until approximately 2009 [123].

³ Officially the Kingdom of Eswatini, and formerly known as Swaziland until 2018.

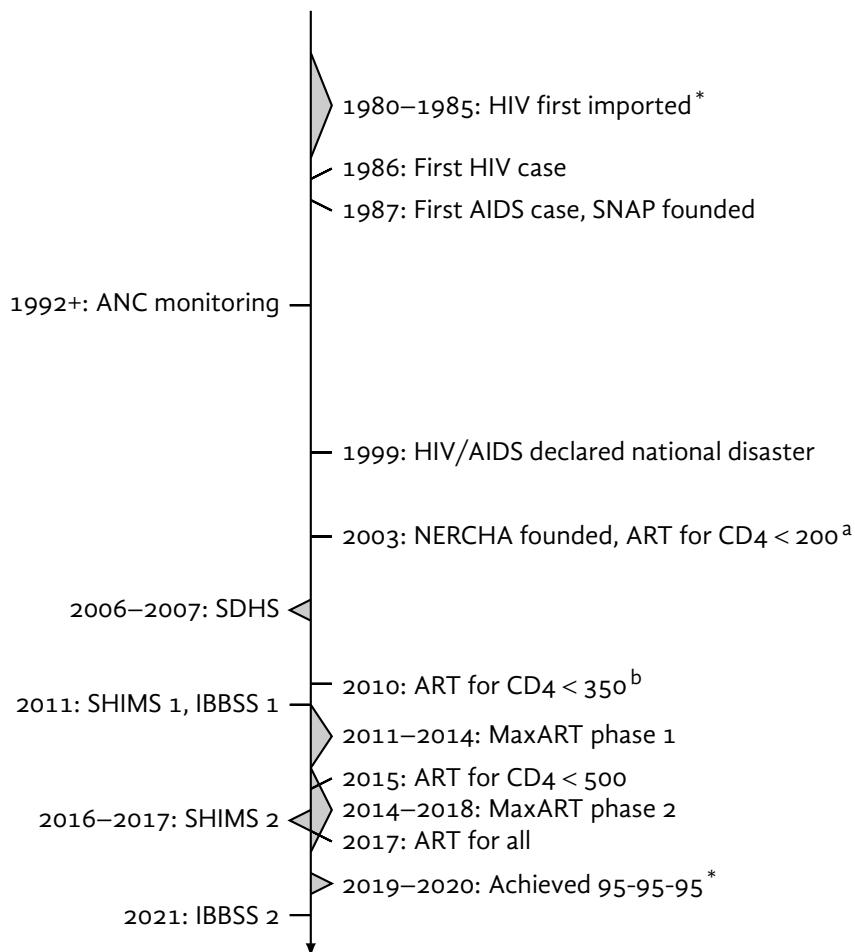


Figure 1.1: Timeline of HIV response in Eswatini

* approximate dates; ^a plus CD4 < 350 and WHO stage III, or any CD4 and WHO stage IV; ^b plus any CD4 and WHO stage III or IV; SNAP: Swaziland National AIDS Programme; ANC: antenatal care; NERCHA: National Emergency Response Council for HIV and AIDS; ART: antiretroviral therapy; SDHS: Swaziland Demographic and Health Survey; SHIMS: Swaziland HIV Incidence Measurement Survey; IBBSS: Integrated Biological-Behavioral Surveillance Survey for key populations; see also [16, Figure 3.] for a timeline of global HIV response.

1.2.2 Eswatini HIV Epidemic & Response

Figure 1.1 gives a timeline of major events in the Eswatini epidemic response. The exact timing of HIV introduction to specific countries across SSA, including Eswatini, remains unclear [124]. The first cases of HIV and AIDS in Eswatini were diagnosed in 1986 and 1987, respectively [115]. Shortly thereafter, the Swaziland National AIDS Programme (SNAP) was founded within the Ministry of Health as an anchor for the national response [125]. Yet, with limited tools for treatment and prevention, HIV prevalence rose rapidly, from 4% in 1992 to 42% in 2004 among women attending antenatal care (ANC) clinics (Figure B.11) [126].⁴ Over the same period, crude death rate roughly doubled, magnified by fragile healthcare infrastructure and a co-epidemic of tuberculosis [115]. In 2006, 23% of children under 18 were orphaned (one or both parents were dead), increasing to 37% of children aged 15–17, though not

⁴ ANC data generally overestimate overall HIV prevalence due to non-representative sampling [127, 128].

necessarily due to HIV [129]. A more detailed description of HIV incidence and prevalence trends is given in § 3.3.2.

In 1999, King Mswati III declared HIV as a national disaster and launched the Crisis Management and Technical Committee to coordinate a multi-sectoral response to the epidemic [125]. This committee was replaced in 2003 by the National Emergency Response Council on HIV and AIDS (NERCHA) [125], which continues to coordinate response via National Strategic Frameworks over successive 5-year time horizons [123, 130, 131]. Also in 2003, ART first became available in Eswatini [126], after which eligibility and coverage have steadily increased alongside WHO recommendations.

The earliest efforts to prevent sexual HIV transmission in Eswatini focused on voluntary counselling and testing (VCT), condom promotion, and behaviour change communication, including specific efforts to reach youth [132]. While condom use has increased (see also § 3.2.2.4), it's not clear whether numbers of sexual partners have changed over time [133]. In 2011, Eswatini began two major HIV campaigns: *Soka Uncobe*: "conquer through circumcision" [134] and *MaxART*: Maximizing ART for Better Health and Zero New HIV Infections [135, 136]. *Soka Uncobe* sought to increase male circumcision from 8 to 80%, and was funded by the two Swaziland HIV Incidence Measurement Surveys (SHIMS) in 2011 [134] and 2016–17 [137]. Despite prior evidence of acceptability and large demand creation efforts, male circumcision only reached 30% by 2016 [137] and 37% by 2020 [138]. *MaxART* included two phases with the following specific goals. Phase 1 (2011–15) sought to: scale up HIV testing to reach 250,000 people per year, reach 90% of eligible PLHIV with ART, and reduce 1-year ART loss to follow-up from 22% to 10%. Phase 2 (2014–17) sought to: determine the impact of early ART for all on retention and viral suppression, assess the role of community engagement in ART scale-up, and explore differences in systems and experiences pre vs. post intervention. Most *MaxART* goals were met [136, 139], and Eswatini became one of the first countries globally to achieve the UNAIDS 95-95-95 goals by 2020 [12, 102]. Additional details of ART scale-up in Eswatini are given in § 3.2.6.2.

As of the 2018 National Strategic Framework [131], Eswatini has moved to decentralize the HIV response and support a broad set of tools to "micro-target" local drivers of transmission. These tools include: continued promotion of HIV education and condoms, continued resources for testing and treatment, structural interventions to reduce gender based violence and stigma [140], STI treatment and VMMC services, and scale-up of PrEP for young women, serodiscordant couples, and key populations.

1.2.2.1 Data Sources

Major HIV data sources for Eswatini are summarized in Table 1.2, and briefly described as follows. Summary statistics were extracted from reports and publications in all cases, except two FSW surveys [108, 141], for which individual-level data were obtained and analyzed directly.

General Population. The 2006–07 Demographic and Health Survey (DHS) [129] was the first nationally representative, household-based survey in Eswatini covering numerous demographic and health topics. The survey included dried blood spot HIV testing, covering 88.1% of women and 81.1% of men. Adjusted HIV prevalence was stratified by sex, age, and other demographic factors, as well as marital status and numbers of sexual partners in the past 12 months (p12m). The survey also included data on sexual health and behaviour, including condom use at last sex, STI symptoms in p12m, and HIV testing history. The two SHIMS in 2010–11 [134] and 2016–17 [137] were conducted with the aim of estimating

Table 1.2: Main HIV data sources for Eswatini

Ref	ID	Dates ^a	Population ^b	N ^c	HIV ^d
[129]	DHS'06	07/06–02/07	GP 15+	9,143	P
[134]	SHIMS1	12/10–06/11	GP 18–49	18,169	P, I
[137]	SHIMS2	08/16–03/17	GP 15+	9,146	P, I
[108]	KP'11	09/11–10/11	KP 15+	328	P
[141]	KP'14	09/14–01/15	KP 18+	781	—
[109]	KP'21	10/20–01/21	KP 18+	676	P, I

^a Baseline data collection (MM/YY); ^b GP: general population; KP: key populations, specifically female sex workers, and men who have sex with men; ^c Respondents aged xx–49 who completed baseline survey; ^d Estimates of HIV via blood test, P: prevalence, I: incidence.

population-level incidence before and after *Soka Uncobe*. Similar to the DHS, both SHIMS were nationally representative, household-based surveys; however, SHIMS focused specifically on HIV variables, and additionally estimated ART cascade steps and HIV incidence. In SHIMS1 [134], a large prospective 6-month cohort was used to estimate incidence and validate recency testing [142] as a cross-sectional measure of incidence, whereas in SHIMS2 [137], incidence was estimated via the validated recency test. Compared to the DHS, participation rates were lower in SHIMS1 (81.7% and 65.0% among women and men, for the baseline survey), and similar in SHIMS2 (88.0% and 78.5%).

Female Sex Workers. The first behavioural surveillance survey among FSW in Eswatini reached only 37 FSW during 2001–02 and did not include HIV testing [109]. In 2011, a larger survey reached 328 FSW via respondent-driven sampling and included HIV testing and detailed behavioural data [108, 143]. This study found unadjusted HIV prevalence of 70.3%, highlighting a concentrated sub-epidemic among this key population even within the high-prevalence Eswatini epidemic [108]. A follow-up study in 2014 aimed to estimate FSW and MSM population sizes, identify venues for HIV service delivery, and provide additional data on service gaps [141]; this study used location-based snowball sampling [144] to reach 781 FSW, but did not include HIV testing. Finally, a fourth survey in 2020–21 sought to estimate FSW and MSM population sizes, HIV prevalence and incidence, prevalence of viral suppression, as well as identify behavioural and structural factors associated with HIV [109]; the study recruited 676 FSW via respondent-driven sampling.

1.3 Modelling HIV Transmission

Mathematical models of infectious disease transmission date back at least 100 years [145]. Transmission models are distinguished from statistical models by mechanistic and iterative representations of transmission, such that nonlinear dynamics can be simulated [5]. Transmission models can be further classified by several factors, including whether simulations are stochastic (random) vs. deterministic, and whether the basic model units are individuals (individual-based models) vs. groups of individuals (compartmental-based models); further differences among models are discussed in § 4.1.6 and [5, 8].

1.3.1 Deterministic Compartmental Models

Deterministic Compartmental Models (DCMs) are a popular type of transmission model which make two defining assumptions: 1) modelled populations can be stratified into distinct states (compartments), where individuals in each state are indistinguishable from one another — i.e., compartments are homogeneous; and 2) stochastic effects are negligible, which can be justifiable for large populations [146]. Despite the limitations associated with these assumptions [8, 147], DCMs remain popular due to their simplicity — in design, implementation, parameterization, calibration, and analysis — and smaller data needs vs. stochastic individual-based models [5, 8].

DCMs are specified as a set of first order ordinary differential equations of the form:

$$\frac{d}{dt} y_i = f_i(y, \theta, t) \quad (1.1)$$

where: $y_i(y)$ is the number of individuals in state i at time t ; θ is a set of model parameters; and f_i defines the rate of change in y_i as a function of all other y , θ , and t , reflecting mechanistic assumptions about infection transmission and other state transitions. For example, if the average rate of transition from state k to $k+1$ is η , then f_k would include a term “ $-\eta y_k$ ” and f_{k+1} would include a term “ $+\eta y_k$ ”.⁵ Usually, the most complex rate to specify is the “force of infection”, or incidence rate per susceptible. This rate is specified to reflect assumed pathways of transmission and mediators thereof, such as: numbers, types, and patterns of sexual partnerships; frequency and types of sex act per partnership; biological susceptibility and infectiousness per sex act; as well as coverage and efficacy of any interventions. These modelled pathways and mediating factors are inevitably simplified to remain tractable. Indeed, early DCMs were simple enough to solve analytically, which helped establish fundamental principles [145]. However, most modern DCMs must be solved computationally, for which many techniques and software packages exist (e.g., see footnote 7).

1.3.2 Applications of Transmission Modelling to Support HIV Response

Modelling of HIV transmission began shortly after discovery of the virus [148]. Early models focused on generating mechanistic insights into key determinants of epidemic dynamics [146, 149]. However, by now such models have been used in numerous applications to support epidemic response, including:

- generating mechanistic insights about epidemic dynamics [4, 10, 150]
- projecting HIV incidence, prevalence, mortality, etc. [151, 152]
- quantifying the contribution of particular contexts of transmission [153, 154]
- inferring parameter values through model fitting [8, 155]
- projecting the impact of interventions, and combinations thereof [3, 156, 157]
- uncertainty and sensitivity analysis of model outputs [7, 9, 158, 159] or clinical trial results [160]
- and economic analyses [161–163]

⁵ A constant transition rate also implies an exponentially-distributed duration in the originating state; see § B.1.1 for further details.

The movement towards more applied vs. theoretical modelling has encouraged development of more complex models, which include additional population stratifications and historical interventions. Yet, increases in model complexity are often at odds with the limited quantity and quality of available data to support them. Thus, many modellers are involved in data synthesis efforts to generate plausible model inputs [18, 155, 164, 165]. As model complexity and applications to specific policy questions have grown, so too has healthy scrutiny of modelling assumptions [45, 63, 152]. Such scrutiny must be embraced by modellers in order to remain transparent, humble, and ultimately accurate, especially when models are used to guide allocation of massive resources for millions of people.

1.3.3 Risk Heterogeneity

The central role of individuals with more sexual partners in STI and HIV transmission has long been recognized in so-called “core group theory” [166–168]. This theory has since been generalized to consider “risk heterogeneity” more broadly, reflecting differences in acquisition and/or onward transmission risk within a given population. Such heterogeneity can be driven by biological factors such as co-infection, individual-level factors such as numbers of sexual partners, and network-level factors such as patterns of sexual mixing, as well as upstream structural factors which influence all of the above. Indeed, risk heterogeneity is an important factor in all infectious diseases [11], and can even be considered to comprise phenomena like superspreading events [169]. In the context of HIV, risk heterogeneity is directly related to key populations, who experience multiple intersecting drivers of risk, as described in § 1.1.2.1.

Risk heterogeneity has several key implications for transmission dynamics:

- Epidemic potential and challenge of control is greater with vs. without risk heterogeneity, given otherwise equivalent conditions; for example, under random mixing, the basic reproduction number R_0 is proportional to $\mu + \sigma^2/\mu$, where μ and σ^2 are the mean and variance of contact rates [148]; under like-with-like mixing by risk, R_0 increases further [170].
- Endemic “equilibrium” prevalence is lower with vs. without risk heterogeneity [148]; this is because rapid early transmission among higher risk groups results in “saturation” of infection and/or immunity within these groups, where fewer and fewer contacts can result in transmission; by contrast, transmission among lower risk groups is reduced vs. the homogeneous case, because such groups have (by definition) lower than average risk [148].
- Turnover of individuals in/out of risk states/groups, sometimes called “episodic risk”, mediates the influence of risk heterogeneity on epidemic dynamics [167]; where slow turnover can contribute to “sustaining populations” with high infection prevalence [168], while fast turnover can erode “saturation” effects through net replacement of infected individuals with susceptible individuals in higher risk groups [10].
- The relative impact of prioritizing prevention resources to higher risk groups will be greater than without prioritization [45]; unfortunately, power asymmetries and stigma often undermine efforts to prioritize resources to marginalized higher risk groups [46, 171, 172].

1.3.3.1 Where to Draw the Line

The importance of risk heterogeneity is well-recognized. However, there are many potential factors that contribute to risk heterogeneity, and even more ways of representing each factor within a model. Recognizing time and data constraints to model building, it's rarely obvious *which factors* should be included in a model, *how* they should be included, and *what happens* if they are not adequately modelled. For example: Should the modelled population be stratified by age, or risk, or both? How many age and/or risk groups should be modelled? In other words: "*Where to draw the line?*" [11]. The answers to such questions likely depend on both the modelled context and application. This uncertainty in appropriate model specification is sometimes called "structural uncertainty" [9, 11]. However, unlike model specification problems in classic statistics, the ratio of structural uncertainty vs. available data in transmission modelling is generally too high to use information criteria-based approaches (e.g., [173]) to select a "good" or "optimal" model structure.

Only a few studies have sought to thoroughly explore how different representations of major factors could influence HIV model outputs — and even then, these studies have focused on the model-estimated impact of specific interventions in specific epidemic contexts [7, 9].⁶ Such structural comparison studies are impressive feats considering the challenges of implementing, parameterizing, and calibrating a single model structure, let alone several. These studies generally found that increasing model complexity reduced the projected impact of generic prevention interventions — reflecting the influence of risk heterogeneity on the challenge of epidemic control — and that no clear threshold of "sufficient" complexity emerged, beyond which model outputs stopped changing with further complexity. The generalizability of these findings to other contexts and interventions also remains unclear.

1.4 Research Questions

Considering the issue of "where to draw the line" with respect to model complexity, the original aim of this thesis was to offer generalizable insights as to when different factors of risk heterogeneity matter most.⁷ However, preliminary work reviewing prior models and implementing a benchmark model revealed another, equally important issue:

Models with the same structure and using the same data could differ further due to differences in assumptions made during data analyses and model implementation.

For example: survey data may give the numbers of sexual partners reported by respondents in the past month, but these numbers may or may not be multiplied by 12 to define a "yearly partnership rate" (model input), reflecting implicit assumptions of short vs. long partnership durations, respectively. For another example: a model may be stratified by age, but the model may or may not also consider differences by age in rates of HIV testing, treatment initiation, etc. Such assumptions therefore reflect another dimension to operationalized "risk heterogeneity", which is especially relevant in applied modelling.

⁶ Notably, [7] and several other works [3] were effectively a direct response to an (in)famous study [96] that made bold conclusions based on a very simple model with little justification for model design or parameterization.

⁷ What is a PhD research proposal if not overambitious?

Thus, the overarching research question of this thesis is:

How do modelling assumptions influence outputs of compartmental HIV transmission models?

where modelling assumptions are conceptualized as:

- **model structure:** which stratifications of the population and/or processes are explicitly represented?
- **model parameterization:** which data are used as model inputs and calibration targets, and how?
- **model implementation:** which equations are used to define the rates of transmission and transition between compartments?

and model outputs include: direct estimates (e.g., HIV incidence over time), counterfactual scenarios (e.g., comparison of possible intervention impacts), and qualitative interpretation of a collection of results.

Of course, comprehensive study of these numerous assumptions and outputs across epidemic contexts is beyond the scope of a single thesis. Rather, I sought to explore these aspects mainly in the context of heterosexual HIV transmission and sex work within Eswatini, through the following specific aims, each reflecting a chapter of the thesis:

- Chapter 2 systematically reviews the structure and assumptions used in prior compartmental HIV transmission models exploring ART scale-up in Sub-Saharan Africa
- Chapter 3 details the design, parameterization, and calibration of a “benchmark” compartmental model of heterosexual HIV transmission in Eswatini, with specific focus on precise interpretation of input data, and adjustment for potential biases
- Chapter 4 applies this model to examine the impact of different assumptions within the force of infection equation on modelled epidemic dynamics and the relative contribution of specific transmission pathways
- Chapter 5 further applies the model to explore how differences in who is assumed to be reached by ART scale-up can influence model-estimated ART prevention impacts

Finally, Chapter 6 offers some concluding remarks.

Chapter 2

Scoping Review of Risk Heterogeneity in Compartmental Models of ART as Prevention

Most of this chapter is copied verbatim from [174].

2.1 Introduction

As of 2019, two thirds (25.7 million) of all people living with HIV globally were in Sub-Saharan Africa (SSA), where an estimated one million new HIV infections were acquired in 2019 [12]. In SSA and elsewhere, HIV treatment via antiretroviral therapy (ART) remains a key element of combination HIV prevention [20].

Eligibility to initiate ART has seen continued expansion over the years — i.e., earlier and earlier initiation during HIV disease — following evidence of individual-level health benefits [89, 90] and partner-level prevention benefits [93, 94]. Expansion cumulated with the current recommendation of immediate ART following HIV diagnosis, or “universal test-and-treat” [20]. Parallel to ART expansion, interest has grown in estimating the population-level prevention benefits of ART, via both model-based studies [3, 96, 160, 175] and recent large-scale community-based trials [97–99]. Mixed results from these trials [97–99] have renewed interest in understanding potential determinants of population-level ART prevention benefits [64, 101].

Risk heterogeneity is a well-established determinant of HIV epidemic emergence and persistence [148, 176]. Such heterogeneity is defined by various factors affecting acquisition and onward transmission risk. Systematic model comparison studies have found that projected prevention impacts of ART scale-up were smaller when more heterogeneity was captured in the model [7, 177]. Moreover, populations experiencing barriers to viral suppression may be at highest risk for acquisition and onward transmission, including key populations such as women and men who sell sex, and men who have sex with men [105, 178]. Data also suggest that subgroups not formally described as key populations, such as youth, men who have sex

with women, including clients of sex workers, may also experience barriers to engagement in ART care [179–181]. Indeed, data suggest that ART scale-up in practice has not reached subgroups equally [106].

Given the critical role of transmission modelling in estimating the prevention impacts of ART [3, 175], we sought to examine how heterogeneity in risk and ART uptake has been represented in mathematical models used to assess the prevention impacts of ART scale-up in SSA. We conducted a scoping review and ecological regression with the following objectives. Among non-linear compartmental models of sexual HIV transmission used to simulate the prevention impacts of ART in SSA:

1. In which epidemic contexts (geographies, populations, epidemic phases) have these models been applied?
2. How was the model structured to represent key factors of risk heterogeneity?
3. What are the potential influences of representations of risk heterogeneity on the projected prevention benefits of ART in the overall population?

2.2 Methods

We conducted a scoping review according to the PRISMA extension for scoping reviews (Appendix A.4).

2.2.1 Conceptual Framework for Risk Heterogeneity

We defined “factors of risk heterogeneity” as epidemiological phenomena and stratifications of populations, rates, or probabilities which may/not be included in transmission models. We defined 4 domains in which such factors might influence the transmission impact of ART:

- **Biological Effects:** differential transmission risk within HIV disease course that may coincide with differential ART coverage [182]
- **Behaviour Change Effects:** differential transmission risk due to behavioural changes related to engagement in the ART cascade [68, 183]
- **Network Effects:** differential transmission risk within sub-populations that increases the challenge of epidemic control through core group dynamics [168, 176, 184]
- **Cascade Effects:** differential transmission risk within sub-populations who experience barriers to ART care and achieving viral suppression, such as youth and key populations [38, 105, 106, 185]

We then compiled a list of key factors of risk heterogeneity, and their possible mechanisms of influence on ART prevention impact (Table 2.1).

2.2.2 Search

We searched MEDLINE and EMBASE via Ovid using search terms related to Sub-Saharan Africa (SSA), HIV, and transmission modelling (Table A.1). Search results were de-duplicated and screened by title and abstract in Covidence [192], followed by full-text screening using the criteria below. One reviewer (JK) conducted the search, screening, and data extraction.

2.2 METHODS

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Table 2.1: Factors of heterogeneity in HIV transmission and their possible mechanisms of influence on the prevention impact of ART interventions

Factor	MP ^a	Definition	Possible mechanism(s) of influence on ART prevention impact
Acute Infection	β_i	Increased infectiousness immediately following infection [18, 186]	Biological: transmissions during acute infection are unlikely to be prevented by ART
Late-Stage Infection	β_i	Increased infectiousness during late-stage infection [18, 186]	Biological: transmissions during late-stage are more likely to be prevented by ART
Drug Resistance	β_i	Transmitted factor that requires regimen switch to achieve viral suppression [187]	Biological: transmissions during longer delay to achieving viral suppression will not be prevented by ART
HIV Morbidity	$Q; A$	Reduced sexual activity during late-stage disease [188, 189]	Behaviour Change: reduced morbidity via ART could increase HIV prevalence among the sexually active population
HIV Counselling	$Q; A; \alpha$	Reduced sexual activity and/or increased condom use after HIV diagnosis [68]	Behaviour Change: increased HIV testing with ART scale up can contribute to prevention even before viral suppression is achieved
Activity Groups	$Q; \alpha$	Any stratification by rate of partnership formation [190]	Network: higher transmission risk among higher activity
Age Groups	$Q; \alpha$	Any stratification by age	Network & Cascade: higher transmission risk and barriers to viral suppression among youth [106, 191]
Key Populations	$Q; \alpha$	Any epidemiologically defined higher risk groups [13]	Network & Cascade: higher transmission risk and barriers to viral suppression among key populations [105]
Group Turnover	θ	Individuals move between activity groups and/or key populations reflecting sexual lifecourse [168]	Network & Cascade: counteract effect of stratification due to shorter periods in higher risk [10]; viral suppression may be achieved only after periods of higher risk
Assortative Mixing	Φ	Any degree of assortative mixing (like-with-like) by age, activity, and/or key populations	Network: assortative sexual networks compound effect of stratification [190]
Partnership Types	$A; \alpha$	Different partnership types are simulated, with different numbers of sex acts and/or condom usage [29]	Network: longer duration and lower condom use among main vs. casual/sex work partnerships counteracts effect of stratification
ART Cascade Gaps	$\delta; \tau$	Slower ART cascade transitions among higher activity groups or key populations [105, 106]	Cascade: ART prevention benefits may be allocated differentially among risk groups

^a MP: Model Parameters — β_i, β_s : transmission probability per act (infectiousness, susceptibility); A : number of sex acts of each type per partnership; α : proportion of sex acts unprotected by a condom; Q : partnership formation rate; Φ : mixing matrix (probability of partnership formation); μ : mortality rate; v : entry rate; θ : internal turnover between activity groups; δ : diagnosis rate; τ : ART initiation rate (and retention-related factors).

2.2.2.1 Inclusion/Exclusion Criteria

Table A.2 lists complete inclusion/exclusion criteria and related definitions. We included peer-reviewed, primary modelling studies that used non-linear compartmental models of sexual HIV transmission to project the prevention impacts of ART in any setting within SSA. We included studies published in English anytime before Jan 1, 2020, that simulated at least one scenario with increasing ART coverage, possibly alongside other interventions. The included studies formed Dataset A, used to complete objectives 1 and 2. A subset of Dataset A formed Dataset B, used to complete objective 3. Studies in Dataset B met three additional criteria: 1) examined scale-up of ART coverage alone (vs. combination intervention); 2) examined ART intervention for the whole population (vs. ART prioritized to subgroups); and 3) reported HIV incidence reduction and/or cumulative HIV infections averted relative to a base-case scenario reflecting status quo.

2.2.3 Data Extraction

Data extraction used the full text and all available supplementary material. Data were extracted per-study for objectives 1 and 2, and per-scenario for objective 3, possibly including multiple time horizons. Detailed variables definitions are given in Appendix A.2.

2.2.3.1 Epidemic Context

For objective 1, we extracted data on geography, epidemic phase, and key populations explicitly considered in the model. We categorized studies by country, SSA region, and scale of the simulated population (city, sub-national, national, regional). We classified epidemic size at time of ART intervention using overall HIV prevalence (low: <1%, medium: 1–10%, high: >10%), and epidemic phase using overall HIV incidence trend (increasing, increasing-but-stabilizing, stable/equilibrium, decreasing-but-stabilizing, and decreasing).

We extracted whether any of the following key populations were modelled: female sex workers (FSW); male clients of FSW (Clients); men who have sex with men (MSM); transgender individuals; people who inject drugs (PWID); and prisoners. FSW were defined as any female activity group meeting 3 criteria: <5% of the female population; <1/3 the client population size; and having >50x the partners per year of the lowest sexually active female activity group [29, 193]. Clients were defined as any male activity group described as clients of FSW, and being >3x the FSW population size. We also extracted whether any groups in the model were described as MSM, transgender, PWID, or prisoners.

2.2.3.2 Factors of Risk Heterogeneity

For objective 2, we examined if/how the factors of risk heterogeneity outlined in Table 2.1 were simulated in each study. We examined the number of *risk groups* defined by sex/gender and/or sexual activity, and any *turnover* of individuals between activity groups and/or key populations.

We classified how *partnership types* were defined: generic (all partnerships equal); based only on the activity groups involved; or overlapping, such that different partnership types could be formed between the same two activity groups. We extracted whether partnerships considered different numbers of sex acts and condom use, and whether models simulated any degree of assortative *mixing* by activity

groups (preference for like-with-like) vs. proportionate (random) mixing. The number of *age groups* was extracted, and whether *mixing* by age groups was proportionate, strictly assortative, or assortative with age differences. We extracted whether age conferred any transmission risk beyond mixing, such as different partnership formation rates.

Finally, we extracted whether rates of HIV diagnosis, ART initiation, and/or ART discontinuation differed across risk strata (sex/gender, activity, key populations, and/or age), and if so, how they differed.

2.2.3.3 Prevention Impact of ART Scale-Up

For objective 3, we extracted the following data for each intervention scenario within Dataset B: the years that ART scale-up started (t_0) and stopped (t_f); the final overall ART coverage achieved and/or the final ART initiation rate (per person-year among PLHIV not yet in care); the criteria for ART initiation (e.g. CD4 count); and the relative reduction in transmission probability on ART. Then, we extracted the relative reduction in incidence and/or proportion of infections averted relative to the base-case scenario for available time horizons since t_0 .

We conducted an ecological analyses across all modelled scenarios to examine the relationship between factors of risk heterogeneity and projected ART impacts, adjusting for other factors that could influence impacts. For each factor of risk heterogeneity, we compared projected ART impacts (incidence reduction/infections averted) across different factor levels (whether or not, and how the factor was modelled). We estimated the effect of each factor level on ART impacts using linear multivariable regression, with generalized estimating equations [194] to control for clustering due to multiple estimates per study/scenario. Time since t_0 was included as a covariate, and two variables were removed due to missingness. No variable selection was used to avoid biasing effect estimates [195]. We also plotted impacts vs. time since t_0 , stratified by factor levels.

2.3 Results

The search yielded 1384 publications, of which 94 studies were included (Figure 2.1). These studies (Dataset A) applied non-linear compartmental modelling to simulate ART scale-up in SSA, of which 40 reported infections averted/incidence reduction due to population-wide ART scale-up without combination intervention, relative to a base-case reflecting status quo (Dataset B).

2.3.1 Epidemic Context

Table 2.2 summarizes key features of contexts within SSA where the prevention impacts of ART have been modelled. 61 studies modelled HIV transmission at the national level; studies also explored regional (1), sub-national (16), and city-level (16) epidemic scales. South Africa was the most common country simulated (52 studies); Figure A.1 illustrates the number of studies by country. East Africa was the most represented SSA region, being simulated in 77 studies, followed by Southern (72), West (28), and Central Africa (13).

ART prevention impacts were most often modelled in high-prevalence (> 10%) epidemics (41 studies) and medium-prevalence (1–10%) epidemics (23) (Figure A.2a). No studies reported overall HIV prevalence

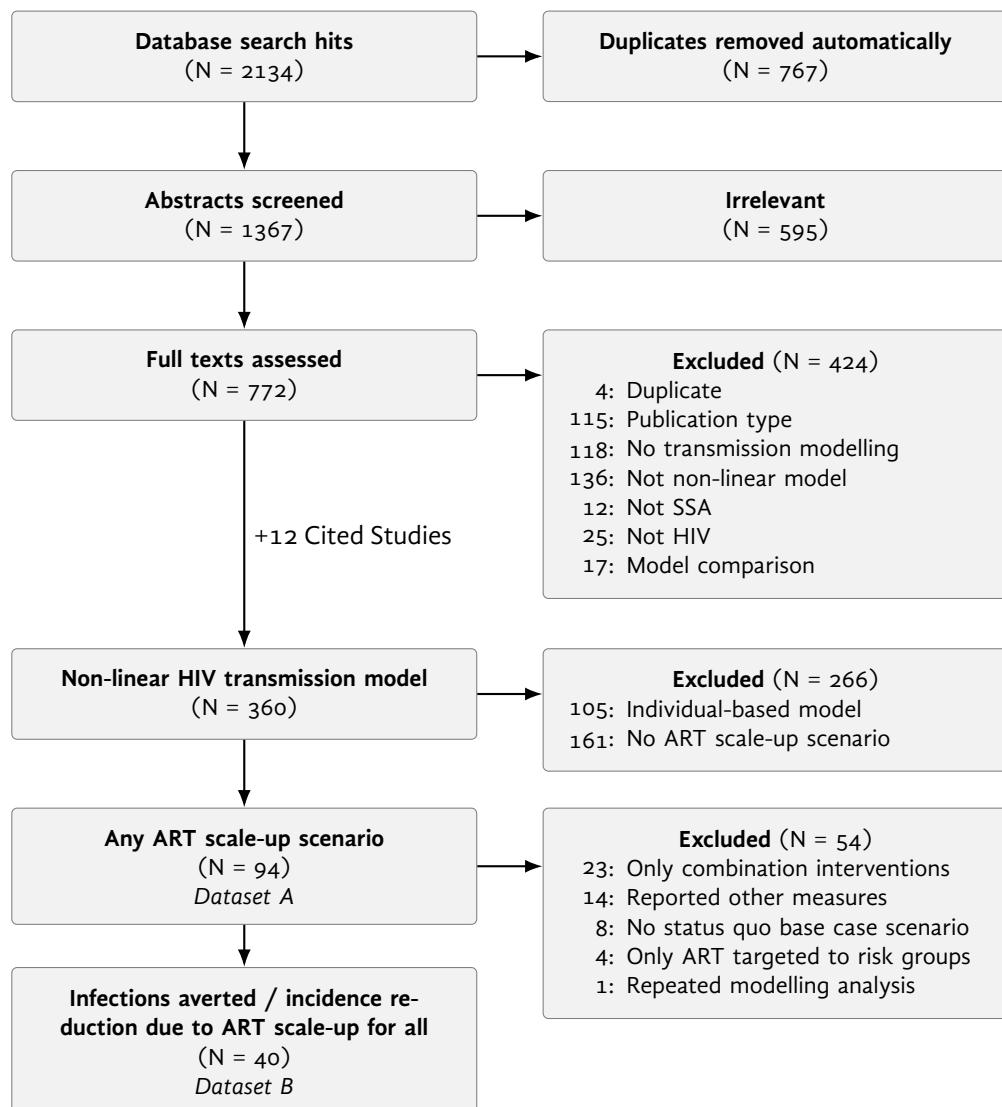


Figure 2.1: PRISMA flowchart of study identification

Table 2.2: Summary of epidemic contexts within Sub-Saharan Africa where the prevention impacts of ART have been modelled

Study Characteristic		Studies
Geographic scale	Regional	1
	National	61
	Sub-national	16
	City	16
Modelled countries ^a	South Africa	52
	Kenya	22
	Zambia	10
	Other	29
HIV prevalence	Low (<1%)	0
	Mid (1-10%)	23
	High (>10%)	41
	Unclear/Varies	30
Incidence trend at scenario divergence	Decreasing	10
	Dec-to-stable	24
	Stable	11
	Inc-to-stable	1
	Increasing	2
	Unclear/Varies	46
Key populations included	FSW ^b	39
	Clients ^c	31
	MSM	28
	Transgender	0
	PWID	11
	Prisoners	2

Total studies: 94. FSW: female sex workers; Clients: clients of sex workers; MSM: men who have sex with men; PWID: people who inject drugs; ^a does not sum to 94 as some studies modelled multiple countries; ^b groups described as FSW, not considering the epidemiological definitions given in Appendix A.2.2.1; ^c likewise for clients, and excluding studies where clients were modelled as a proportion of another risk group.

of < 1% at time of intervention, although for 30 studies, HIV prevalence was not reported or varied across simulated contexts/scenarios. The median [min, (IQR), max] year of intervention was 2014 [1990, (2010, 2015), 2040]; at which time HIV prevalence (%) was 15 [2, (6, 19), 32] (Figure A.2a); and incidence (per 1000 person-years) was 14 [1, (9, 20), 50] (Figure A.2b). Most reported incidence trends were decreasing or stable (45 of 48 reporting, Figure A.2c).

2.3.1.1 Key Populations

FSW were explicitly modelled in 39 studies. Among these (of studies where it was possible to evaluate): 21 (of 25) were < 5% of the female population; 14 (of 24) were < 1/3 the size of the client population; and 15 (of 22) had > 50x partners per year vs. the lowest sexually active female activity group. Clients of FSW were modelled as a unique group in 31 studies, among which 8 (of 17 reporting) were > 3x the size of the FSW population. In another 8 studies, clients were defined as a proportion of another group, among which 6 (of 7) were > 3x the FSW population size. Studies explicitly modelled men who have sex with men (MSM) in 28 studies; transgender in 0; people who inject drugs (PWID) in 11; prisoners in 2.

2.3.2 Heterogeneity Factors

2.3.2.1 Biological Effects

The median [min, (IQR), max] number of states used to represent HIV disease (ignoring treatment-related stratifications) was 5 [1, (3, 6), 25] (Figure A.2d), and 2 studies represented HIV along a continuous dimension using partial differential equations. States of increased infectiousness associated with acute infection and late-stage disease were simulated in 68 and 74 studies, respectively.

The relative risk of HIV transmission on ART was 0.08 [0, (0.04, 0.13), 0.3] (Figure A.2e), representing an average “on-treatment” state in 78 studies, vs. a “virally suppressed” state in 15. Treatment failure due to drug resistance was simulated in 24 studies, including: 23 where individuals experiencing treatment failure were tracked separately from ART-naive; and 1 where such individuals transitioned back to a generic “off-treatment” state. Another 6 studies included a similar transition that was not identified as treatment failure vs. ART cessation. Transmissible drug resistance was simulated in 9 studies.

2.3.2.2 Behavioural Effects

Reduced sexual activity during late-stage HIV was simulated in 25 studies, including at least one state with: complete cessation of sexual activity (14); reduced rate/number of partnerships (9); and/or reduced rate/number of sex acts per partnership (6).

Separate health states representing diagnosed HIV before treatment, and on-treatment before viral suppression were simulated in 30 and 17 studies, respectively. 22 studies modelled behaviour changes following awareness of HIV+ status, including: increased condom use (12); fewer partners per year (4); fewer sex acts per partnership (3); serosorting (1); and/or a generic reduction in transmission probability (8).

ART cessation was simulated in 35 studies, including: 16 where individuals no longer on ART were tracked separately from ART-naive; and 19 where such individuals transitioned back to a generic “off-treatment” state. Another 6 studies included a similar transition that was not identified as treatment failure vs. ART cessation.

2.3.2.3 Network Effects

Populations were stratified by activity (different rates and/or types of partnerships formed) in 59 studies, and by sex/gender in 64. The number of groups defined by sex/gender and/or activity was 6 [1, (2, 9), 19] (Figure A.2f); and by activity alone (maximum number of groups among: women who have sex with men, men who have sex with women, MSM, or overall if sex/gender was not considered) was 3 [1, (1, 3), 18]. The highest activity groups for females and males (possibly including FSW/clients) comprised 2 [< 1 , (2, 4), 23] and 9 [< 1 , (2, 14), 35]% of female and male populations, respectively (Figures A.2h and A.2i).

Turnover between activity groups and/or key populations was considered in 28 studies, of which 9 considered turnover of only one specific high-activity group or key population. Another 7 studies simulated movement only from lower to higher activity groups to re-balance group sizes against disproportionate HIV mortality.

Among 59 studies with activity groups, sexual mixing was modelled as assortative in 57 and proportionate in 2. Partnerships had equal probability of transmission in 39 studies, including all studies without activity groups. Partnerships were defined by the activity groups involved in 44 studies, among which transmission was usually lower in high-with-high activity partnerships than in low-with-low, due to fewer sex acts (31) and/or increased condom use (23). Transmission risk in high-with-low activity partnerships was defined by the: susceptible partner (9); lower activity partner (11); higher activity partner (3); or both partners' activity groups (15); yielding indeterminate, higher, lower, or intermediate per-partnership transmission risk, respectively. Partnerships were defined based on overlapping types, such that different partnership types could be formed between the same two activity groups in 11 studies. All overlapping partnership types had differential total sex acts and condom use.

Age groups were simulated in 32 studies, among which, the number of age groups was 10 [2, (4, 34), 91] (Figure A.2g), and 2 studies simulated age along a continuous dimension. Sexual mixing between age groups was assumed to be assortative either with (23) or without (3) average age differences between men and women; or proportionate (6). Differential risk behaviour by age was modelled in 29 studies.

2.3.2.4 Cascade Effects

Differential transition rates along the ART cascade were considered in 21 studies, including differences between genders in 15; age groups in 7; and key populations in 12. Another 2 studies did not simulate differential cascade transitions, but justified the decision using context-specific data. Differences between genders included rates of HIV diagnosis (11); ART initiation (6); and ART cessation (1), with cascade engagement higher among women, in most cases attributed to antenatal services. Differences between age groups also affected rates of diagnosis (6); ART initiation (1); but not ART cessation (0). Among key populations, *lower* rates of diagnosis, ART initiation, and retention were simulated in 0, 2, and 4 studies respectively, while *higher* rates were simulated in 8, 2, and 1.

2.3.3 ART Prevention Impact

Dataset B comprised 40 studies, including 125 scenarios of ART scale-up. Relative incidence reduction (IR) with ART scale-up as compared to status quo was reported in 23 studies (61 scenarios); proportion of cumulative infections averted (CIA) due to ART scale-up in 24 (75); and 7 (11) reported both. Some scenarios included multiple time horizons. Table 2.3 summarizes projected ART prevention impacts (IR, CIA), stratified by heterogeneity and contextual factors, plus adjusted effect estimates for each factor from multivariable analysis. Figure A.3 illustrates unadjusted impacts stratified by factor levels, while Figures 2.2 illustrates adjusted effect estimates. Compared to models with homogeneous risk, including risk heterogeneity via static activity groups but without key populations was associated with slightly higher impacts—adjusted effect (95% CI): 4 (−14, 22)% IR, 24 (12, 36)% CIA. Including key population(s) and assuming similar ART cascade across groups was also associated with higher impact: 72 (−31, 175)% IR, 20 (11, 28)% CIA. However, including turnover of one/more higher risk group(s) was associated with smaller ART prevention impacts: −82 (−153, −11)% IR, −86 (−103, −70)% CIA. Taken together, models that captured heterogeneity in risk across activity groups and/or key population(s) with turnover were associated with reduced ART prevention impacts.

2.3 RESULTS

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Table 2.3: Projected ART prevention impacts, stratified by factors of risk heterogeneity and contexts

Factor	Level	Incidence Reduction (%)				Cumulative Infections Averted (%)			
		N ^a	Median (IQR)	Effect (95% CI) ^b		N ^a	Median (IQR)	Effect (95% CI) ^b	
Risk Stratif. & Cascade Diff.	None	98	19 (7, 44)	REF		45	29 (18, 47)	REF	
	Activity (No KP)	22	35 (22, 46)	4 (-14, 22)		39	6 (3, 22)	24 (12, 36)	
	+ KP (Same)	5	41 (6, 50)	72 (-31, 175)		8	10 (3, 21)	20 (11, 28)	
	+ KP (Priority)	1	85 (85, 85)	136 (-73, 199)		23	21 (11, 41)	131 (97, 166)	
Activity Turnover	No	117	26 (8, 45)	REF		87	20 (5, 35)	REF	
	Yes	9	22 (21, 50)	-82 (-153, -11)		28	18 (7, 38)	-86 (-103, -70)	
Sex/Gender Stratif. & Cascade Diff.	No	97	21 (7, 44)	REF		39	29 (18, 44)	REF	
	Yes (Same)	22	41 (30, 53)	-4 (-32, 23)		48	8 (3, 24)	-49 (-62, -36)	
	Yes (Men Low)	7	21 (2, 22)	5 (-41, 50)		28	16 (4, 35)	-125 (-143, -108)	
Partnership Types	Generic	107	21 (8, 44)	REF		48	28 (15, 42)	REF	
	By Groups	16	33 (22, 52)	-22 (-53, 9)		66	11 (3, 28)	34 (20, 49)	
	Overlapping	3	50 (45, 62)	8 (-52, 69)		1	58 (58, 58)	-9 (-60, 43)	
Time Horizon (years)	0-10	36	17 (7, 35)	REF		40	14 (3, 26)	REF	
	11-20	63	20 (8, 42)	3 (-3, 9)		60	22 (8, 38)	9 (2, 17)	
	21-30	15	47 (39, 65)	3 (-7, 13)		11	23 (7, 47)	12 (6, 19)	
	31+	12	46 (24, 57)	12 (5, 20)		4	34 (29, 40)	5 (1, 8)	
HIV Prevalence (%)	11+	112	22 (8, 44)	REF		75	18 (4, 35)	REF	
	1-10	14	43 (36, 49)	-9 (-49, 31)		39	26 (11, 36)	-9 (-20, 2)	
	0-1	0	—	—		1	49 (49, 49)	-3 (-30, 24)	
HIV Incidence Trend ^c	Increasing	2	40 (38, 43)			5	32 (29, 41)		
	Inc-to-stable	1	97 (97, 97)			1	68 (68, 68)		
	Stable	17	21 (20, 29)			24	4 (2, 7)		
	Dec-to-stable	81	15 (6, 43)			11	1 (-8, 28)		
	Decreasing	1	57 (57, 57)			13	29 (19, 38)		
RR Transmission on ART	0.0-0.039	11	22 (14, 35)	REF		44	6 (2, 27)	REF	
	0.04-0.099	42	49 (34, 67)	55 (-22, 89)		60	27 (15, 38)	-41 (-54, -29)	
	0.1+	73	12 (5, 30)	9 (-31, 48)		11	19 (1, 33)	-20 (-26, -13)	
CD4 Threshold for ART Initiation	Symptomatic	3	38 (37, 41)	47 (-25, 68)		24	4 (2, 7)	-30 (-46, -15)	
	200	3	28 (26, 32)	REF		4	28 (24, 30)	REF	
	350	10	29 (22, 38)	15 (-3, 28)		18	18 (13, 27)	3 (-2, 7)	
	500	15	29 (16, 43)	27 (-8, 45)		13	29 (23, 35)	17 (10, 24)	
	Any	41	56 (22, 75)	30 (-14, 47)		22	51 (28, 62)	42 (37, 48)	
	Mixed	54	10 (5, 31)	1 (-31, 32)		34	16 (5, 37)	63 (54, 72)	
ART Coverage Target (%) ^c	0-59	3	28 (26, 31)			11	30 (13, 43)		
	60-84	13	29 (21, 41)			22	22 (8, 39)		
	85+	13	46 (36, 66)			21	36 (26, 43)		
Acute Infection	No	35	22 (10, 57)	REF		15	38 (24, 50)	REF	
	Yes	91	26 (9, 44)	52 (-13, 91)		100	16 (5, 32)	51 (36, 66)	
Late-Stage Infection	No	38	39 (13, 56)	REF		12	36 (20, 48)	REF	
	Yes	88	22 (8, 43)	-23 (-37, -8)		103	18 (5, 34)	-37 (-65, -9)	
Trans. Drug Resist.	No	114	21 (7, 43)	REF		102	18 (5, 36)	REF	
	Yes	12	72 (39, 85)	-4 (-46, 39)		13	26 (20, 30)	-3 (-8, 3)	
HIV Morbidity	No	102	21 (7, 45)	REF		73	27 (13, 42)	REF	
	Any	24	34 (22, 46)	35 (-16, 54)		42	6 (3, 23)	-20 (-26, -14)	
HTC Behav. Change	No	112	21 (7, 45)	REF		81	23 (11, 38)	REF	
	Any	14	41 (29, 49)	-39 (-73, -4)		34	6 (3, 22)	-13 (-18, -7)	

^a N: number of unique scenarios and time horizons; sums across factor levels may be less than 126 and 115 due to missing variables.^b Effect estimates from linear multivariable regression with generalized estimating equations [194]; effects are illustrated in Figure C.20. ^c Omitted from regression model due to missing data. RR: relative risk; HTC: HIV testing and counselling; KP: key populations. priority: modelled ART cascade transitions were faster in KP vs. overall due to prioritized programs; same: cascade transitions were assumed the same in KP as overall. Factor definitions are given in Appendix B.

After including risk heterogeneity, further capturing differential ART cascade across activity groups or key populations was associated with differences in projected ART prevention impacts. Models stratified by sex/gender, and those that captured lower ART cascade among men were associated with a smaller CIA: -49 (-62, -36)% and -125 (-143, -108)%, respectively; although similar effects were not observed for IR: -4 (-32, 23)% and 5 (-41, 50)%. Where key populations were explicitly modelled, including ART cascade prioritized to any key population(s) was associated with increased impact, enough to overcome reductions due to turnover: 136 (73, 199)% IR, 131 (97, 166)% CIA. No studies in Dataset B examined lower ART cascade among key population(s).

2.4 Discussion

Model-based evidence continues to support evaluation and mechanistic understanding of ART prevention impacts. Such evidence may be sensitive to modelling assumptions about risk heterogeneity. Via scoping review, we found that stratification by sexual activity and key population(s) was considered in approximately two-thirds and two-fifths of studies to date, respectively; one-third considered risk group turnover and one-quarter considered differential ART cascade by any risk group. In multivariable ecological analysis, we found that projected incidence reductions and proportions of infections averted were influenced by risk heterogeneity when risk group turnover and differential ART cascade were also considered.

Our findings suggest that the proportion of onward transmission prevented through ART may be reduced via turnover. Data suggest considerable within-person variability in sexual risk among key populations, including MSM, FSW, and clients of FSW [196–198], as well as in the wider population [199]. This risk variability is often reflected in compartmental models as risk group turnover. Previous modelling suggested that turnover could *increase* the prevention benefits of treatment [200]; however, the model in [200] was calibrated to overall equilibrium prevalence, allowing the reproduction number to decrease with increasing turnover. By contrast, when calibrating to group-specific prevalence with turnover, greater risk heterogeneity is inferred with vs. without turnover, and the reproduction number may actually increase [10]. Turnover of higher risk groups can also reduce ART coverage in those groups through net outflow of treated individuals, and net inflow of susceptible individuals, some of whom then become infected [10]. Thus, mechanistically, turnover could reduce the transmission benefits of ART. These findings suggest that turnover is important to capture as part of modeling risk heterogeneity, and as such, models would benefit from surveys, cohorts, and repeated population size estimates that can provide data on individual-level trajectories of sexual risk, such as duration in sex work [168].

Most models assumed equal ART cascade transition rates across subgroups, including diagnosis, ART initiation, and retention. However, recent data suggest differential ART cascade by sex, age, and key populations [38, 106, 201, 202]. These differences may stem from the unique needs of subgroups and is one reason why differentiated ART services are a core component of HIV programs [55, 180]. Moreover, barriers to ART may intersect with transmission risk, particularly among key populations, due to issues of stigma, discrimination, and criminalization [64, 203]. Our ecological analysis estimated that differences in cascade by sex (lower among men) or risk (key populations prioritized) had a large influence on projected ART prevention benefits. Thus, opportunities exist to incorporate differentiated cascade data, examine the intersections of intervention and risk heterogeneity, and to consider the impact of HIV services as delivered on the ground. Similar opportunities were noted regarding modelling of pre-exposure prophylaxis in SSA

[204]. Depending on the research question, the modelled treatment cascade may need to include more cascade steps and states related to treatment failure/discontinuation.

The next generation of ART prevention impact modelling can be advanced by leveraging rapid growth in data on risk heterogeneity and its intersection with intervention heterogeneity [6, 27, 28]. Key populations often reflect intersections of risk heterogeneity with turnover, and intervention heterogeneity (cascade differences), which together suggest the unmet needs of key populations play an important role in the overall dynamics of HIV transmission in SSA [205, 206]. Although none of the models in the review considered a lower ART cascade among key populations, data suggest large cascade differences, most notably lower proportions across the cascade, among key populations in SSA [105, 185, 201]. Similarly, we found that the number of modelled clients per female sex worker, and the relative rate of partnership formation among female sex workers vs. other women did not always reflect available data syntheses for sex work [29, 168]. Among studies with different partnership types, only 1/5 modelled main/spousal partnerships—with more sex acts/lower condom use—between two higher risk individuals, while 4/5 modelled only casual/commercial partnerships among higher risk individuals. However, data suggest that female sex workers form main/spousal partnerships with regular clients and boyfriends/spouses from higher risk groups [29]. Improved modelling and prioritization of services designed to reach key populations will rely on continued investment in community-led data collection for hard-to-reach populations.

Our scoping review has several limitations. First, we examined key populations based as traditionally defined [13], based on social and economic marginalization and criminalization in SSA, and future work would benefit from examining risk heterogeneity across more subgroups, such as mobile populations and adolescent girls and young women, where data suggest cascade disparities and risk heterogeneity [207, 208]. Second, our conceptual framework for risk heterogeneity did not explicitly examine heterogeneity related to anal sex, which is associated with higher probability of HIV transmission; nor did we examine structural risk factors like violence [209, 210]. Third, we did not extract whether models were calibrated, and if so, which parameters were fixed vs. fitted. If certain parameters were fitted, it could explain some counterintuitive effect estimates. For example, models with vs. without increased infectiousness in late-stage HIV might infer lower earlier-stage infectiousness through model fitting, such that overall infectiousness is roughly the same. Then, when simulating ART scale-up to individuals with earlier-stage HIV, the estimated prevention benefit could be relatively lower. A similar mechanism could explain increased ART prevention impacts when including acute infection. Importantly, we conducted an ecological analysis, and within-model comparisons like [7, 184] that explore the influence of each key factor identified in this review would be an important next step.

In conclusion, model-based evidence of ART prevention impacts could likely be improved by: 1) capturing risk heterogeneity with risk group turnover, as a determinant of inferred risk heterogeneity during model calibration, and to reflect challenges to maintaining ART coverage among risk groups with high turnover; 2) integrating data on differences in ART cascade between sexual risk groups, to reflect services as delivered on the ground; and 3) capturing heterogeneity related to key populations, to reflect intersections of transmission risk and barriers to HIV services that may undermine the prevention benefits of ART.

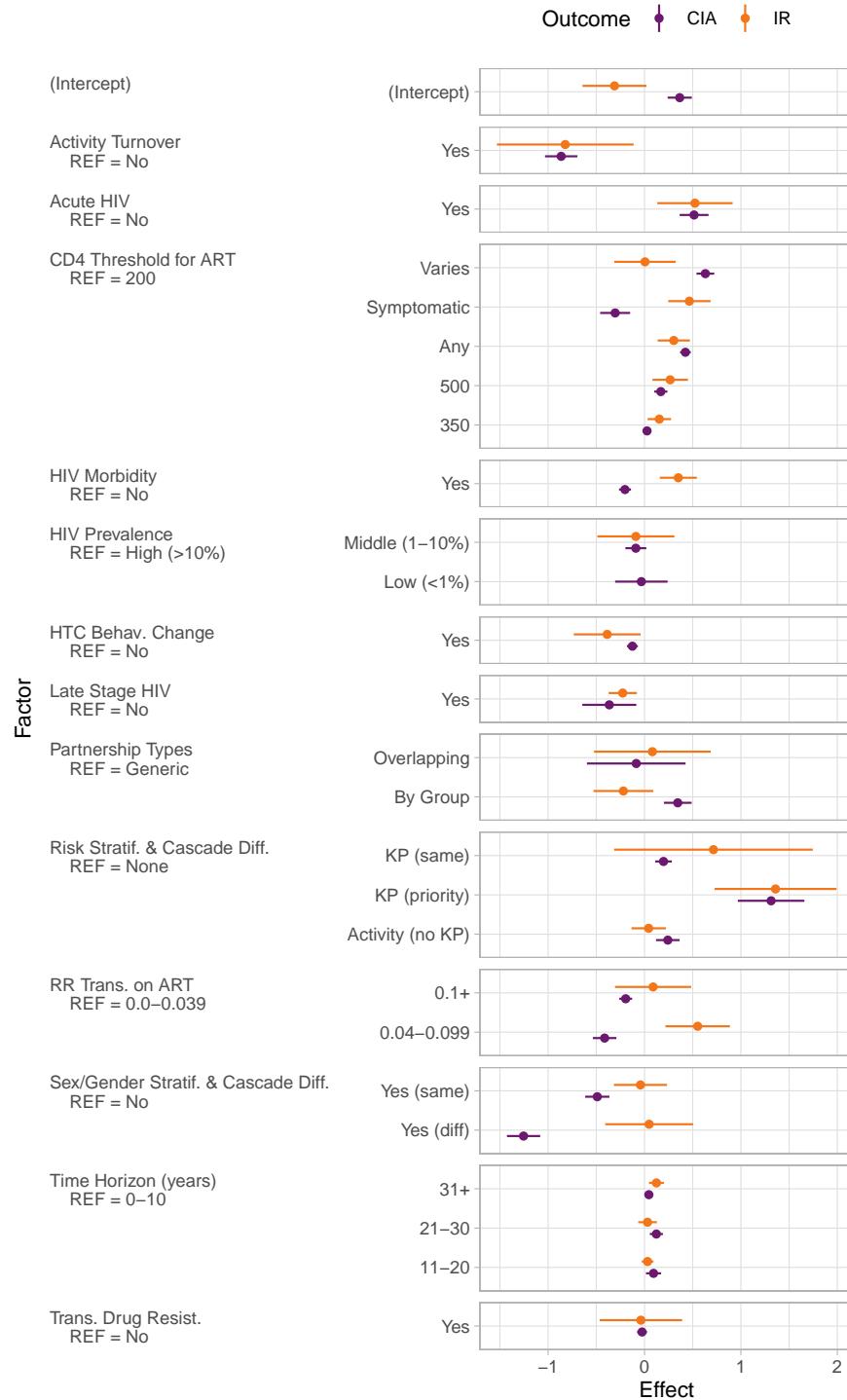


Figure 2.2: Effect estimates for factors of heterogeneity on incidence reduction (%), IR and cumulative infections averted (%), CIA from linear multivariable regression with generalized estimating equations.

Numerical results given in Table 2.3. RR: relative risk; HTC: HIV testing and counselling; KP: key populations. priority: modelled ART cascade transitions were faster in KP vs. overall due to prioritized programs; same: cascade transitions were assumed the same in KP as overall. Factor definitions are given in Appendix A.2.

Chapter 3

Model Structure, Parameterization, & Calibration

This chapter details the development of a deterministic compartmental model of heterosexual HIV transmission in Eswatini, to address downstream research questions in Chapters 4 and 5. Drawing on the insights from Chapter 2, the model aims to capture key determinants of heterosexual transmission dynamics, including sex work, numbers of sexual partners, levels of condom use, anal sex, and ART scale-up. The model was implemented in Python v3.8.10 with Numpy v1.22.2, and solved numerically using 4th order Runge-Kutta [211] using a timestep of 0.05 years. Post-hoc analysis was conducted in R v3.6.3. All code and selected results are available on GitHub.¹

The remainder of this chapter is organized as follows:

- § 3.1 outlines the model *structure* and notation, including the population stratifications and sexual partnership types considered.
- § 3.2 details the data, analyses, and assumptions used for model *parameterization* — i.e., estimating prior distributions for model parameters, including: HIV initialization in Eswatini; HIV transmission probabilities and modifiers thereof; progression rates through HIV stages and the ART cascade of care; analysis of primary survey data to distinguish higher vs. lower risk Swati FSW; risk group sizes, rates of turnover, sexual partnership numbers, sex frequencies, partnership durations, and mixing.
- § 3.3 details the data, analyses, and assumptions used for model *calibration* — i.e., inferring parameter posterior distributions, under which model outputs best match calibration targets, including: overall and (where possible) group-specific HIV prevalence, incidence, and ART cascade attainment.
- § 3.4 presents the *results* of model calibration, including: posterior parameter distributions, comparison of model outputs vs. calibration targets, and a descriptive summary of modelled transmission dynamics over time.
- § 3.5 provides *discussion* on the chapter methods and results, and notes the limitations of the model.

¹ github.com/mishra-lab/hiv-fsw-art

Table 3.1: Overview of model dimensions and stratifications

Dimension	Index	Strata
Sex	(s)	1 Heterosexual Women 2 Heterosexual Men
Activity group	(i)	1 Lowest Activity 2 Medium Activity 3 Lower Risk Sex Work 4 Higher Risk Sex Work
HIV status	(h)	1 Susceptible 2 Acute HIV 3 CD4 > 500 4 350 < CD4 < 500 5 200 < CD4 < 350 6 CD4 < 200 (AIDS)
ART cascade	(c)	1 Undiagnosed 2 Diagnosed 3 On ART 4 Virally Suppressed 5 Virally Un-suppressed
Partnership types	(p)	1 Main / Spousal 2 Casual 3 Occasional Sex Work 4 Regular Sex Work
Sex act types	(a)	1 Vaginal 2 Anal

See footnote 2 regarding indices in the code.

Notably, § 3.2 features several methodological contributions to support model parameterization, including:

- § 3.2.7: original analysis of primary data to distinguish higher vs. lower risk FSW
- § 3.2.8: an adjustment for reporting bias in partner numbers data using polling booth data
- § 3.2.10.2 an adjustment for censoring in risk group turnover/duration data
- § 3.2.11.1: an adjustment for bias due to partnership duration in partner numbers data
- § 3.2.14 a balancing approach to support more flexible mixing patterns

3.1 Model Structure & Notation

The model aims to capture heterosexual HIV transmission among the Swati population aged 15–49. The model stratifies the modelled population along five dimensions, including: 2 sexes (s), 4 activity groups (i), 6 HIV states (h), and 5 cascade states (c); the fifth dimension tracks seroconcordant HIV+ partnerships and includes strata for each of 4 partnership types (p) plus 1 extra stratum — see § 4.2 for full details. In total, $2 \times 4 \times (1 + 5 \times 5 \times 5) = 2016$ states are modelled, since the cascade and partnership dimensions are only applicable to PLHIV ($h > 1$). These dimensions are summarized in Table 3.1 and Figure 3.1. Two types of sex acts (a) are also considered.

3.1 MODEL STRUCTURE & NOTATION

29

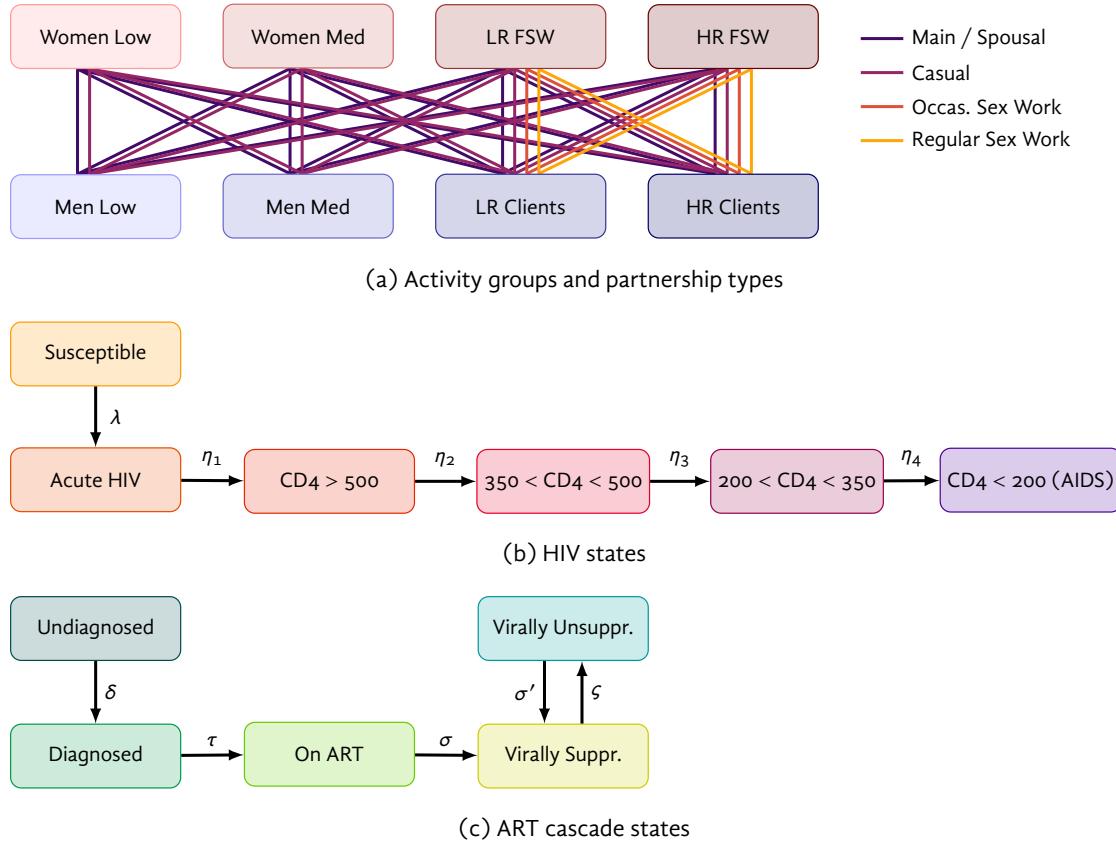


Figure 3.1: Model structure and transitions

Low: lowest activity; Med: medium activity; LR/HR: lower/higher risk; FSW: female sex workers; Clients: of FSW; CD4: CD4+ T-cell count per mm³; Not shown: turnover amongst activity groups in (a).

Sexual activity groups were defined to reflect common stratifications in the available data, and persistent differences in HIV incidence and prevalence [129, 137, 212, 213] — reflecting acquisition and/or onward transmission risk. The lowest sexual activity group ($i = 1$) comprises individuals who had 0–1 sexual partners in the past 12 months (p12m), but did not engage in sex work. The medium activity group ($i = 2$) similarly comprises individuals who had 2+ sexual partners in p12m but did not engage in formal sex work. The highest two activity groups among women ($i = 3, 4$) comprise lower and higher risk FSW (see § 3.2.7 for more details), and the highest two activity groups among men ($i = 3, 4$) likewise comprise lower and higher risk clients of FSW.

Four types of sexual partnerships are modelled, in order to capture different partnership durations relevant to Chapter 4, and different trends in condom use relevant to inferred transmission dynamics across groups — i.e., all downstream analyses. The four partnership types are: long-term/spousal partnerships ($p = 1$, lowest condom use, 14–19 years); short-term partnerships ($p = 2$, medium condom use, 3–18 months); one-off new/occasional sex work partnerships ($p = 3$, highest condom use, 1 sex act); and regular sex work partnerships ($p = 4$, medium condom use, 2–24 months). Figure 3.1a illustrates the modelled activity groups and possible partnership types between them.

HIV infection is stratified into acute-HIV and stages defined by CD4 count (Figure 3.1b) to reflect changes in mortality [214], historical ART eligibility [215–218], and, with CD4 as a proxy for viral load,

infectiousness [18]. The modelled ART cascade (Figure 3.1c) includes the steps associated with the “90-90-90” targets, plus a generic “virally un-suppressed” state reflecting any combination of treatment failure, discontinuation, or loss to follow-up after achieving viral suppression. Loss to follow-up prior to viral suppression is not explicitly modelled, but subsumed into rates of ART initiation and viral suppression.

Notation. If X is a variable (e.g., population, parameter, calibration target) stratified by dimensions a, b, c , then $X_{ab_1c_{23}}$ denotes the values of X for a particular but *unspecified* stratum of a , the *specific* stratum $b = 1$, and the *aggregated* strata $c = 2, 3$ (the aggregating operation is context-dependent, e.g., sum for probabilities). Additionally, the indices $sihc$ from Table 3.1 denote “self” strata, whereas $s'i'h'c'$ denote “other” strata — i.e., individuals’ partners.² Finally, I re-use several dummy variables throughout the chapter: ρ for proportions, λ for rates, T for time periods, and f for constants.

3.2 Parameterization

Model parameterization involves specification of parameter values (model inputs), such as proportions, probabilities, rates, and ratios. These parameters are used to define the initial conditions and rates of transition between modelled states. Some transition rates are fixed, such as rates of progression through HIV infection stages, while other transition rates vary with time, such as rates of HIV diagnosis and ART initiation. The transition rate for susceptible-to-infected — i.e., *transmission* — is defined by a complex “force of infection” equation which mechanistically integrates biological, behavioural, and interventional determinants of transmission; Chapter 4 develops this equation in detail, including modifications to overcome limitations of prior equations.

The true values of many parameters are uncertain due to several potential sources of error. Thus, prior distributions are specified for 73 parameters (Table B.1), and the joint posterior distributions of these uncertain parameters are then inferred via model calibration, as described in § 3.3 and 3.4. Proportions and probabilities were generally modelled using a beta approximation of the binomial distribution (BAB, see § B.1.2), while rates and ratios were generally modelled using a gamma, skewnormal, or inverse gaussian distribution to guarantee positive values.

3.2.1 Initialization

The first cases of HIV and AIDS in Eswatini were diagnosed in 1986 and 1987, respectively [115], although HIV may have been present several years earlier [124]. As such, I initialize the model in 1980 with no HIV, and simulate introduction of HIV at a random year between 1980 and 1985 (uniform prior). HIV introduction is modelled as exogenous infection of 0.01% (~ 24) individuals in the model,³ distributed across activity groups in proportion to their size, comprising: 5% acute HIV ($h = 2$), 65% with $CD4 > 500$ ($h = 3$) and 30% with $350 < CD4 < 500$ ($h = 4$), all undiagnosed ($c = 1$). The population size of EmaSwati aged 15–49 in 1980 was defined as 243,000 from [219].

² In the code: R uses one-based indexing, which match the notation here directly, while Python uses zero-based indexing, which therefore appear as $i \rightarrow i - 1$ in the code. Also, the model code reorders states in the ART Cascade dimension for computational efficiency, with $c = 1$: Undiagnosed; 2: Diagnosed; 3: Virally Un-suppressed; 4: On ART; 5: Virally Suppressed.

³ No further import/export of HIV to/from Eswatini is considered thereafter in the model. HIV transmission between Eswatini and neighbouring countries, including South Africa and Mozambique, has likely continued throughout the epidemic due to labour migration and other factors [124]. However, I assume that such transmissions have low overall influence on epidemic dynamics.

3.2.2 Probability of HIV Transmission

I parameterized the overall probability of transmission per sex act β as the product of a base rate β_0 , and independent relative effects corresponding to multiple factors. Such factors (indexed f) included: sex act type a , condom use, prevalence of circumcision among susceptible men, partner HIV infection stage h' and viral suppression via ART c' , as well as prevalence of STI co-infection/symptoms among both partners. Thus, β was defined as:

$$\beta_{asis'i'h'c'} = \beta_0 R_{\beta,f_1} \dots R_{\beta,f_N} \quad (3.1)$$

The impact of each factor (except ART) on the probability of HIV transmission is described in the following subsections, while the prevalence of each factor is given in § 3.2.3. The impact of ART on transmission is described in § 3.2.5.1.

3.2.2.1 HIV Infection Stage

Boily et al. [18] synthesized per-act transmission probability in the absence of ART from 43 studies in 25 populations. Among 7 studies reporting stage of HIV infection (early, asymptomatic, late), infection stage explained 95% of variance in per-act probability of transmission in [18]. Such differences in transmission are most likely due to differences in viral load, which is associated with HIV stage [220, 221]. The probability of transmission during the middle asymptomatic period, was reported as mean (95% CI) 0.072 (0.053, 0.097)% per act, reflecting β_0 . To improve model fit (see § 3.3), the 95% CI was increased to (0.053, 0.15)%, which was used to define a gamma prior distribution for β_0 . This probability was assumed to apply to vaginal intercourse, based on the studies considered.

For early infection ($h = 2$), Boily et al. [18] estimated the relative infectiousness of the first 5 months of infection as 9.2 (4.5, 18.8) times higher than the asymptomatic period. However, both the duration and infectiousness of the acute phase have been long debated [19, 77, 186]. In a recent reanalysis of the Rakai cohort data, Bellan et al. [155] estimate a much smaller contribution of the acute phase to overall infection, summarized as 8.4 (0, 63) “excess hazard-months” (EHM). This excess risk represents the joint uncertainty and collinearity in the estimated duration of 1.7 (.55, 6.8) months and relative infectiousness of 5.3 (.79, 57). Thus, I sampled the duration $\delta_{h=2}$ from a gamma prior with mean (95% CI) 1.7 (.55, 6) months, and relative infectiousness $R_{\beta,h'=2}$ from a gamma prior with 5.3 (1, 15) times the asymptomatic period (confidence intervals were adjusted to fit the gamma distributions, and to ensure $1 < \text{EHM} < 63$).

For late-stage disease, defined as 6–15 months before death in [18], Boily et al. estimated the relative rate of transmission as 7.3 (4.5, 11.9). However, I defined later HIV stages by CD4 count, including $200 < \text{CD4} < 350$ ($h = 5$) and $\text{CD4} < 200$ ($h = 6$, AIDS), which reflects closer to 50 and 18 months before death in the absence of ART, respectively. Therefore, I combined estimates from several sources [18, 221, 222] to define two gamma prior distributions with mean (95% CI) 1.6 (1.3, 1.9) and 8.3 (4.5, 13), for the relative rate of HIV transmission in these two stages ($h = 5, 6$), respectively. For $\text{CD4} > 350$ ($h = 3, 4$), I assumed no change from the baseline probability β_0 .

3.2.2.2 Sex Act Types

The model considers vaginal and anal intercourse, further stratified by sex (male-to-female/insertive vs. female-to-male/receptive). For vaginal intercourse, evidence for differential risk by sex is mixed, with some studies reporting no difference [222, 223], and others reporting up to 2-times higher male-to-female ($s' = 2, s = 1$) transmission vs. female-to-male ($s' = 1, s = 2$) [18, 224]. To reflect this uncertainty, I sampled the relative rate of male-to-female vs. female-to-male transmission from Unif[1, 2]; in applying this relative rate, both male-to-female and female-to-male transmission probabilities were adjusted such that the overall mean was preserved.

Baggaley et al. [225] synthesized the per-act transmission probability for anal intercourse, with most data from MSM studies. Analyses in [225] were not stratified by HIV stage, so I assumed the same relative rates derived in § 3.2.7 applied equally to vaginal and anal intercourse. Overall female-to-male (insertive) per-act transmission probabilities were similar for anal intercourse [210] (without ART): 0.14 (0.04, 0.29)% vs. vaginal intercourse [18] (without commercial sex exposure): 0.164 (0.056, 0.481)%; thus I assumed that female-to-male (insertive) transmission probabilities for anal vs. vaginal intercourse were equal. By contrast, male-to-female (receptive) per-act transmission probabilities were approximately 10 higher in anal intercourse [225] (without ART): 1.67 (0.44, 3.67)% vs. vaginal intercourse [18] (without commercial sex exposure): 0.143 (0.088, 0.233)%; thus I assumed a fixed 10-fold increase in male-to-female transmission probability for anal vs. vaginal intercourse. See § 3.2.12 for sex act frequency within each partnership type.

3.2.2.3 Circumcision

Relative risk in per-act HIV female-to-male transmission for circumcised vs. uncircumcised men via vaginal intercourse has been estimated as approximately 0.50, with 95% CI spanning (0.29, 0.96) [17, 18, 223]. Since circumcision status is unrelated to the research question, I fixed this effect at 50% relative risk. For anal intercourse, Wiysonge et al. [226] estimated that circumcision resulted in .27 (.17, .44) the odds of HIV acquisition for the insertive partner. It can be shown that relative reduction in incidence represents a lower bound on relative reduction in per-act transmission probability.⁴ Thus, for anal intercourse, I similarly fixed the per-act effect at 27%. Finally, there is inconclusive evidence to suggest that circumcision status affects male-to-female/receptive transmission [226, 227], so I assumed no effect. See § 3.2.3.1 for prevalence of circumcision in Eswatini over time.

3.2.2.4 Condoms

The most recent meta-analysis of condom effectiveness (when used) in heterosexual couples by Giannou et al. [228] estimated a relative risk of approximately 0.26 (0.13, 0.43). No significant differences were noted between female-to-male vs. male-to-female transmission. A recent study among men who have sex with men found a similar effect for anal sex [229]. Thus, condom effectiveness was fixed at 74%. See § 3.2.3.2 for the proportions of sex acts where condoms are used in Eswatini over time (parameterized separately).

⁴ See § 3.2.7 for more discussion.

3.2.2.5 Genital Ulcer Disease

Genital ulcer disease (GUD) is another established risk factor for HIV transmission [230, 231]. Some, but not all GUD is associated with sexually transmitted infections (STIs), and some, but not all STIs can cause GUD [231]. GUD is thought to increase both HIV susceptibility and infectiousness through a variety of mechanisms [231–233], but HIV may also facilitate transmission of various STIs through immunosuppression [234]. The meta-analysis by Boily et al. [18] found that presence of STI alone was not associated with increased HIV transmission: RR 1.11 (0.30, 4.14), but GUD was: RR 5.29 (1.43, 19.6), with most studies examining GUD among the HIV-susceptible partner. One study [235] estimated RR 2.58 (1.03, 5.69) of transmission for GUD among the HIV-positive partner. Most studies defined GUD status as any experience of symptoms during the study period (e.g., past 12 months, p12m), since precise delineation of GUD episodes is challenging. Moreover, individuals may take action to reduce onward STI transmission, such as accessing treatment, having less sex, and using condoms [129]. Thus, the true effect of GUD on HIV transmission via unprotected sex during active GUD episodes may be larger. However, if estimates of GUD prevalence and GUD effect (on HIV transmission) use consistent definitions (e.g., any GUD in p12m), then the time-averaged effect can be applied without need to estimate GUD episode duration. On the other hand, association of GUD and HIV transmission may not reflect *causation*, but rather *confounding* by uncontrolled exposure risk. As such, I applied factors for increased susceptibility and infectiousness due to GUD in accordance with group-specific p12m GUD prevalence (see § 3.2.3.3), with median 95% CI (1.2, 7.0) and (1.2, 3.4) (gamma priors), respectively.

3.2.3 Prevalence of Transmission Modifiers

3.2.3.1 Circumcision

Traditional (non-medical) circumcision in Eswatini is rare, reported as approximately 0.7% of men aged 15–49 in 2016 [137]. Voluntary medical male circumcision (VMMC) increased circumcision coverage to 8.2% by 2007, following demand for mainly hygienic reasons [129]. In 2007, the government further increased scale-up of VMMC services as part of HIV prevention efforts [129], leading to 17.1% coverage in 2011 [134], 30.0% in 2017 [137], and 37% in 2021 [138]. Since VMMC continues to be a key element of Eswatini’s HIV response [138], I assumed that coverage could reach and plateau at 50–90% (95% CI) by 2050. There is minimal evidence of differential condom use by circumcision status [134], so I assumed no differences. Similarly, while circumcision differed by union status in [137] (e.g., 22.1% circumcised among men in a union vs. 31.7% among men not in a union), differences did not persist after re-stratifying these men into groups with 0–1 vs. 2+ partners per year, as described in § 3.2.8. In Zambia, circumcision status was not associated with paying for sex [236].

3.2.3.2 Condom Use

Condom use is typically reported as either categorical for a recent period, usually 30 days, e.g., “never, rarely, sometimes, often, always”; or binary for the most recent sex act. Both report types may be subject to reporting bias, but the “last sex” more directly translates into a proportion of sex acts. The direction of reporting bias may vary with social context, with [237] suggesting over-reporting of condom use,

Table 3.2: Estimates of condom use in Eswatini

Partnership Type	Year	Population	Type	%	(95% CI)	Ref	Notes
Main	2006	Women	last sex	23.5	(23.2, 23.9)	[129]	a
		Men	last sex	23.1	(19.4, 26.9)	[129]	a
	2016	Women	last sex	52.7	(52.5, 52.9)	[137]	a
		Men	last sex	33.7	(30.8, 36.7)	[137]	a
Main or Casual	1988	Women	currently	0.6	(0.4, 1.3)	[239]	b
		Men	currently	7.3	(5.9, 12.1)	[239]	b
	2002	FSW	last sex	60	—	[122]	cd
			always	45.8	—	[122]	cd
	2006	Women	last sex	36.5	—	[129]	
		Men	last sex	47.2	—	[129]	
	2011	Women	always	30	—	[129]	
		Men	always	34	—	[129]	
		FSW	last sex	51.1	(41.8, 60.4)	[108]	de
			always	20.8	(14.7, 26.9)	[108]	de
Casual	2014	FSW	last sex	80.6	(64.7, 89.6)	[141]	g
	2016	Women	last sex	58.3	—	[137]	
		Men	last sex	53.1	—	[137]	
	2006	Women	last sex	53.5	—	[129]	
Sex Work Unspecified		Men	last sex	66.0	—	[129]	
	2016	Women	last sex	64.9	—	[137]	
		Men	last sex	73.7	—	[137]	
	2002	FSW	last sex	90	—	[122]	d
New Sex Work			always	74.4	—	[122]	d
	2020	FSW	always	50	—	[109]	
	2011	FSW	last sex	84.8	(57.9, 92.4)	[108]	ef
			always	56.7	(47.8, 65.6)	[108]	d
Regular Sex Work	2014	FSW	last sex	88.5	(54.9, 95.9)	[141]	g
	2011	FSW	last sex	82.9	(56.8, 90.0)	[108]	ef
			always	38.6	(29.5, 47.7)	[108]	e
	2014	FSW	last sex	85.6	(47.9, 95.0)	[141]	g

^a Back-calculated as described in § 3.2.3.2; ^b 95% CI from urban & rural data; ^c Described as “non-paying partners” in the survey;

^d Two major cities only (Manzini & Mbambane); ^e RDS-adjusted; ^f 95% CI lower bound reduced by 25% due to possible reporting bias; ^g 95% CI bounds from regions with lowest and highest reported condom use.

and [238] suggesting under-reporting of condom use. As such, I made no systemic adjustments to the available condom use data. Table 3.2 summarizes the available condom use data for Eswatini, deriving from [108, 122, 129, 137, 141, 239].

Main/Spousal & Casual. No direct estimates of condom use in main/spousal partnerships are available; condom use at last sex (with a non-paying partner) was either reported overall or for casual partners only.⁵ However, the proportions of individuals with various relationship statuses (e.g., polygynous union, non-polygynous union, not in a union, see § 3.2.8) can be used to back-calculate condom use in main/spousal partnerships for both 2006 [129] and 2016 [137]. To do so, I assumed whether “last sex” among individuals in unions with 2+ partners was with their main/spousal partner or with a casual partner; or more generally, what proportion of most recent sex acts was with a casual partner. I repeated the

⁵ “Higher risk” partners were defined in [129] as: “Sexual intercourse with a partner who was neither a spouse nor lived with the respondent”, effectively matching the model definition of “casual” partnerships.

back-calculation assuming 5% and 95%, yielding the confidence intervals shown in Table 3.2. Estimates of condom use in non-paying partners were lower among FSW vs. the wider population in 2011 (20.8% vs. ~32% “always”), but higher in 2014–16 (80.1% vs. ~55.7% “last sex”). Therefore, I assumed no differences in condom use among FSW vs. the wider population for main/spousal or casual partnerships.

Sex Work. All data on sex work partnerships in Eswatini is from FSW (i.e., not their clients). A 2001 study in Ghana [240] suggested that FSW were more likely than their clients to report having used a condom. As such, I adjusted the lower bound of 95% CI for condom use in sex work partnerships ($p = 3, 4$) as either 75% of the reported lower bound, or the lowest reported region-specific estimate. Estimates for 2002 [122] were obtained from two major cities only (Manzini and Mbambane); since early condom availability was mainly urban, treated these estimates as 95% CI upper-bounds, and defined the lower bound as 20% of the reported values.

Anal Sex. Owen et al. [164] estimate that among FSW globally, condom use in anal sex is approximately 79 (66, 94)% that of condom use in vaginal sex.⁶ In Eswatini [108, 141], relative condom use in anal sex vs. vaginal sex ranged from 44% among new clients in 2011 to 88% among regular clients in 2014. So, I sampled relative condom use in anal vs. vaginal sex from a BAB prior distribution with 95% CI: (50, 95)%.

Sampling & Trends. While levels of condom use reported by men and women do not always agree, the levels should agree in simulated partnerships. To reflect uncertainty due to the discrepancy, I sampled condom use for each year and partnership type from BAB prior distributions having 95% CI that spans the range of estimates from men and women (where applicable), including the widest points of all confidence intervals. I further expanded the confidence intervals in some cases by enforcing a maximum value of $N = 100$ for the BAB distribution. I assume that condom use was effectively zero in 1980 [239]. I also assume and enforce two conditions that: condom use must be monotonic increasing over time; and condom use must be highest in new sex work partnerships, and lowest in main partnerships, for all sampled parameter values. For each available year, I simultaneously sample condom use for all partnership types, and samples failing the condition are discarded. As illustrated in § B.1.3, this sampling strategy minimizes differences between the prior and sampled-with-constraint distributions. For each partnership type, I then smoothly interpolate between sampled levels of condom use over the available years using monotone piecewise cubic interpolation [241].

3.2.3.3 Genital Ulcer Disease

Self-reported prevalence of GUD in p12m among sexually active women and men aged 15–49 was approximately 7% in 2006 [129, Table 13.14]. This prevalence was not stratified by numbers of partners, so I modelled GUD prevalence among the lowest risk women and men as 7% times the proportion sexually active (see § 3.2.8). Among the medium risk groups, I sampled GUD prevalence uniformly between 7% and the prevalence modelled among FSW (below).

The 2011 and 2014 FSW surveys did not ask respondents about GUD specifically, but about any STI symptoms in p12m.⁷ In the wider population [129], approximately 60% of women self-reporting any STI symptoms specifically reported GUD in p12m; thus, self-reported STI symptoms among FSW may

⁶ I integrated the reported confidence intervals using the delta method after assuming binomial-distributed proportions.

⁷ The survey question about STI symptoms was: “*In the last 12 months, have you had symptoms of a sexually transmitted infection including discharge from your vagina or sores on or around your vagina or anus*”.

overestimate p12m GUD prevalence. Approximately 50% and 25% of FSW reported STI symptoms in 2011 and 2014, respectively. Reflecting uncertainty related to self-reported estimates, STI vs. GUD, and sampling bias, I sampled p12m GUD prevalence among lower risk FSW from a BAB distribution with 95% CI (10, 40)%. Per analysis in § 3.2.7, I assumed that STI (and thus GUD) prevalence was approximately 3 (1.5, 5) times higher among higher risk FSW (gamma prior), with an upper bound of 100%. FSW data also suggest declining STI prevalence between 2011 and 2014, which could reflect scale-up of STI testing and treatment for FSW [126]. However, STI prevalence among Swati youth in 2017–18 remained high [242]. Thus, to reflect uncertainty in STI/GUD prevalence trends, I sampled a relative reduction in GUD prevalence for all populations between 2020 and 2050 from a uniform distribution spanning [0.2, 1].

Finally, no Eswatini-specific data are available for clients of FSW, but studies in Zimbabwe [243], Senegal [244] and Zambia [236] have found 2.5–3.7 (95% CI span 1.4–5.0) the odds of STI symptoms during the past 6–12 months among clients vs. non-clients. Yet, I assumed that even higher risk clients could not have greater GUD prevalence than lower risk FSW. Thus, I defined GUD prevalence among lower risk clients as midway between that of the medium risk groups and lower risk FSW, and among higher risk clients as sampled uniformly between lower and higher risk FSW.

3.2.4 HIV Progression & Mortality

3.2.4.1 HIV Progression

The length of time spent in each HIV stage is related to rates of progression between stages η_h , rates of additional HIV-attributable mortality by stage $\mu_{HIV,h}$, and treatment via antiretroviral therapy (ART). Lodi et al. [245] estimate median times from seroconversion to CD4 < 500, < 350, and < 200 cells/mm³, while Mangal [214] directly estimate the rates of progression between CD4 states η_h in a simple compartmental model. Based on these data, I modelled mean durations ($1/\eta_h$) of:⁸ 0.142 years in acute infection ($h = 2$, from § 3.2.2.1); 3.35 years in CD4 > 500 ($h = 3$); 3.74 years in 350 < CD4 < 500 ($h = 4$); and 5.26 years in 200 < CD4 < 350 ($h = 5$); plus the remaining time until death in CD4 < 200 ($h = 6$, AIDS). Since the duration in acute infection ($h = 2$) is randomly sampled, the remaining duration in CD4 > 500 ($h = 3$) is adjusted accordingly.

3.2.4.2 HIV Mortality

Mortality rates by CD4-count in the absence of ART were estimated in multiple African studies [214, 246, 247]; based on these data, I estimated yearly HIV-attributable mortality rates $\mu_{HIV,h}$ as: 0 during acute phase ($h = 2$); 0.4% during CD4 > 500 ($h = 3$); 2% during 350 < CD4 < 500 ($h = 4$); 4% during 200 < CD4 < 350 ($h = 5$); and 20% during CD4 < 200 ($h = 6$, AIDS).

⁸ Assuming exponential distributions for durations in each CD4 state (see § B.1.1 for more details).

3.2.5 Antiretroviral Therapy

Viral suppression via antiretroviral therapy (ART) influences the probability of HIV transmission, as well as rates of HIV progression and HIV-related mortality. The model considers individuals on ART before ($c = 3$) and after ($c = 4$) achieving full viral load suppression (VLS), as defined by undetectable HIV RNA in blood samples. Among retained patients initiating ART (see § 3.2.6.2 for rates), time to VLS is usually described as “within 6 months” [248]. Mujugira et al. [82] estimated the median time to VLS as 3.1 [IQR: 2.8, 5.5] months from 1592 HIV serodiscordant couples; however this time may be underestimated due to the trial conditions and population. The distribution of time to VLS (Figure 1 in [82]) also featured a heavy tail, suggesting heterogeneity in time to VLS (see § 3.2.6.1 for implications). For example, time to VLS may be prolonged due to social and economic barriers to care [120, 249]. Considering these data, I sampled the time to VLS (duration in cascade state $c = 3$) from a gamma distribution with 95% CI (0.33, 1.0) years.

3.2.5.1 Probability of HIV Transmission on ART

All available evidence suggests that viral suppression by ART to undetectable levels prevents HIV transmission, i.e., undetectable = untransmittable (“U=U”) [250]. Thus, I assumed zero HIV transmission from individuals with VLS ($c = 4$). However, HIV transmission may still occur during the period between ART initiation to viral suppression ($c = 3$) [82]. Donnell et al. [221] estimate an adjusted incidence ratio of 0.08 (0.0, 0.57) for all individuals on ART. However, in [221] and [94], the 1 and 4 (respectively) genetically linked infections from individuals on ART all occurred within 90 days of ART initiation, suggesting that risk of transmission only persists before viral suppression. Adjusting the incidence denominator (person-time) to 90 days per individual who initiated ART in [221] results in approximately 3.13 times higher estimated incidence ratio: 0.25 for this specific period.⁹ Thus, I sampled relative infectiousness on ART but before viral suppression ($c = 3$) from a BAB distribution with mean (95% CI) of 0.25 (0.01, 0.67). Finally, I assumed that the virally un-suppressed state ($c = 5$) had half the reduced infectiousness of $c = 3$, yielding 95% CI: (0.50, 0.83).

3.2.5.2 HIV Progression & Mortality on ART

Effective ART stops CD4 cell decline and results in some CD4 recovery [83, 251]. Most CD4 recovery occurs within the first year of treatment [83]. Due to the limited number of modelled treatment states, I model this initial recovery to be associated with the pre-VLS ART state ($c = 3$). Gabillard et al. [85] and Lawn et al. [251] estimate an increase of between 25–39 cells/mm³ per month during the first 3 months of treatment. After initial increases, CD4 recovery is modest and plateaus. Battegay et al. [83] report approximate increases of 22.4 cells/mm³ per year between years 1 and 5 on ART. Since HIV states $h = 4, 5, 6$ correspond to 150, 150, and 200-wide CD4 strata, I model rates of movement along $h = 6 \rightarrow 5 \rightarrow 4 \rightarrow 3$ as 0.167, 0.167, 0.125 per month, respectively, during pre-VLS ART ($c = 3$) and 0.1 per year after VLS ($c = 4$).

Since higher CD4 states are modelled to have lower mortality rates (see § 3.2.4.2), the modelled recovery of CD4 cells via ART described above implicitly affords a mortality benefit. However, HIV infection is

⁹ In [221], individuals who initiated ART contributed approximately 9.4 months per-person (273 persons / 349 person-years, Tables 2 and 3); thus the first 3 months of each individual represent $3/9.4 = 0.319$ fewer person-months of follow-up.

associated with increased risk of death by non-AIDS causes — i.e., unrelated to CD4 count — including cardiovascular disease and renal disease [21]. Lundgren et al. [89] estimated 61% reduction in non-AIDS life-threatening events due to ART. For the same CD4 strata, Gabillard et al. [85] also report approximately 2-times higher mortality rates within the first year of ART vs. thereafter, suggesting that VLS is associated with 50% mortality reduction independent of CD4 increase. Thus, I modelled an additional 50% reduction in mortality among individuals with VLS ($c = 4$), and half this (25%) reduction before achieving VLS ($c = 3$).

3.2.6 Rates of HIV Diagnosis, ART Initiation, Viral Un-suppression & Re-suppression

Rates of HIV diagnosis δ , ART initiation τ , viral un-suppression ζ (including treatment failure, discontinuation, or loss to follow-up), and viral re-suppression σ' (Figure 3.1c) were defined to reflect historical trends and ART eligibility for Eswatini [215–218], as described in detail below. These rates were further calibrated to reproduce observed cascade attainment over time in Eswatini (e.g., proportion on ART among those diagnosed with HIV). Similar to condom use, rates were interpolated between specified years using monotone piecewise cubic interpolation [241].

3.2.6.1 HIV Diagnosis

Multiple Eswatini studies report the proportions of women and men who tested for HIV in the p12m. However, this proportion may not directly reflect the yearly rate of diagnosis, because individuals may test more frequently based on their perceived risk [252]. Indeed, EmaSwati living with HIV were more likely to have reported previously testing for HIV in 2006 [129, Table 14.9], 2011 [253, Table 5], and 2016 [137, Table 7.3]. Additionally, the proportion tested in p12m likely underestimates the *rate* of testing due to repeat testers. Assuming an exponentially-distributed time spent untested in the period under consideration (consistent with inherent compartmental modelling assumptions), the testing rate λ can be calculated from the proportion tested ρ over period T via:

$$\begin{aligned}\rho &= 1 - \exp(-\lambda T) \\ \lambda &= -\log(1 - \rho)/T\end{aligned}\tag{3.2}$$

Moreover, [238] found approximately 70% underreporting of ever testing for HIV in face-to-face interviews vs. anonymous polling booth surveys, with consistent results across married and unmarried women and men.

Yet, preliminary model calibration using reported HIV testing rates (with 95% CI) described below as HIV diagnosis rates directly caused the model to overestimate HIV+ status awareness vs. the available data (see § 3.3.2.3, Table 3.9). This apparent discrepancy between reported population-level testing rates and HIV+ status awareness is in fact common, and could be explained by testing rate heterogeneity [254] — i.e., the existence of “fixed” sub-populations who test frequently and those who test rarely or never. Without further stratifying the modelled population along this testing frequency dimension, it is impossible to capture this heterogeneity directly. However, an alternative solution is to reduce modelled HIV diagnosis rates to reproduce the available data on HIV+ status awareness via model calibration. To this end, I parameterized HIV diagnosis rates over time based on reported testing rates (below), with a

global reduction factor $f \sim \text{Unif}(0.5, 1)$. I further specified diagnosis rates using non-FSW women as a reference group, with separate time-varying *relative* rates defined for FSW and men. Confidence intervals for relative rates were assumed using a standard deviation of 0.2 for FSW and 0.1 for men (gamma priors).

HIV Testing Rates. Early HIV testing in Eswatini was mainly available to pregnant women via antenatal clinics, though a small number of youth and men also accessed HIV testing services [255, 256]. Based on antenatal clinic data [257], I modelled a gradual increase in rates of HIV diagnosis among women from zero to 95% CI (5, 15)% (gamma prior) per year from 1990 to 2002, when the national HIV testing and counselling program was formally introduced [126]. I assumed no initial differences between FSW and other women, due to the lack of specific key populations prevention programs [258]. I further assumed that HIV diagnosis among men initially occurred at 10% the rate of women.

By 2006, $\rho = 21.9$ (20.6, 23.3)% of women and 8.9 (7.8, 10.0)% of men had tested for HIV and received the results in p12m [129]¹⁰ — relative rate for men vs. women: 0.377 (0.207, 0.597). Further scale-up of HIV testing began in 2006 via provider-initiated testing and improved integration with the general health care system [126]. Between 2007 and 2010, such efforts doubled the number of testing locations (119 to 241) and tripled the number of total yearly tests (53,000 to 154,000) [123, 126]. By 2011, an estimated $\rho = 46.8\%$ of women, 28.4% of men, and 61.7 (55.6, 67.5)% of FSW had tested for HIV in p12m [108, 253]¹¹ yielding testing rates of $\lambda = 0.631, 0.333$, and 0.962 per year, respectively — relative rates: 0.529 (0.352, 0.743) for men, and 1.521 (1.206, 1.980) for FSW.

Phase 1 of the MaxART program [135] ran from 2011 to 2014, with a primary objective to increase HIV testing. An estimated 284,680 people were reached with 389,658 tests by the end of Phase 1 (2014). By 2016, 57.1% of women and 47.8% of men had tested in p12m [137], yielding testing rates of $\lambda = 0.846$ and 0.650 per year, respectively. The relative rate for men increased to 0.770 (0.587, 0.978); however, this increase was *not* applied (2011 relative rate maintained) to improve model fit (see § 3.3). In 2014 [141] and 2020 [109] approximately $\rho = 75\%$ of FSW had tested in p12m ($\lambda = 1.386$) as such, I applied a relative rate of 1.62, (1.29, 2.07) for 2016. I held all rates of HIV diagnosis after 2016 fixed.

3.2.6.2 ART Initiation

Rates of ART initiation τ were modelled to reflect time-varying eligibility, availability, loss to follow-up, and differences between sex/activity groups.

Eligibility. Historical ART eligibility in Eswatini has generally followed the evolving World Health Organization (WHO) guidelines [20, 84, 91, 92]. Initial eligibility included one of [215]:

- $\text{CD4} < 200 \text{ cells/mm}^3$ and any WHO clinical stage
- $\text{CD4} < 350 \text{ cells/mm}^3$ and WHO clinical stage III
- any CD4 count and WHO clinical stage IV

Eligibility was revised in 2010 [216] to:

- $\text{CD4} < 350 \text{ cells/mm}^3$ and any WHO clinical stage

¹⁰ Unless otherwise noted, “*tested for HIV*” will imply “*and received the results*” throughout this section.

¹¹ The adjustment for missing ages 15–17 in [253] from § 3.3.2.1 was applied to the reported 50.1% of women and 31.7% of men aged 18–49 who tested in p12m, assuming 20% of women and 10% of men aged 15–17 tested in p12m.

- any CD4 count and WHO clinical stage III or IV

and again in 2015 [217] to:

- $CD4 < 500 \text{ cells/mm}^3$ and any WHO clinical stage
- in a discordant partnership or having a specified illness (any CD4 count or WHO clinical stage)

before adoption of the current “*ART for all*” guidelines in late 2016 (modelled as effectively January 2017) [136, 218]. Phase 2 of MaxART also began in 2015, offering immediate ART via 14 health facilities in a stepped wedge design (6 facilities added per year) [136]. Relative to the 114 total facilities offering ART nationally at this time [130], I assumed this trial had minimal direct impact on population-level ART initiation — notwithstanding valuable insights gained regarding effective implementation [136].

I implemented the CD4-only eligibility criteria directly in the model, which is structured to match these 200, 350, and 500 $CD4 \text{ cells/mm}^3$ thresholds (Figure 3.1b). For eligibility by WHO clinical stages (not explicitly modelled), I estimated relative rates of ART initiation based on the following data from South Africa [259, Table 4] and Saudi Arabia [260, Table 2], respectively:

- 43/111 (39%) and 14/46 (30%) of PLHIV with $200 < CD4 < 350$ were at stages III or IV;
assumed: 35% PLHIV with $200 < CD4 < 350$ were eligible for ART pre-2010
- 13/79 (16%) and 6/76 (8%) of PLHIV with $CD4 > 350$ were at stage III;
assumed: 15% PLHIV with $350 < CD4 < 500$ were eligible for ART pre-2010 (5% with $CD4 > 500$)
- 5/79 (6%) and 1/76 (1%) of PLHIV with $CD4 > 350$ were at stage IV;
assumed: 20% PLHIV with $350 < CD4 < 500$ were eligible for ART 2010–2015 (5% with $CD4 > 500$)

I assumed that roll-out of eligibility changes in 2010, 2015, and 2017 each occurred over a 1-year period.

Availability and Initiation. ART first became available in Eswatini in late 2003 via a one-hospital pilot project [126]. Early ART scale-up was modest, with 31 facilities offering ART by the end of 2009 [261]; however, this number increased rapidly to 110 facilities by the end of 2011 [126]. Phase 1 of MaxART (2011–2014) sought to further increase ART coverage among eligible PLHIV [135], including decentralization to lower level facilities, bringing the total number of facilities to 170 by 2015 [262]. Finally, national adoption of “*Test and Start*” in 2017 likely further reduced delays in ART initiation, while loss to follow-up was reduced throughout the years of ART scale-up [136].

Considering these data, I modelled the yearly ART initiation rate among eligible diagnosed PLHIV as: effectively $\tau = 0$ in 2003, gradually increasing to 1.5 (0.5, 3.0) by 2010; then to 9 (6, 12) by 2012; and stabilizing at 12 by 2018. This maximum rate of $\tau = 12$ corresponds to a mean effective delay of one month between diagnosis and ART initiation; this value was chosen in part to avoid numerical instability when solving the model with very high rates.

Group Differences. In 2011, conditional ART coverage (among diagnosed) was greater among men vs. women (Table 3.9), suggesting greater ART initiation among men vs. women. Yet, unconditional ART coverage (among PLHIV, regardless of diagnosis) were approximately equal (31.4 and 33.2%, respectively), and so conditional differences may be explained by the fact that women were more likely to be diagnosed at an earlier HIV stage via antenatal care, and thereafter not yet eligible for ART. Thus, I assumed no differences in ART initiation among men vs. women. A similar mechanism could partially explain differences in conditional coverage between FSW vs. women overall (36.9 vs. 48.0%), as FSW were more slightly likely to know their status (74.1 vs. 69.1%). However, FSW face unique barriers to

accessing ART related to stigma and material insecurity [38]; as such, I sampled a relative rate for ART initiation among FSW from [0.5, 1] (uniform prior).

3.2.6.3 ART Failure

The modelled virally un-suppressed state ($c = 5$) reflects any combination of treatment failure (i.e., due to resistance mutations), discontinuation, or loss to follow-up (LTFU) after achieving viral suppression. The model does not explicitly simulate emergence and/or transmission of drug resistance, nor multiple unique ART regimens. As of 2016, resistance mutations to at least 1 of 3 drugs in combination regimens were identified in 10% ART-naive PLHIV in Eswatini, and 16% PLHIV with prior ART exposure [263]. However, the extent to which these individual mutations can cause complete treatment failure remains unclear. Additionally, while transmissible resistance mutations could become more prevalent over time, emergence of new drugs can combat the population-level impacts of this resistance [264].

All available data suggests that retention in ART care — i.e., not discontinued or LTFU — has improved over time in Eswatini [137, 265, 266]. Assuming an exponentially-distributed retention time (consistent with inherent compartmental modelling assumptions), I averaged the available data [266, Table 6] to calculate the effective yearly ART attrition rate as: 16.5% in 2008, 13.8% in 2010, 14.1% in 2012, and 8.3% in 2014. One-year LTFU was reported as 1% in 2016 [137], but it's not clear whether this definition was consistent with the earlier estimates. Many measures of LTFU may also overestimate true LTFU by failing to account for transfers between clinics and deaths [267, 268]; it's not clear whether the reported measures for Eswatini account for transfers or deaths.

LTFU was estimated to be 1.3 times higher among men vs. women in South Africa [267], which would be consistent with observed lower viral suppression among men vs. women on ART in Eswatini (Table 3.9) [267]. The same study estimated that LTFU did not significantly differ by the modelled CD4-strata [267]. No estimates of LTFU were available for FSW specifically in Eswatini, but among 354 FSW on ART in [109] (2021), 103 knew the results of viral load monitoring in p12m, of whom only 8 self-reported undetectable viral load. Such data may again reflect the unique barriers to accessing ART faced by FSW [38].

Considering all of the above data, I assumed: a yearly rate of viral un-suppression ζ among non-FSW women of 15% until 2010, decreasing to 5% by 2018; plus relative rates for men and FSW: [1, 1.5] (uniform priors).

3.2.6.4 Viral Re-suppression

The rate of viral re-suppression σ' aims to reflect the average delay associated with the steps of switching regimens (in case of treatment failure), or the steps of re-engaging in HIV care (in case of LTFU).

For treatment failure, viral un-suppression must first be identified. Availability of viral load monitoring in Eswatini was limited until at least 2010 [216], but incorporated into standard of care by 2015 (yearly testing) [217]. Without viral load testing, treatment failure can still be indicated clinically [216]. After suspecting treatment failure, at least three months of additional monitoring is typically required to rule-out issues of adherence [216–218], before another regimen is started. Moreover, second/third-line regimen options were limited in Eswatini until at least 2014 [130, 269]. Upon switching to an improved regimen, I assume that viral suppression occurs at the same rate as among ART-naive PLHIV (see § 3.2.5).

For LTFU, no data directly indicate the average duration out of care in Eswatini. A recent model-based analysis of Kenyan data [270] suggests an average between 8 months and 2 years. Considering large-scale, multisectorial efforts to improve ART care in Eswatini, it is likely that duration out of care has declined since 2010. Thus, I sampled the initial rate of viral re-suppression σ' from a gamma prior with 95% [0.5, 1.0], which increased by a factor of 1.5 over 2010–2018. I assumed no differences between groups.

3.2.7 Risk Heterogeneity Among FSW

Existing HIV transmission models which include FSW have rarely sub-stratified this population, such as to reflect differential HIV risk or distinct typologies of sex work [29, 271]; yet such heterogeneities may influence transmission dynamics. Among the studies identified in Chapter 2, only three sub-stratified FSW by risk-related factors: Cremin et al. [272] defined three levels of risk via regression analysis, Low et al. [273] distinguished between occasional and full-time FSW, while Shannon et al. [30] sub-stratified FSW by work environment, violence exposure, and context-specific structural factors. Seven other studies, reflecting two unique models [157, 274], employed age stratification of all activity groups, including FSW; these models had several risk-related parameters which varied by age.

The model structure here (Figure 3.1a) was designed to capture *within-FSW* risk heterogeneity. The objective of the following analysis was therefore to parameterize higher vs. lower risk FSW. I sought to define these groups based on biobehavioural and/or contextual factors which are demonstrably associated with HIV risk, and which can be mechanistically incorporated into a transmission model — i.e., through the force of infection equation. Later, the parameterization of these groups was validated through model fitting to relative differences in HIV prevalence § 3.3.2.1.

Many cross-sectional studies of HIV among FSW quantify the association of risk factors with HIV serostatus [29, 275–277]. However, serostatus reflects cumulative risk exposure, whereas sexual risk behaviour is dynamic [168, 278], as is use of prevention resources [198]. For example, while HIV prevalence often increases with age, HIV incidence among women can peak before age 25 [208]. Thus, risk factors associated with HIV serostatus are not necessarily mechanistically related to HIV acquisition. Indeed, FSW may reduce risk behaviours in response to seroconversion [279]. Cohort studies that measure incidence can help identify risk factors for HIV acquisition [280, 281], but large sample sizes are often required to accurately estimate overall incidence rate, let alone risk factors [282].

3.2.7.1 FSW Survey Data

Three biobehavioural surveys, in 2011 [108] ($N = 325$), 2014 [141] ($N = 781$), and 2021 [109] ($N = 676$) provide HIV status and biobehavioural data on FSW in Eswatini. The 2011 and 2021 surveys featured serologic HIV testing, and employed respondent driven sampling (RDS, details in [143]). The 2014 survey relied on self-reported HIV status, andd employed venue-based snowball sampling, based on the Priorities for Local AIDS Control Efforts (PLACE) methodology, which aims to identify areas of higher incidence [144]. More details about each study are given in § 1.2.2.1 and Table 1.2. I analyzed the individual-level data from 2011 and 2014 (data from 2021 not yet available) to explore the potential association of biobehavioural factors with HIV risk, so that such factors could then be used to distinguish between lower risk vs. higher risk FSW.

3.2.7.2 HIV Status

Only the 2011 and 2021 studies included serologic testing for HIV. Among those tested in 2011 ($N = 317$, 98%), 70% were HIV+, yielding RDS-adjusted prevalence estimate of 61% (CI: 51–71%) [108]. Among serologically HIV–, 11% self-reported HIV+ status (false positive), and among serologically HIV+, 26% self-reported HIV– status (false negative or undiagnosed). Overall, self-reported HIV status underestimated HIV prevalence in 2011 by a factor of approximately 0.78 (55 vs 70%). Unadjusted HIV prevalence in 2021 was 58.8%, with 88% (363/411) reporting previous awareness of HIV+ status.

In 2014, self-reported HIV prevalence was 38% among respondents who reported (85%). This 38% is surprisingly low considering that the PLACE methodology explicitly aimed to sample venues with higher HIV incidence [144], and 2014 vs. 2011 respondents were older (median 27 vs. 25 years), had been selling sex longer (median 5 vs. 4 years), and tested more frequently (87 vs. 75% tested at least once in the past year, 82 vs. 63% among self-reported HIV–). Perhaps the differences are attributable to the sampling methodology. Among respondents who self-reported HIV+ status, the 2014 survey also asked for age of HIV diagnosis (6% missing). Age of HIV diagnosis supports crude time-to-event analysis (next section), which can account for confounding by age and censoring, as compared to logistic regression on HIV status, keeping in mind the limitations of self-reported HIV status.

3.2.7.3 Risk Factors for HIV

Next, I explored the potential association of risk factors with HIV via the following three models:¹²

1. Logistic regression on serologic HIV status (2011 data)
2. Logistic regression on self-reported HIV status (2014 data)
3. Cox proportional hazards for interval-censored time to HIV infection, with interval from self-reported sex work debut to either self-reported time of HIV diagnosis or survey date (2014 data);
Figure 3.2 illustrates the four potential censoring cases in this framework.

An important limitation to all models is that risk factors reported by FSW at the time of survey are assumed to be fixed characteristics of the respondents, rather than dynamic characteristics that vary over time. Additionally, respondents with any missing variables for each individual model were excluded from that model.

Risk factors were selected based on prior knowledge of plausible mechanistic influence on HIV incidence and/or prevalence. The risk factors explored are summarized in Table 3.3, including univariate and multivariable association under each model. Variable selection for multivariable models was performed using backward selection as described by Lawless and Singhal [283], using a $p \leq 0.1$ (per variable) threshold for stepwise variable retention. Estimated conditional effects of variables retained in the multivariable logistic regression models are illustrated in Figure 3.3.

Following variable selection, each multivariable model was used to estimate the total HIV+ status odds ratio (logistic) or HIV incidence hazard ratio (Cox) for each respondent in the respective survey — i.e., $e^{X_i \beta}$ for respondent i — representing an overall “risk score” under each model. Respondents were then

¹² Logistic regression models were implemented using `lrm` from: cran.r-project.org/package=rms.

Cox proportional hazards models were implemented using `coxaalen` from: cran.r-project.org/package=coxinterval.

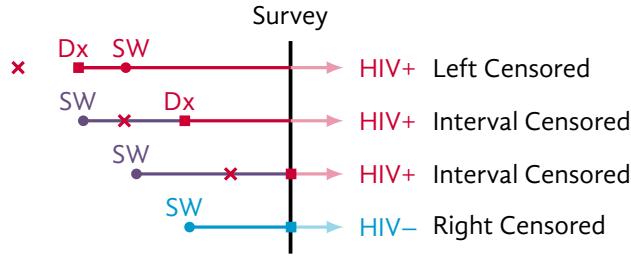


Figure 3.2: Illustration of time-to-event analysis framework for cross-sectional FSW survey data

✗: HIV infection; SW: time of sex work debut; Dx: time of HIV diagnosis.

Table 3.3: Risk factors explored for association with HIV+ status among FSW in Eswatini

Factor	2011 LR				2014 LR				2014 CPH			
	Univar		Multivar		Univar		Multivar		Univar		Multivar	
	OR	p	OR	p	OR	p	OR	p	HR	p	HR	p
Age ^a	1.11	<0.001*	—	—	1.14	<0.001*	1.15	<0.001*	1.09	<0.001*	1.09	<0.001*
Years selling sex ^a	1.13	<0.001*	1.13	<0.001*	1.12	<0.001*	—	—	1.08	<0.001*	—	—
Monthly sex work income ^b	0.98	0.155	—	—	0.98	0.097	0.97	0.084	0.98	0.019*	0.97	0.001*
Non-paying partners ^c	0.88	0.307	—	—	1.07	0.233	—	—	1.05	0.312	—	—
Monthly new clients ^c	1.01	0.412	—	—	1.05	<0.001*	1.07	<0.001*	1.04	<0.001*	1.04	<0.001*
Monthly regular clients ^c	1.01	0.351	—	—	1.03	0.002	—	—	1.02	<0.001*	1.02	0.034*
Non-paying condom use ^d	0.90	0.703	—	—	0.90	0.673	—	—	0.92	0.677	—	—
New client condom use ^d	0.60	0.100	—	—	0.48	0.006*	1.25	0.599	0.56	0.004*	—	—
Regular client condom use ^d	0.58	0.110	—	—	0.39	<0.001*	0.35	0.004*	0.49	<0.001*	0.50	<0.001*
Any anal sex past month	0.97	0.896	—	—	1.89	0.015*	—	—	1.57	0.015*	1.27	0.260
Any STI symptoms past year	2.29	<0.001*	2.41	<0.001*	2.75	<0.001*	2.80	<0.001*	2.17	<0.001*	2.05	<0.001*

^a OR per year; ^b OR per Swati lilangeni per month; ^c OR per partner; ^d 2011: always vs. not always, 2014: at last sex. — indicates variable was not selected in the multivariable model. LR: logistic regression on HIV+/- status; CPH: Cox proportional hazards on time to self-reported HIV seroconversion. OR: odds ratio; HR: hazard ratio; p: p-value. 2011 data based on serologic HIV test; 2014 data based on self-reported HIV status, age of sex work debut, and age of HIV diagnosis.

stratified into the top 20% and bottom 80% by these risk scores. The values of each variable were compared between these two strata using a test for the ratio of the means [284] to support model parameterization; these ratios are summarized in Table 3.4, and the distributions of variable values across the two strata are illustrated in Figure B.4.

3.2.8 Wider Population: Bias Adjustment

The remaining women and men (besides FSW and clients) are stratified by numbers of partners in the past 12 months (p12m): 0–1 and 2+. The 2006–07 DHS [129], 2011 SHIMS [134], and 2016–17 SHIMS2 [137] surveys provide the numbers of respondents who reported 2+ partners in the past 12 months (p12m): 13.5, 18.2, 14.5% among men, and 1.6, 3.8, 4.1% among women, respectively.¹³ However, such reports are likely substantially biased by social desirability bias due to the face-to-face interview format [238, 285–287]. Moreover, these data do not provide information on the types of partners reported — i.e., those reporting 1 partner in p12m are not necessarily in a main/spousal (vs casual) partnership, and

¹³ From Tables 14.7.1 and 14.7.2 (ages 15–49) in [129], Table 3 (ages 18–49) in [134], Table 15.3.A (ages 15+) in [137], with manual adjustment for survey skip patterns in [129, 137].

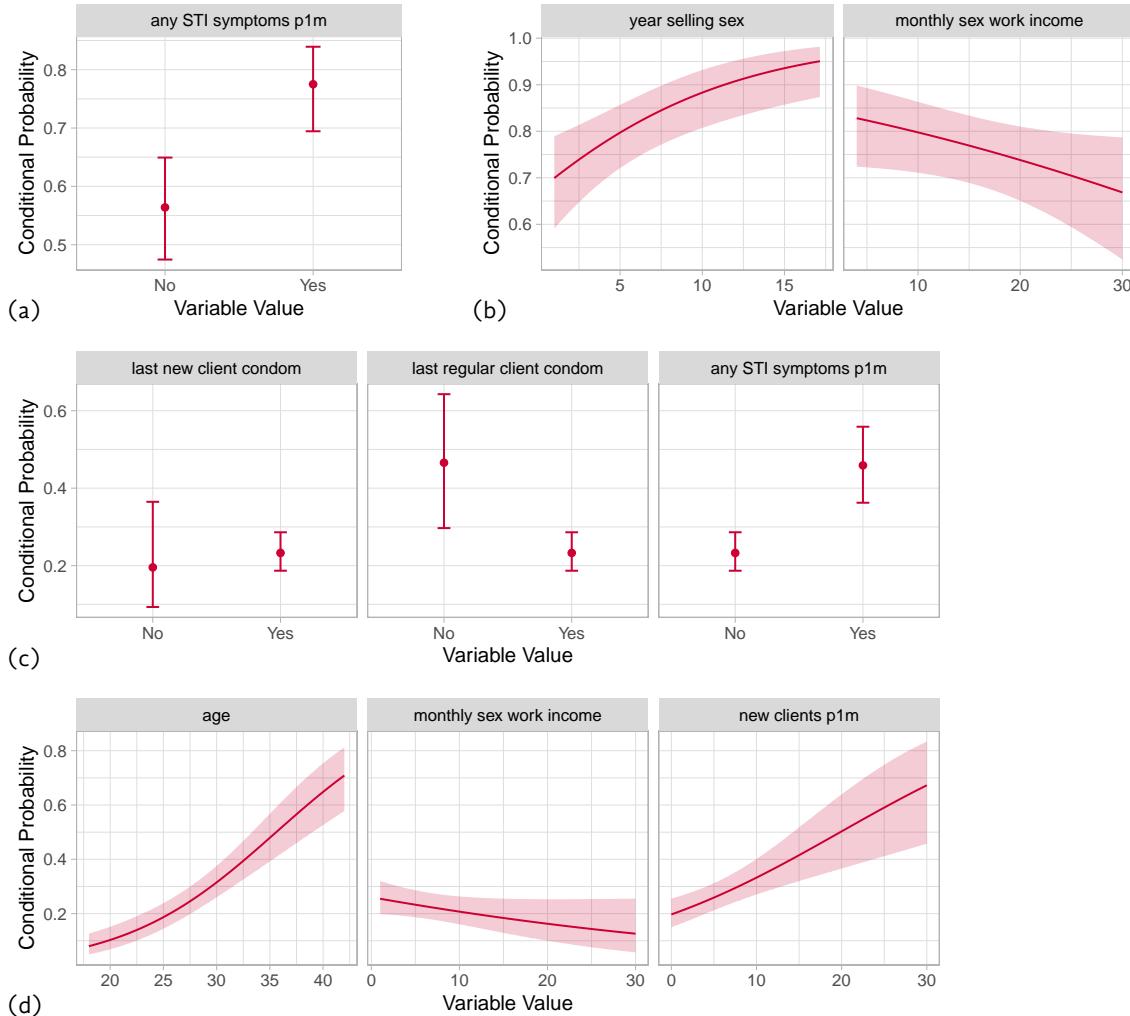


Figure 3.3: Predicted conditional effects (probability) of variables in multivariable logistic regression models for HIV status

(a) 2011, serologic HIV status, factor variables; (b) 2011, serologic HIV status, continuous variables; (c) 2014, self-reported HIV status, factor variables; (d) 2014, self-reported HIV status, continuous variables; conditional probabilities shown for fixed covariates at arbitrary values.

Table 3.4: Ratios of HIV risk factor variables among higher vs. lower risk FSW in Eswatini

Factor	2011 LR		2014 LR		2014 CPH	
	High / Low	Ratio (95% CI)	High / Low	Ratio (95% CI)	High / Low	Ratio (95% CI)
Age	31.8 / 24.7	1.29 (1.22, 1.36)*	32.6 / 26.2	1.24 (1.20, 1.28)*	33.5 / 26.6	1.26 (1.21, 1.31)*
Years selling sex	11.3 / 4.03	2.81 (2.41, 3.25)*	10.0 / 5.47	1.83 (1.64, 2.03)*	10.2 / 5.83	1.75 (1.54, 1.98)*
Monthly sex work income ^a	15.1 / 15.2	1.00 (0.86, 1.15)	6.77 / 7.06	0.96 (0.82, 1.11)	6.32 / 7.28	0.87 (0.73, 1.02)
Non-paying partners	1.42 / 1.43	0.99 (0.81, 1.19)	1.56 / 1.11	1.40 (1.11, 1.72)*	1.53 / 1.19	1.29 (0.98, 1.62)
Monthly new clients	5.50 / 6.98	0.79 (0.49, 1.15)	8.39 / 4.15	2.02 (1.63, 2.44)*	8.36 / 4.41	1.90 (1.43, 2.39)*
Monthly regular clients	9.35 / 9.05	1.03 (0.69, 1.42)	11.1 / 8.25	1.35 (1.13, 1.57)*	12.4 / 8.61	1.44 (1.18, 1.71)*
Non-paying condom use ^{bc}	0.26 / 0.35	0.73 (0.40, 1.11)	0.77 / 0.81	0.95 (0.84, 1.06)	0.76 / 0.81	0.95 (0.81, 1.08)
New client condom use ^{bc}	0.68 / 0.76	0.89 (0.73, 1.06)	0.79 / 0.91	0.86 (0.79, 0.94)*	0.74 / 0.94	0.79 (0.69, 0.88)*
Regular client condom use ^{bc}	0.38 / 0.46	0.83 (0.45, 1.28)	0.67 / 0.91	0.74 (0.65, 0.82)*	0.60 / 0.92	0.65 (0.55, 0.75)*
Any anal sex past month	0.59 / 0.41	1.41 (1.06, 1.84)*	0.17 / 0.07	2.43 (1.47, 3.85)*	0.23 / 0.07	3.24 (1.95, 5.34)*
Any STI symptoms past year ^c	0.79 / 0.43	1.86 (1.54, 2.25)*	0.59 / 0.15	3.94 (3.15, 5.03)*	0.61 / 0.17	3.67 (2.87, 4.79)*
HIV prevalence ^d	0.94 / 0.64	1.46 (1.30, 1.63)*	0.66 / 0.29	2.29 (1.92, 2.75)*	0.71 / 0.31	2.32 (1.94, 2.80)*

High / Low: mean variable value among higher / lower risk groups, as defined by the top 20% / bottom 80% in multivariable model-predicted risk score: odds ratio from logistic regression (LR); hazards ratio from Cox proportional hazards (CPH). ^a Swati lilangeni per month; ^b 2011: always vs. not always, 2014: did use condom at last sex; ^c proportion of respondents; ^d 2011: serologic HIV status; 2014: self-reported HIV status; * statistically significant, $p < 0.05$.

neither are those reporting 2+ partners in p12m. This section develops and applies a new method to adjust for these potential reporting biases, and simultaneously estimate the numbers of main/spousal and casual partners among each stratum. The results of these analyses then directly inform activity group sizes in § 3.2.9.3 and numbers of partners in § 3.2.11.3.

3.2.8.1 Reported Partner Numbers

Both the 2006 DHS [129, Tables 14.6.1 and 14.6.2] and 2016-17 SHIMS [137, Tables 15.4.A and 15.4.B] summarize the numbers of women and men by partners in p12m and by marital/union status, but summaries are stratified by each factor separately, not jointly. However, making the following assumptions, I estimated the jointly-stratified proportions of individuals. Let W_{2+} , W_1 , and W_0 denote women reporting 2+, 1, and 0 partners, respectively, and likewise with M_{2+} , M_1 , M_0 for men (all partners reflect p12m).¹⁴ The assumptions were:

- W_{2+} included all women in non-polygynous unions (married or cohabiting) reporting sex with a “casual” (non-marital, non-cohabiting) partner
- M_{2+} included all men in polygynous unions, plus all men in non-polygynous unions reporting sex with a casual partner
- the remaining W_{2+} and M_{2+} formed only casual partnerships
- all women and men in non-polygynous unions reporting no sex with a casual partner reported 1 partner (W_1 and M_1)
- the remaining W_1 and M_1 formed only casual partnerships

Figure 3.4 illustrates the resulting proportions of women and men in each union / partners in p12m stratum in 2006-07 (a) and 2016-17 (b).

¹⁴ Regarding notation in this section, $W_{2+} = P_{s_1 i_{234}} / P_{s_1}$, $W_1 + W_0 = P_{s_1 i_1} / P_{s_1}$, and likewise for men (M , $s = 2$).

3.2 PARAMETERIZATION

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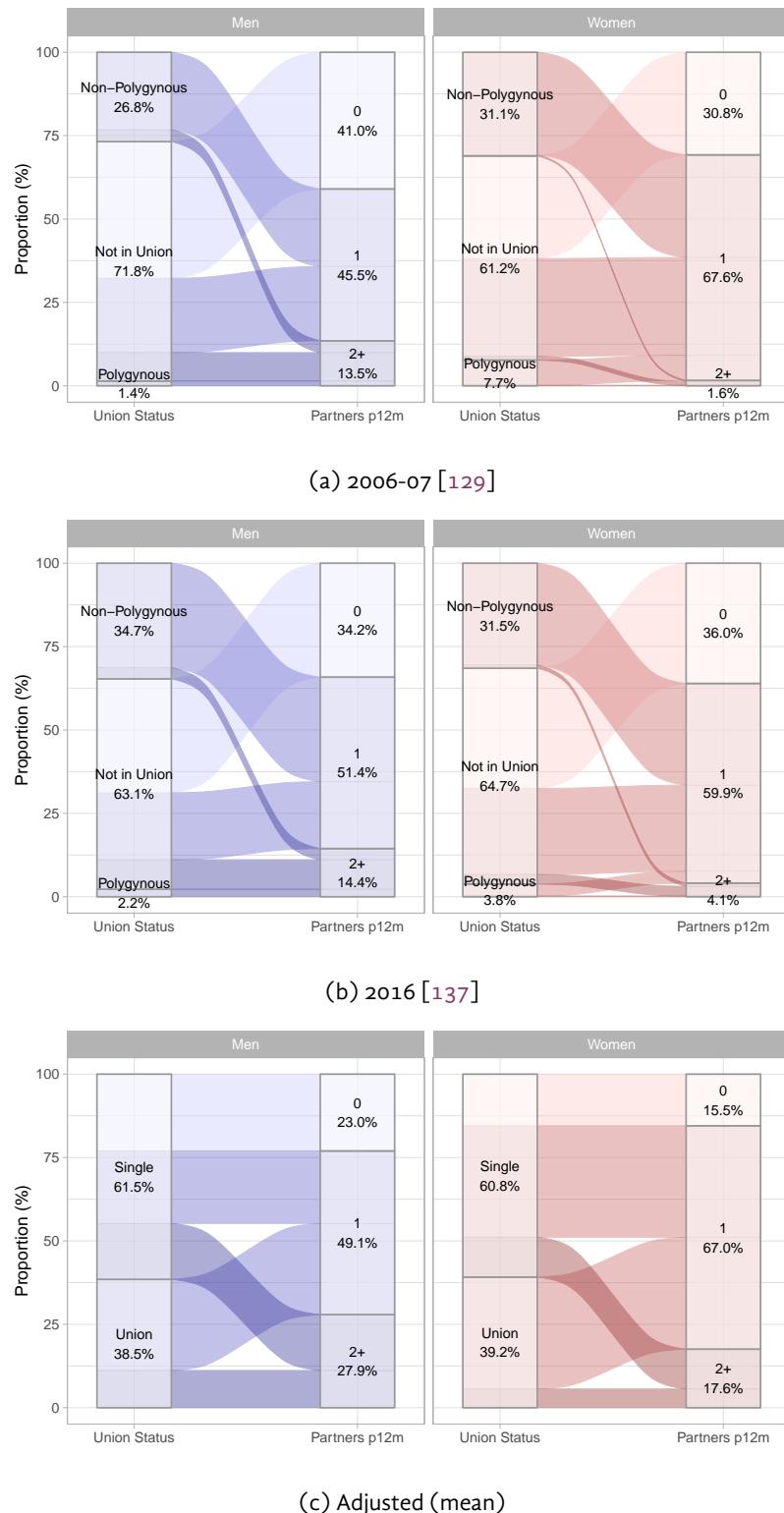


Figure 3.4: Reported proportions of women and men aged 15–49, stratified by union status and numbers of partners in the past 12 months

3.2.8.2 Bias Adjustment: Rationale

I was motivated to examine potential reporting bias because M_{2+} is consistently much greater than W_{2+} . In fact, this difference is common in surveys [288, 289], and could be explained by either: (a) a small number of women with many partners, such as FSW, who may also not be reached by the survey, or who may not fully report partner numbers; (b) over-reporting of partnerships by men; or (c) under-reporting of partnerships by women. Further stratification of women reporting 2+ partners in [129, Table 14.7.1] revealed that 94% reported exactly 2 whereas 6% reported 3+, suggesting that explanation (a) is less likely unless women with 3+ partners are under-reported or indeed missing from the survey.

Gregson et al. [290] (Zimbabwe), Nnko et al. [291] (Tanzania) and Clark, Kabiru, and Zulu [292] (Kenya) explored explanations (b) and (c) through measures of consistency; their results suggested that under-reporting of non-spousal partnerships by women (c) was more likely, perhaps due to social norms and pressures; such norms in Eswatini are explored in [293–296]. In fact, a review comparing computer-based tools vs. face-to-face interviews for surveying sexual behaviour [43] found that both women and men may under-report sexual partners, but women more so. A notable 2008 study in Benin [238] found that 7 times as many married women (21 vs. 3%) and 3 times as many married men (53 vs. 18%) reported any extramarital sex in p12m in a survey via anonymous polling booth vs. face-to-face interview. Similarly, 5 times as many unmarried women (13.5 vs. 2.8%) reported exchanging sex for money, gifts or favours in p12m, while 4 times as many unmarried men (62 vs. 14%) reported non-transactional sex with a woman in p12m. Such findings were similar to those from Zimbabwe (1990s) [290].

3.2.8.3 Bias Adjustment: Approach

To account for the above potential reporting biases and qualitative insights from [293–296], I modelled the adjusted proportions of Swati women and men in each union / partners in p12m stratum as follows. Let W_{s1} and W_{u1} denote sub-proportions of W_1 who are single and in a union, respectively, and likewise for W_{s2+} , W_{u2+} , M_{s1} , M_{u1} , M_{s2+} , and M_{u2+} . Further, let W_{s1} denote the reported proportion of women (average of 2006-07 and 2016-17), vs. W'_{s1} denoting the adjusted proportion. I assumed that a fraction of W_0 belongs in W'_{s1} — i.e., a fraction of women reporting 0 partners in p12m truly had 1 casual (non-main/spousal) partner. I modelled this relationship through an odds ratio $\varphi_{W,s1:0}$, which is roughly equivalent in interpretation to the proportion ratios estimated by Béhanzin et al. [238].¹⁵

$$\varphi_{W,s1:0} = \frac{W'_{s1}}{W'_0} \Big/ \frac{W_{s1}}{W_0} \quad (3.3)$$

I defined similar odds ratios $\varphi_{W,s2+:s1}$, $\varphi_{W,u2+:u1}$, $\varphi_{W,u1:0}$, $\varphi_{W,u1:s1}$, and $\varphi_{W,u2+s2+}$, and likewise for men. These strata and the corresponding adjustments / reallocations of women from reported to adjusted strata are illustrated in Figure 3.5. To resolve the adjusted values W' then requires solving the (nonlinear) system of 6 equations corresponding to the 6 odds ratios φ , subject to $\sum_i W'_i = 1$ and $0 \leq W'_i < 1$. An exact solution is not guaranteed, but the sum squared error from all equations can be minimized. The odds ratios φ were then defined as follows, including sampling distributions.

Union Status. I assumed that under-reporting of main/spousal partnerships was minimal, but that some “main” partnerships may not be captured in the definition “married/cohabiting” from [129, 137];

¹⁵ Odds ratios ensure no proportions become greater than one or negative.

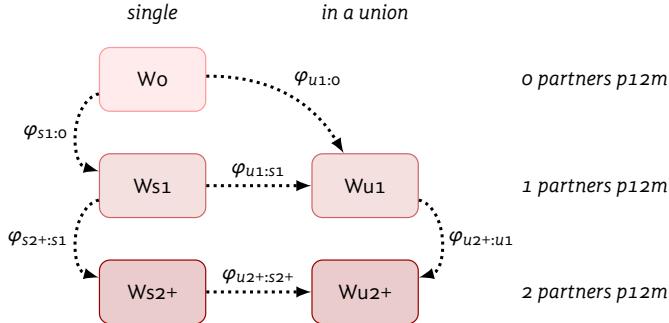


Figure 3.5: Illustration of how the proportions of women (and equivalently men) are adjusted / reallocated between union / partners in p12m strata based on odds ratios φ

p12m: within the past 12 months; Wo: 0 partners in p12m; Ws1: single (not married/cohabiting) and 1 partner in p12m; Wu1: in a union (married/cohabiting) and 1 partner in p12m; Ws2+: single and 2+ partners in p12m; Wu2+: in a union and 2+ partners in p12m. φ : odds of truly being in the second (arrowhead) vs. first (tail) group.

thus $\varphi_{u1:0}$, $\varphi_{u1:s1}$, and $\varphi_{u2+s2:u1}$ would be small but greater than 1 (horizontal transitions in Figure 3.5). Moreover, based on the median age of marriage, 23–29 [129], approximately half of respondents aged 15–49 would have been married, whereas only 28–39% of women and men reported being in a union (Figure 3.4a and 3.4b), although some marriages end in divorce/widowing [129]. Thus, I sampled each of $\varphi_{u1:0}$, $\varphi_{u1:s1}$, and $\varphi_{u2+s2:u1}$ from $1 + \text{Gamma}(\alpha, \beta = 1)$ with $\alpha = .5$ for women and $\alpha = .3$ for men, yielding mean (95% CI): 1.50 (1.00, 3.51) and 1.30 (1.00, 2.90), respectively.

Partner Numbers. Next, regarding partner numbers, I defined $\varphi_{s1:0}$, φ_{s2+s1} , and $\varphi_{u2+s2:u1}$ as follows (vertical transitions in Figure 3.5). The median age of first sex in Eswatini was approximately 18 for women and 19.5 for men [129]. Thus, the 31–36% of women and 34–41% of men aged 15–49 reporting no partners in p12m (Figure 3.4a and 3.4b) is likely overestimated, although some individuals may be abstinent in p12m following sexual debut. I assumed that women had 3 and men had 2 times the odds of actually having 1 casual partner in p12m while reporting no partners. Thus, I sampled $\varphi_{s1:0}$ from $1 + \text{Gamma}(\alpha, \beta = 1)$ with $\alpha = 2$ for women and $\alpha = 1$ for men, yielding mean (95% CI): 3.00 (1.24, 6.57) and 2.00 (1.03, 4.69), respectively. Drawing on [238], I assumed that “single” women and men (not married/cohabiting) were less likely to report multiple partners in p12m, but women more so. Thus, I sampled φ_{s2+s1} from $1 + \text{Gamma}(\alpha, \beta = 1)$ with $\alpha = 4$ for women and $\alpha = 1$ for men, yielding 5.00 (2.09, 9.77) and 2.00 (1.03, 4.69). I made a similar assumption about married/cohabiting women and men, with the same odds for men, but even greater odds of non-reporting among women. I sampled $\varphi_{u2+s2:u1}$ from $1 + \text{Gamma}(\alpha, \beta = 1)$ with $\alpha = 6$ for women and $\alpha = 1$ for men, yielding 7.00 (3.20, 12.67) and 2.00 (1.03, 4.69).

3.2.8.4 Bias Adjustment: Results

The mean resulting adjusted proportions W' and M' from solving the system with the assumed odds ratios φ are illustrated in Figure 3.4c, which can be compared to the reported proportions in (a) and (b). Figure B.7 also illustrates the empiric density distributions for each element W'_i and M'_i . Numerically, the mean (95% CI) estimates were:

- $W'_0 = 17$ (9, 27)% of women and $M'_0 = 25$ (13, 35)% of men had 0 partners in p12m
- $W'_1 = 66$ (57, 75)% of women and $M'_1 = 49$ (37, 61)% of men had 1 partners in p12m
- $W'_{2+} = 17$ (10, 27)% of women and $M'_{2+} = 26$ (15, 44)% of men had 2+ partners in p12m
- $W'_{u1}/W'_{01} = 38$ (21, 57)% women and $M'_{u1}/M'_{01} = 35$ (23, 50)% men with 0–1 partners in p12m were in a main/spousal partnership
- $W'_{s1}/W'_{01} = 41$ (19, 65)% women and $M'_{s1}/M'_{01} = 31$ (15, 55)% men with 0–1 partners in p12m were in a single casual partnership
- $W'_{u2+}/W'_{2+} = 32$ (9, 55)% women and $M'_{u2+}/M'_{2+} = 38$ (13, 62)% men with 2+ partners in p12m were in a main/spousal partnership, and the rest had only casual partnerships.

3.2.9 Activity Group Sizes

Population sizes of all activity groups are modelled as proportions of the total population, which are assumed to remain roughly constant. Individuals can, however, move between groups (see § 3.2.10.2) — i.e., groups are open populations — and disproportionate mortality due to HIV between groups may cause higher risk groups to shrink over time. Overall population growth is discussed in § 3.2.10.1.

3.2.9.1 Female Sex Workers

The proportion of women who report sex work in national demographic and health surveys is generally considered unreliable due to social desirability bias, particularly if the survey is face-to-face and household-based [44, 238, 285, 287, 290]. Therefore, FSW population size estimates require targeted surveys and unique methodologies [52, 53]. In both [141] and [109], the Swati FSW population size was estimated using a combination of unique object method, service multiplier method, prior survey participation, and network scale-up method (NSUM) [52]. In 2011 [141], regional FSW population size estimates ranged from 0.7% to 6.5% of all women, with overall population-weighted mean across regions of 2.9%; in 2021 [109], the mean (95% CI) estimates were 2.43 (1.17, 5.02)%. To reflect this uncertainty in the model, a BAB distribution was fitted such that 95% of the probability fell between 0.7% and 6.5%, and used as the prior distribution for the proportion of women who are FSW: $P_{s_1 i_{34}}/P_{s_1}$. Then, following the analysis in § 3.2.7, the proportion of all FSW in the higher risk FSW group was fixed at 20%, and likewise the lower risk group at 80%.

3.2.9.2 Clients of FSW

Similar to FSW, household-based surveys are not considered reliable data sources for estimating the population size of clients of FSW [238]. However, few surveys are designed to reach clients of FSW, and no direct estimates of FSW size exist for Eswatini. So, I use a common approach for inferring the FSW client size [240], similar to the “multiplier method” [297]. Given the FSW population proportion $P_{s_1 i_{34}}$, the number of average yearly new and regular sex work clients per FSW $Q_{p_{34}s_1 i_{34}}$, the frequency of sex per partnership-year $F_{p_{34}}$, and the total number of yearly commercial sex acts per client year $Q_{p_{34}s_2 i_{34}} F_{p_{34}}$,

the total client population $P_{S_2 i_{34}}$ is defined as:

$$\sum_i P_{S_2 i_{34}} = \frac{\sum_{pi} P_{S_1 i} Q_{p_{34} S_1 i_{34}} F_{p_{34}}}{\sum_{pi} Q_{p_{34} S_1 i_{34}} F_{p_{34}}} \quad (3.4)$$

Then, as with FSW, the proportion of total clients in the higher risk client group is defined as 20% of all clients, and likewise for the lower risk group at 80%. Using $Q_{p_{34} S_1 i_{34}}$, $Q_{p_{34} S_2 i_{34}}$, and $F_{p_{34}}$ as defined below in § 3.2.11.2, the client population size $P_{S_2 i_{34}}$ estimated by this method was 14.5 (5.2, 33.9)% of men.

3.2.9.3 Wider Population

Based on the results of § 3.2.8, I defined the sizes of the modelled lower and medium activity groups, and the average numbers of main/spousal partnerships per person. I assumed that W'_{2+} and M'_{2+} included FSW and client population sizes, respectively. Thus, the populations size of medium activity women was defined as $P_{S_1 i_2} = W'_{2+} - P_{S_1 i_{34}}$. Sampling W'_{2+} from a BAB distribution with 95% CI (10, 27)%, the resulting 95% CI for medium activity women $P_{S_1 i_2}$ was (6, 25)% of women. The lowest activity women population size was then defined as $1 - P_{S_1 i_{234}}$, representing (73, 90)% of women. Since there is greater uncertainty in the client population size, the same approach for the medium activity men population size $P_{S_2 i_2}$ could yield negative values. Instead, I sampled $P_{S_2 i_2}$ directly from a BAB distribution with 95% CI (10, 17)%, yielding 95% CI for $P_{S_2 i_{234}}$ of (15, 50)% of men, which is close to (15, 44)% from M_{2+} . The lowest activity men were then then defined as $1 - P_{S_2 i_{234}}$, representing (50, 85)% of men.

3.2.10 Turnover

3.2.10.1 Births & Deaths

The modelled population considers ages 15–49, reflecting commonly reported data and the majority of sexual activity. In the absence of mortality, individuals would therefore remain within the modelled “open cohort” population for 35 years. The estimated average yearly mortality rate for these ages was 1.44% around 2006 [129, Table 15.2]. However, this estimate includes HIV/AIDS-attributable mortality, which I model separately (see § 3.2.4.2), accounting for approximately 64% of deaths around that time [298]. Thus, the overall exit rate from the modelled cohort due to reaching age 50 (“aging out”) and non-HIV-attributable mortality was: $\mu = 1/35 + (1 - .64)1.44\% = 3.78\%$.

I estimated the rate of entry into the modelled population v to fit population size of ages 15–49 in Eswatini [219], and approximate population growth rates [299], given that I model HIV/AIDS-attributable mortality separately. Specifically, I assumed a population growth rate $g = v - \mu$ in the absence of HIV/AIDS of 4% in 1980, 3% in 2000, 1.5% in 2010, and 1.5% in 2020 (monotonic cubic interpolation). I sampled g in 2050 from a uniform prior with 95% CI (0.7%, 1.5%), reflecting uncertainty in estimated projections [299]. Finally, I calculated the population entry rate as $v = g + \mu$. These parameter values were informally validated by comparison of model outputs with Swati population sizes for ages 15–49 from [219]. The distribution of activity groups among individuals *entering* the model, denoted E_{Si} , is different from the distribution among individuals *currently* in the model P_{Si} , but E_{Si} is computed automatically as described below in § 3.2.10.2.

3.2.10.2 Activity Group Turnover

In addition to overall population turnover (entry/exit from the open population), I model movement of individuals between activity groups within the model. Activity group turnover reflects the fact that risk is not constant over sexual life course, and reported duration in higher activity contexts can be short [29]. Previous modelling has shown that activity group turnover (sometimes called “episodic risk”) can strongly influence parameter fitting and intervention impact [10, 200]. I model turnover from activity group si to si' as a constant rate $\theta_{sii'}$, which implies an assumption that (in the absence of HIV) duration in group si is exponentially distributed with mean D_{si} [300]:

$$D_{si} = \frac{1}{\mu + \sum_{i'} \theta_{sii'}} \quad (3.5)$$

where μ is the overall exit rate from § 3.2.10.1. As shown previously [10], the relative sizes of each sex-activity group P_{si} can be maintained at fixed values by satisfying the following “mass-balance” equation:

$$vP_{si} = vE_{si} + \sum_{i'} \theta_{sii'} P_{si'} - \sum_i \theta_{sii} P_{si} \quad (3.6)$$

Specific turnover rates $\theta_{sii'}$ and entrant activity group sizes E_{si} can then be uniquely resolved by specifying $N_i(N_i - 1) = 12$ non-redundant and compatible constraints, where specifying each D_{si} is one such constraint.

Censored Durations. Cross sectional sex work surveys will often ask respondents about their duration in sex work. These durations might then be taken to be the average durations in sex work; however, this will be an underestimate, because respondents will continue selling sex after the survey [196].¹⁶

Figure 3.6 illustrates a steady-state population with 5 women selling sex at any given time. The steady-state assumption implies that a women leaving sex work after D years will be immediately replaced by a women entering sex work whose eventual duration will also be D years. Let D be this true duration, and D_s be the duration reported in the survey. If we assume that the survey reaches women at a random time point during the duration D , then $D_s \sim \text{Unif}(0, D)$, and the mean reported duration is $E[D_s] = \frac{1}{2}E[D]$. Thus, $E[D] = 2E[D_s]$ would be an estimate of the true mean duration from the sample. In reality, sex work surveys may be more likely to reach women who have already been selling sex for several months or years, due to delayed self-identification as sex worker [35]. Thus, we would expect that $f = E[D]/E[D_s] \in (1, 2)$, which we can use to compute the mean exit rate as described in § B.1.1.

Another observation we can make from Figure 3.6 is that women who sell sex longer are more likely to be captured in the survey. That is, while the sampled durations are representative of women who *currently* sell sex, these durations are biased high vs. the population of women who *ever* sell sex. It’s not clear whether this observation is widely understood and kept in mind when interpreting sex work survey data.

Duration Selling Sex. The FSW survey data for 2011 [108], 2014 [141], and 2021 [109] include questions on the respondent’s current age, and age of first selling sex; the difference between these ages can then define a “duration selling sex”. Using this approach, the unadjusted years selling sex among Swati FSW

¹⁶An alternate example would be to take the mean age of a population as the life expectancy! Thanks to Saulius Simcikas and Dr. Jarle Tufto for help identifying and discussing this bias: stats.stackexchange.com/questions/298828.

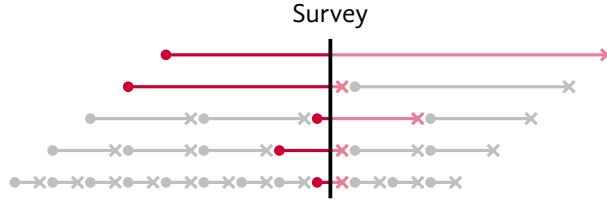


Figure 3.6: Illustrative steady-state population of 5 FSW, with varying true durations in sex work D , vs. the observed durations in sex work D_s via cross-sectional survey.

were median [IQR]: 4 [2, 7] in 2011 and 5 [3, 9] in 2014, with histograms shown in Figure B.5. However, such estimates have three sources of bias: sampling error, censoring, and measurement error.

Sampling error was addressed through RDS-adjustment in 2011 and 2021, yielding estimates of the proportions of FSW who have been selling sex for 0–2, 3–5, 6–10, and 10+ years. The adjusted proportions are not significantly different between 2011 and 2021, and indicate fewer years selling sex vs. the unadjusted proportions, which would be consistent with challenges in reaching women in the first year(s) of sex work [35]. I fit an exponential distribution to the cumulative adjusted proportions (Figure B.6), yielding an estimated distribution mean λ^{-1} of 4.2 (3.5, 5.3) years. However, as discussed above, these reported years are still right censored, and thereby underestimate the eventual duration in sex work among respondents by a factor $f \leq 2$. Thus, the overall mean duration in sex work would be given by $\bar{D} = f \lambda^{-1}$. Yet, additionally, the current definition of duration selling sex includes a hidden assumption that FSW sell sex continuously after starting. In fact, 348/777 (45%) FSW reported having ever stopped selling sex in the 2014 survey [141] (other surveys did not ask). Among these FSW, the expected duration selling sex in the current period (i.e., since re-starting most recently) must be less than half ($\rho < 1/2$) of the durations calculated above. Thus, an adjusted overall mean duration can be calculated as $\bar{D} = (0.45\rho + 0.55)f\lambda^{-1}$. Taking $\rho \sim \text{Unif}(0.2, 0.4)$ and $f \sim \text{Unif}(1.5, 2)$, we obtain \bar{D} with mean (95% CI): 5.13 (3.87, 6.72), similar to the pooled estimate for African FSW up to 2010: 5.5 years [196].

Finally, I assumed that higher risk FSW stay in sex work longer by a factor of R_D with 95% CI (1.54, 3.25) (gamma prior, Table 3.4). Thus, durations in sex work among higher risk (D_{HR}) and lower risk (D_{LR}) FSW can be resolved using:

$$\begin{aligned}\bar{D} &= 0.2 D_{HR} + 0.8 D_{LR} \\ R_D &= D_{HR}/D_{LR}\end{aligned}\tag{3.7}$$

yielding mean (95% CI) D_{LR} : 4.07 (2.96, 5.48) and D_{HR} : 9.33 (6.30, 13.13) (gamma priors).

Duration Buying Sex. Data to inform the average duration spent buying sex among clients is limited. Fazito et al. [196] estimated mean durations of 4.6–5.5 years based on studies in Benin [301] and Kenya [302]. Hodgins et al. [303, Table G] also gives pooled estimates for the proportions of men in Sub-Saharan Africa who paid for sex ever vs. in p12m during 2000–2020. Estimates ranged from 8.8 (6.5, 11.7)% of men aged 25–34 who ever bought sex, to 2.2 (1.5, 3.2)% of men aged 35–54 who bought sex in p12m. Based on these data, I defined a gamma prior distribution for the duration buying sex with 95% CI (4, 15) years, applied to both higher and lower risk clients.

Lowest & Medium Activity Groups. Data on individual-level changes to numbers of non-sex work partners in p12m is even more sparse than data related to sex work; so, it's unclear to what extent individuals move between the lowest and medium activity groups throughout their sexual life course. Data from

Uganda, Zimbabwe, and South Africa [288] suggested that sexual activity (proportion sexually active and mean numbers of partners) was approximately stable with age (after sexual debut and before age 49), with modest trends toward lower activity at older age. However, these population-level data do not necessarily suggest that the same individuals have multiple partnerships each year. Reflecting this uncertainty, I sampled the rate of turnover from medium to lowest activity for both women and men from a gamma prior with 95% CI (5, 50)% per year.

Additional Turnover Assumptions. The above assumptions specify 3 key constraints for each sex: two durations D_{si} and one turnover rate $\theta_{sii'}$. Since higher and lower risk FSW (and clients) are conceptualized as mutually exclusive groups, I modelled no turnover between these groups: $\theta_{s_i_3 i'_4} = \theta_{s_i_4 i'_3} = 0$ (+2 constraints). Next, since FSW often enter sex work shortly after sexual debut [35, 202], and sexual activity is roughly constant or slightly declining with age [288], I assumed that $E_{si} = f P_{si}$,¹⁷ with $f = 2$ for FSW, $f = 1.5$ for clients, and $f = 1$ for medium activity women and men (+3 constraints); then $f < 1$ for the lowest activity women and men is computed automatically. Finally, since exiting sex work is unlikely to be an abrupt transition to monogamous or zero sexual activity [29, 304], I further assumed that (50, 90)% of women exiting sex work transition to the medium activity group (BAB prior) (+1 constraint); in the absence of relevant data, I made a similar assumption regarding clients, with (25, 90)% former clients transitioning to the medium activity group (+1 constraint). These 10 < 12 total constraints then allow two degrees of freedom to resolve the values of $\theta_{sii'}$ and E_{si} . A non-negative solution to the system of constraints is solved as described in [10],¹⁸ repeated at each timestep as v varies with time.

3.2.11 Partnership Numbers

This section summarizes the numbers of partnerships modelled among activity groups. Similar to group sizes, I draw on the analysis of FSW data in § 3.2.7 and bias adjustment for wider population in § 3.2.8. However, first in § 3.2.11.1, I critically review the interpretation of reported partner numbers with regards to partnership duration, and develop a related adjustment.

3.2.11.1 Adjusting for Partnership Duration

Sexual partnerships are usually quantified using cross-sectional surveys. In this case, respondents are typically asked to report the numbers of unique partners “ x ” during a standardized recall period ω — e.g., “How many different people have you had sex with during the past year?” Such data can then be used to define a rate of partnership change Q and/or a number of concurrent partnerships K , depending on the modelled force of infection equation (see Chapter 4).

If partnership duration is long and the recall period is short — including $\omega \approx 0$ for “Are you currently in a long-term sexual partnership?” — the reported partnerships mostly reflect ongoing partnerships, and thus $x \approx K$. If partnership duration is short and the recall period is long, — including $\delta \approx 0$ for “How many one-off sexual partners have you had during the past year?” — the reported partnerships mostly reflect complete partnerships, and thus $x/\omega \approx Q$. However, if partnership duration and recall period are similar in

¹⁷ Subject to $f \leq (v - \mu + D_{si}^{-1}) v^{-1}$, which can be derived from Eq. (10) in [10].

¹⁸ Using docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.nnls.html

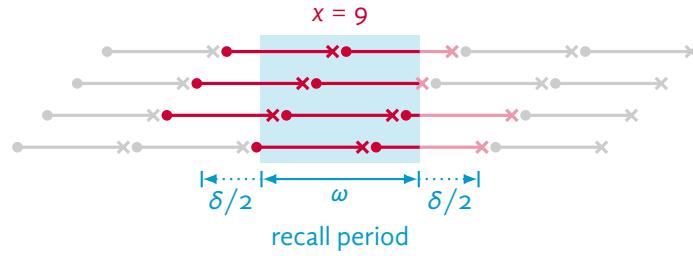


Figure 3.7: Illustration of conceptual framework for quantifying partnerships from the number reported during a given recall period

Circle: partnership start; line: ongoing partnership; cross: partnership end; ω /red: recall period; δ : partnership duration; x : number of reported partnerships for ω .

length, the reported partnerships reflect a mixture of tail-ends, complete, and ongoing partnerships, and thus x overestimates K , but x/ω also overestimates Q . In summary:

- $\omega \ll \delta$: mostly ongoing partnerships; $x \approx K$ (concurrent)
- $\omega \gg \delta$: mostly complete partnerships; $x/\omega \approx Q$ (change rate)
- $\omega \approx \delta$: some tail-ends, some complete, some ongoing; $x > K$, $x/\omega > Q$ (neither)

I developed an approach to estimate Q and K from x , for a known recall period ω and partnership duration δ . The average durations of each type of partnership are estimated in § 3.2.13. The approach draws on a similar assumption as in § 3.2.10.2: that survey timing is effectively random with respect to partnership duration. Then, if either end of the recall period would capture an ongoing partnership, the intersection point would be, on average, at the partnership mid-point. Thus, the recall period is effectively extended by half the partnership duration $\delta/2$ on each end, and δ overall, as illustrated in Figure 3.7. As such, we can define Q and K as:

$$Q = \frac{x}{\omega + \delta} \quad (3.8)$$

$$K = \frac{x\delta}{\omega + \delta} = Q\delta \quad (3.9)$$

As an example, Figure 3.7 illustrates a recall period of $\omega = 1$ year, for which $x = 9$ partnerships are reported, having durations of $\delta = 9$ months. Thus, we can compute $Q = 9/(1 + 0.75) = 5.14$ and $K = 5.14(0.75) = 3.86$, which is a slight underestimate of the true values $Q = 5.33$, $K = 4$, due to the randomness in the exact “location” of the recall period.

3.2.11.2 Sex Work Partnerships

Female Sex Workers. Table 3.4 summarizes the numbers of new and regular clients *per month* reported by Swati FSW, stratified by higher vs. lower risk per the analysis in § 3.2.7.3. These data thus would provide x for $\omega = 1$ month. However, based on the survey questions,¹⁹ it’s not clear whether these reported partner numbers represent the numbers of unique men or unique client visits.

¹⁹The survey questions were: “In the last 30 days, how many (new/regular) clients have you had sex with?”, or similar.

I assumed that all *new* clients were one-off visits; thus the reported partner numbers effectively represented $1/12$ th of the total numbers of yearly partnerships Q_{p_3} . As such, I sampled the yearly rate of new sex work partnerships among lower risk FSW from a gamma distribution with mean (95% CI) as $4.1 (2.5, 6.0) \times 12$, and the *relative* rate among higher risk FSW from $2.0 (1.6, 2.5)$. Since each partnership is assumed to include only one sex act, the partnership duration δ_{p_3} , frequency of sex F_{p_3} , and number of concurrent partnerships K_{p_3} are ill-defined, but can be defined for convenience as $\delta_{p_3} = 1/12$ (years), $F_{p_3} = 12$ (per year), and $K_{p_3} = Q_{p_3}/12$.

For *regular* sex work partnerships, uncertainties remain regarding partnership duration δ_{p_4} (see § 3.2.13), frequency of sex per month $F_{p_4}/12$, and survey responses x reflecting unique clients or total client visits per month. If x reflects the numbers of unique clients, then $Q_{p_4 s_1 i_{34}}$ can be defined via Eq. (3.8) using x directly; whereas if x reflects the numbers of unique visits, then $Q_{p_4 s_1 i_{34}}$ should be defined using $x/(F_{p_4}/12)$. I assumed that $\rho = 2/3$ of respondents interpreted the question as in the former case, and $1 - \rho = 1/3$ as in the latter, such that:

$$x' = \rho x + (1 - \rho) x / (F_{p_4}/12) \quad (3.10)$$

Taking $F_{p_4}/12 = 2$ as the prior mean from § 3.2.12, Eq. (3.10) simplifies to $C' = \frac{5}{6} C$. Then, sampling $C_{p_4 s_1 i_3}$ from a gamma distribution with mean (95% CI) $8.4 (6.0, 11.0)$ from Table 3.4, and δ_{p_4} as specified in § 3.2.13, I defined $Q_{p_4 s_1 i_3}$ and $K_{p_4 s_1 i_3}$ via Eq. (3.8) using $C'_{p_4 s_1 i_3}$ and $\gamma = 1/12$ year. For higher risk FSW, I sampled the *relative* number/rate of regular clients from $1.5 (1.3, 1.7)$ (Table 3.4) as before.

Clients. Across Sub-Saharan Africa, data for clients of FSW on the number of unique FSW visited and the frequency of sex is sparse. Among 64 clients in Kenya, the median number of sex work visits per week was 1.3 (68 per year); most clients (68%) had 1–3 regular FSW partners simultaneously, and visited 0–3 new FSW per year [302]. Among 261 truck drivers at sex work hotspots in Uganda, the mean number of sexual partners was 7.4 in the past 30 days and 44.7 in the past year [305]. Johnson and Dorrington [306] modelled yearly sex work visits among South African clients of FSW as gamma-distributed with age over 10, peaking at 64 visits per year for clients aged 37. To reflect these data, I specified clients overall to have mean (95% CI) 60 (35, 90) sex acts with FSW per year ($K_{p_3 s_2 i_{34}} F_{p_3}/12$, gamma prior). Then, the yearly sex acts among lower and higher risk clients are defined such that higher risk have $2.0 (1.6, 2.5)$ times the number among lower risk. Finally, since the distribution of sex acts between new vs. regular sex work partnerships must match that among FSW, the specific values of $K_{p_3 s_2 i_{34}}$ were computed automatically.

3.2.11.3 Main/Spousal & Casual Partnerships

Drawing on the results in § 3.2.8.4, I defined the numbers of main/spousal and casual partners among each activity group as follows.

Main/Spousal Partnerships. To simplify model fitting, I sampled a common proportion of individuals reporting a main/spousal partnership from a BAB distribution with 95% CI (25, 50)%, applied to all women and men in the lowest activity groups ($C_{p_1 s_1 i_1}$), as well as all women in the medium activity group ($C_{p_1 s_1 i_2}$). Then, Eqs. (3.8) and (3.9) were used to define Q and K , respectively. Since FSW and clients had fewer main/spousal partnerships (see § 3.2.11.3), I calculated the proportion of men in the medium activity group having main/spousal partnerships $K_{p_1 s_2 i_2}$ to balance the total number of main/spousal partnerships among women and men.

Casual Partnerships. I similarly defined a common proportion of women and men in the lowest activity groups reporting casual partnership $x_{p_2 s_{12} i_1}$ with 95% CI (20, 55)%. However, the number of casual partnerships among W_{2+} and M_{2+} remains uncertain. The analysis above provides no information on these values, but the number of partners in p_{12m} for the medium activity groups must be at least about 1.5 to ensure these women and men actually have 2+ partners in p_{12m} . Thus, I sampled the number of casual partners reported by women in the medium activity group $x_{p_2 s_1 i_2}$ from a gamma distribution with 95% CI (1.2, 2), and computed Q and K via Eqs. (3.8) and (3.9). As before, I calculated the numbers of casual partnerships among men in the medium activity group $K_{p_2 s_2 i_2}$ to balance total casual partnerships.

Main/Spousal & Casual Partnerships among FSW & Clients. Among Swati FSW, the mean number of total non-paying partners in the past month was approximately 1–1.5 (Table 3.4), which may include both main/spousal partners and casual partners. Among FSW in South Africa [307] and Kenya [308], while 54 and 72% (respectively) reported being in a relationship, only 6 and 3% were married, although many non-marital partners may still constitute effectively “main” partnerships with respect to condom use and duration. Thus, I assumed that: 50% of all FSW reported a main/spousal partner (i.e., $x_{p_1 s_1 i_{34}} = 0.5$); lower risk FSW reported $x_{p_2 s_1 i_3} = 0.5$ casual partners; and higher risk FSW reported $x_{p_2 s_1 i_4} = 1.0$ casual partners, on average.

Available data suggest that about half of clients also report non-sex work partners, which are not always distinguished as main/spousal vs. casual partnerships [244, 301]. Non-paying partners of FSW are also often clients of other FSW [308, 309]. Yet, clients of FSW also tend to be younger and more likely to be never/formerly married vs. non-client men [301, 310]. So, I assumed that clients reported half the numbers of main/spousal partnerships compared to lowest activity men: $x_{p_1 s_2 i_{34}} = 0.5 x_{p_1 s_2 i_1}$, and 25–100% the numbers of casual partnerships compared to medium activity women (uniform prior). As before, I computed Q and K via Eqs. (3.8) and (3.9).

3.2.12 Sex Frequency

The Eswatini general population data sources [129, 134, 137] did not report on frequency of sex. In South Africa, average numbers of sex acts per week per partnership (non-sex work) was reported as mean 2.5 (IQR: 1–3) [311], with consistent reports across main/spousal partnerships and casual partnerships. Sex frequency among South Africans per month overall (not per-partnership) is also summarized in [312, Figure 3.15], which is roughly consistent with [311], but motivates a smaller lower bound. Median sex frequency per partnership-year in 1998 Rakai, Uganda was approximately 90 acts with the “more frequent” of concurrent partners, and approximately 20 acts with the “less frequent” [313]. Considering these data, I sampled the number of sex acts per year in main/spousal partnerships F_{p_1} from a gamma prior distribution with 95% CI (13, 156), and a relative rate for casual partnerships $F_{p_2}/F_{p_1} \sim \text{Unif}(0.5, 1)$. As described in § 3.2.11.2, I defined $F_{p_3} = 12$ for occasional sex work partnerships, and $F_{p_4} \sim \text{Unif}(12, 36)$ for regular sex work partnerships. I also constrained samples of F_{p_4} such that higher risk FSW never have commercial sex more than twice daily, on average.

Anal Sex. Among Eswatini data sources, only [141] (FSW, 2014) counted sex acts separately for anal and vaginal sex. Among all FSW, the proportion of “average sex acts per week” that were anal (vs vaginal) was 2.9%. However, a previous coital diary study in neighbouring KwaZulu-Natal suggested much higher proportions were anal [314], and face-to-face interview survey design may result in under-reporting

[164]. Owen et al. review studies of anal sex in South Africa, and estimate that 0.6–16.5% of sex acts among the general population are anal [315], vs. 2.4–15.9% among FSW [164]. To reflect this greater uncertainty, the proportions of sex acts which are anal in all partnerships were sampled from a gamma prior distribution with 95% CI (0.6, 16.5)%.

3.2.13 Partnership Duration

As explored in Chapter 4, the durations of sexual partnerships can be key determinants of epidemic dynamics and intervention impact.²⁰ Eswatini-specific data on partnership duration are lacking. Moreover, accurate estimation of partnership duration remains challenging even when data exist, due to censoring, truncation, and sampling biases [316]. Similar to challenges in estimating sex work duration (§ 3.2.10.2), we must distinguish the definition of an “average partnership” as (a) among all partnerships in a population over a given *time period*, vs. (b) among all partnerships in a population *cross-section*. Case (b) will be biased by partnership duration, so the estimated mean duration will longer, while case (a) reflects an unbiased estimate.²¹ The difference between the exponential distribution mean and median should also be kept in mind (see § B.1.1).

Main/Spousal Partnerships. Detailed data on marriage in Eswatini was only captured in 2006 [129, Table 6.1]. The median age of first marriage was 24.3 among women and 27.7 among men (26.0 overall). Approximately 64% of women and 88% of men (76% overall) who were ever married or living together were in a union at age 50–54. However, no data indicated whether any respondents had remarried or entered into a secondary union. Among women aged 40–49, the most recent data on median age of first marriage and proportions ever remarried were 33 years old and 6.6% in South Africa, 20.9 and 3.7% in Lesotho, and 18.7 and 28.4% in Mozambique [317]; such data may not capture non-marital secondary unions. Thus, I assumed $\rho = 5\text{--}20\%$ of unions among EmaSwati aged 50–54 were secondary. Considering that the modelled population only includes ages 15–49, I then defined the mean durations of main/spousal partnerships as $\delta_{p_1} = (0.76 - \rho)(49 - 26) \in (14.5, 18.5)$ years.

In some models, partnership duration is used to define both the total numbers of sex acts per partnership and the partnership change rate (see § 4.1). This change rate might be overestimated by the above definition, since the rate should also consider whether and when divorced/separated individuals form new main/spousal partnerships. The change rate could even be tied to the modelled baseline and HIV-attributable mortality, given that the majority of Swati unions ended via spousal death (83% of unions among women and 56% among men by age 50–54) [129]. For simplicity and consistency with prior approaches, I used the effective duration of 14.5–18.5 years throughout (uniform prior).

Casual Partnerships. No data is available regarding durations of non-marital sexual partnerships in Eswatini, and regional data on are also limited. I synthesized the available partnership duration data from South Africa [318–320], Rural Tanzania [291], and four cities in Kenya, Zambia, Benin, and Cameroon [321]. Based on these data, I defined a gamma prior distribution for the mean duration of casual partnerships δ_{p_2} with 95% CI (0.25, 1.5) years, roughly consistent with prior models [322]. A gamma distribution was chosen vs. uniform or normal to reflect non-uniform belief while preventing negative values.

²⁰ Chapter 4 also discusses the related phenomenon of partnership concurrency, including how concurrency is represented in compartmental models.

²¹ If case (a) durations are exponentially distributed, the durations in case (b) will be gamma-distributed with $\alpha = 2$, $\beta = \lambda$; thus the mean duration in case (b) will be $\alpha/\beta = 2\lambda$ (twice as long).

Sex Work Partnerships. As noted in § 3.2.11.2, duration of occasional sex work partnerships is ill defined, but can be defined to comprise a single sex act with $F_{p_3} \delta_{p_3} = 1$. Data on regular sex work partnerships is severely limited, and sometimes regular paying clients later become non-paying emotional partners [308, 323]. Based on [302], I defined a gamma prior distribution for the mean duration of regular sex work partnerships δ_{p_4} with 95% CI (0.5, 2.0) years.

3.2.14 Mixing

In addition to more concentrated transmission among FSW and their clients via regular and occasional sex work partnerships — which are *only* formed among FSW and clients — other types of partnerships may be formed preferentially between particular activity groups. For example, FSW and clients may be more likely to form main or casual partnerships with each other than with other activity groups. Such preferences are captured in a “mixing matrix” M , where $M_{pii'}$ denotes the total number of type- p partnerships formed between groups i and i' in the population (ignoring sex indices s, s' temporarily) — i.e., who has sex with whom. The mixing matrix $M_{pii'}$ must be symmetric, and have row/column sums equal to the total numbers of partnerships “offered” by any group: $M_{pi} = P_i C_{pi}$ (group size \times partnerships per-person).

3.2.14.1 Classic ϵ Mixing

In many risk/activity-stratified compartmental transmission models, mixing is parameterized via a single parameter $\epsilon \in [0, 1]$, which controls the degree of like-with-like mixing [324]. This approach is often attributed to [325], wherein a key adjustment for imbalanced partner numbers among women vs. men was introduced. The approach defines the *probability* of someone from group i forming a *given* type- p partnership with someone from group i' as:

$$\rho_{pii'} = (\epsilon) I_{ii'} + (1 - \epsilon) \pi_{ii'}, \quad I_{ii'} = \begin{cases} 1 & i = i' \\ 0 & i \neq i' \end{cases}, \quad \pi_{ii'} = \frac{M_{pii'}}{\sum_j M_{pj}} \quad (3.11)$$

where: I represents complete like-with-like mixing (an identity matrix), π represents random mixing (random but proportional to the number of partnerships “offered”), and ϵ effectively interpolates between these two extremes. Thus, $\epsilon = 0$ reflects fully random mixing, and $\epsilon = 1$ reflects fully like-with-like mixing. Then, the total numbers of type- p partnerships between groups i and i' can be defined as $M_{pii'} = M_{pi} \rho_{pii'}$. Three advantages of Eq. (3.11) are: (1) simplicity; (2) ϵ can be directly interpreted as the proportion of partnerships which are formed among like-with-like vs. randomly; and (3) it guarantees that M will be symmetric, even if P and/or C change. Yet, the simplicity of this approach precludes implementation of more complex mixing patterns — such as preferential mixing among two of four total groups — although some modest extensions can be made, such as asymmetric age mixing among women and men [326].

3.2.14.2 Log-Linear Mixing

A more general approach to mixing is developed in [327]. This “log-linear” approach defines the mixing matrix elements $M_{pii'}$ as follows. The expected total numbers of partnerships between risk groups under random mixing are defined as:

$$\Pi_{pii'} = \frac{M_{pi} M_{pi'}}{\sum_j M_{pj}} \quad (3.12)$$

Next, a matrix $\Phi_{pii'}$ is defined, representing the odds of a type- p partnership forming between groups i and i' , compared to random mixing. The matrix Φ must be symmetric, and can be estimated directly from the right kind of data (which is rarely available) [327]. Then, an initial estimate of $M_{pii'}$ is:

$$\begin{aligned} M_{pii'}^{(o)} &= \exp \left[\log \left(\Pi_{pii'} \right) + \Phi_{pii'} \right] \\ &= \Pi_{pii'} \exp \left(\Phi_{pii'} \right) \end{aligned} \quad (3.13)$$

However, this estimate changes the total numbers of partnerships formed by each group: $M_{pi}^{(o)} \neq \Pi_{pi}$, where $M_{pi} = \sum_{i'} M_{pii'}$ and $\Pi_{pi} = \sum_{i'} \Pi_{pii'}$. There is no *a priori* definition of $M_{pii'}$ or adjustment to $\Phi_{pii'}$ that can guarantee the numbers of partnerships will not change.²² However, an iterative proportional fitting procedure [328] can resolve an estimate $M_{pii'}^{(n)}$ that maintains the total numbers of partnerships:

$$M_{pii'}^{(n+1)} = M_{pii'}^{(n)} \frac{\Pi_{pf}}{M_{pf}^{(n)}} \quad f = \begin{cases} i & \text{if } n \text{ is even} \\ i' & \text{if } n \text{ is odd} \end{cases} \quad (3.14)$$

Each step of this procedure can be understood as a re-scaling of the current estimate $M_{pii'}^{(n)}$ row-wise (i) or column-wise (i') to match the numbers of partnerships offered by individuals (Π_{pi}) or their partners ($\Pi_{pi'}$). Each row-step re-introduces discrepancies in the columns, and vice versa, but overall convergence is guaranteed [329].

In practice, Eq. (3.14) adds approximately one decimal of precision per $2n$ for the 4×4 case, thus 15–20 iterations is often sufficient to come within computational precision limits. Since the partnerships matrix $M_{pii'}$ should adapt to reflect changes in group sizes (e.g., due to HIV mortality) or numbers of partnerships offered (e.g., see § 4.2), the matrix must be re-computed at every time point. Thus, the procedure Eq. (3.14) could be considered computationally expensive. However, this approach provides great flexibility and interpretability to specify complex mixing patterns via the odds matrix $\Phi_{pii'}$.

Adding back the sex dimension indices $i \rightarrow si$, $i' \rightarrow s'i'$, two final adjustments are needed for the bipartite (i.e., heterosexual) system. First, I ensure that $M_{s=s'} = \Pi_{s=s'} = 0$. Second, for the case when the total numbers of partnerships offered by women and men do not balance ($\sum_j M_{ps_1j} \neq \sum_j M_{ps_2j}$), I revise the denominator of Eq. (3.12) to $\sum_j \omega_s M_{ps_j}$, where ω_s are weights such that $\sum_s \omega_s = 1$. Similar to the “compromise” parameter θ in [325], if $\omega = \{1, 0\}$, then women’s partnership numbers are matched exactly while men adapt their partner numbers to balance; and conversely for $\omega = \{0, 1\}$. I fixed $\omega = \{0.5, 0.5\}$ for equal adaptation among women and men.

²²I hypothesize that this lack of *a priori* solution is the reason this approach has not been widely used.

3.2.14.3 Odds of Mixing

Despite the flexibility in the odds of mixing matrix $\Phi_{pii'}$, limited data are available to inform specific elements, especially for Eswatini in particular. In Kenya [308], Benin, Guinea, and Senegal [309], and Uganda [323], a disproportionate fraction of non-paying partners of FSW were former and/or current clients. Given this fraction ψ and the proportion of all men who are clients ρ , the odds of these partnerships forming can be computed as:

$$\Phi = \frac{\psi(1-\rho)}{(1-\psi)\rho} \quad (3.15)$$

Taking $\psi \in (0.33, 0.70)$ [308, 309] and $\rho \in (5, 20)\%$ [303], we obtain $\Phi \in (2, 19)$. As noted in § 3.2.11.3, it's not clear whether such partnerships reflect main/spousal or casual partnerships. As such, I sampled a common value for both partnership types, as well as for higher/lower risk FSW and clients: $\Phi_{p_1 i_1 i_3 i_4 i'_3 i'_4}$ from a gamma prior with 95% CI of (2, 19). I further assumed that lowest activity women and men had greater odds of forming main/spousal partnerships with each other, based loosely on age cohorting effects [330], observed like-with-like sexual mixing preferences in numerous other contexts [327, 331, 332], and prior modelling work [174]. I sampled $\Phi_{p_1 i_1 i'_1}$ from a gamma prior with 95% CI of (1.5, 3). I made no further assumptions about preferential mixing (i.e., all other elements $\Phi = 1$). Thus, I assumed that occasional and regular sex work partnerships form randomly with respect to higher vs. lower FSW and their clients.

3.3 Calibration

The parameters described in § 3.2 represent model inputs, many of which are uncertain. For each uncertain parameter, I have specified a prior distribution based on the available data and/or assumptions. Model calibration then aims to reduce this uncertainty — i.e., estimate the joint parameter posterior distribution — by comparing model *outputs* to additional data called “calibration targets”, under different combinations of input parameters. Section 3.3.1 describes the approach to calibration, while § 3.3.2 details the calibration targets used, including estimates of HIV incidence, prevalence, and the cascade of care for the population overall, and stratified by risk group where available. Results of model calibration are given in § 3.4.

3.3.1 Approach

I used a Bayesian approach for model calibration [333]. Let θ denote the complete set of 73 calibrated model parameters (Table B.1), and T the complete set of 69 calibration targets. The goal of calibration is to obtain samples from the posterior distribution of parameters given the targets $p(\theta | T)$. This posterior distribution can be defined via Bayes' rule as:

$$p(\theta | T) = \frac{p(T | \theta) p(\theta)}{p(T)} \quad (3.16)$$

The posterior distribution was characterized empirically via Monte Carlo simulation — i.e., by randomly sampling parameter sets $\theta_s \sim p(\theta)$, and for each set computing the likelihood $p(T | \theta_s)$. This likelihood was defined via independent uncertainty distributions for each calibration target T_i . For example, overall

HIV prevalence in Eswatini was estimated as 27.2%, 95% CI: (25.8, 28.7) in 2016 [137]; using this information, I defined a BAB distribution as the likelihood function for this calibration target $p(T_i | \theta)$. Thus, a parameter set θ_{s_1} which yields model-estimated overall HIV prevalence $T_i(\theta_{s_1}) = 25\%$ in 2016 would have a higher likelihood for this target than a parameter set θ_{s_2} which yields $T_i(\theta_{s_2}) = 20\%$ in 2016. The independent likelihoods for each target were aggregated on logarithmic scale to give the overall likelihood:

$$\log p(T | \theta_s) = \sum_i \log p(T_i | \theta_s) \quad (3.17)$$

Any individual log-likelihood which was beyond computational precision was replaced with an arbitrarily large negative number (-10^6). In order to obtain good coverage of the sampling space, most (58) calibrated parameters were sampled using Latin hypercube sampling [334]. The remaining 15 calibrated parameters were sampled randomly and iteratively until they satisfied a set of relational constraints (see § B.4.1).

Although several iterative methods exist to update the sampling distributions based on the likelihoods, and thereby characterize the posterior distribution more efficiently [333], I did not update the sampling distributions. Rather, I simply took the top 1% of parameter sets θ_s by likelihood, and assume these are approximately representative of the posterior distribution. Within the top 1%, I also did not weight parameter sets by likelihood. I sampled 100,000 parameter sets, yielding $N_j = 1000$ posterior samples and corresponding plausible epidemic simulations or “model fits”.

3.3.2 Calibration Targets

The data sources for Eswatini calibration targets are mainly the same as for Eswatini-specific parameters. I assumed that population-level surveys in 2006 [129], 2011 [212, 213], and 2016 [137] reached FSW and their clients, although respondents may not report selling or buying sex in the context of these surveys.

3.3.2.1 HIV Prevalence

Table 3.5 summarizes the available HIV prevalence data for Eswatini. Uncertainty around each estimate was modelled using a BAB distribution. I made several adjustments to the estimates as follows.

Sampling Error. Population-level HIV prevalence estimates in 2006 and 2016 included expanded 95% CI (vs. standard binomial 95% CI) due to sampling error for women, men, and the population overall (Table B.2 in [129] and Table C.2 in [137]). This expanded 95% CI corresponds to a reduction in effective N vs. the sample N for the binomial distribution, by a factor of 41–75%. I applied this factor to equivalently expand the estimated 95% CI for the corresponding lower risk and non-lower risk women, men, and population overall in 2006 and 2016, and also for all 2011 HIV prevalence estimates [212].

Biased Partner Number Reporting. As discussed in § 3.2.8, I assumed that the proportion of the population reporting 0–1 sexual partners p6m (“lower risk”) is overestimated, and the proportion reporting 2+ (“non-lower risk”) is underestimated. While overall HIV prevalence estimates would not be affected by this reporting bias, HIV prevalence among the lower risk group would be overestimated. To correct this overestimate, I further assumed that HIV prevalence among “observed” non-lower risk (had 2+ partners

Table 3.5: Estimates of HIV prevalence in Eswatini

Population ^a	Year	N	Raw		Adjusted		Used	Ref	Notes
			%	%	(95% CI)				
Overall	2006	8,187	25.9	—	(24.4, 27.3)	✓	[129]	b	
	2011	18,172	32.1	28.0	(27.0, 29.0)	✓	[212]	cd	
	2016	8,533	27.2	—	(25.8, 28.7)	✓	[137]	b	
Women Overall	2006	4,424	31.1	—	(29.4, 32.9)	✓	[129]	b	
	2011	9,843	38.8	34.2	(33.0, 35.4)	✓	[212]	cd	
	2016	4,878	34.3	—	(32.6, 36.0)	✓	[137]	b	
Men Overall	2006	3,763	19.7	—	(17.9, 21.4)	✓	[129]	b	
	2011	8,329	24.1	20.7	(19.6, 21.8)	✓	[212]	cd	
	2016	3,655	18.8	—	(17.3, 20.4)	✓	[137]	b	
LR Overall	2006	7,589	24.9	—	—	✗	[129]		
	2011	16,145	31.9	—	—	✗	[212]		
	2016	7,887	32.2	—	—	✗	[137]		
Non-LR Overall	2006	579	38.3	—	—	✗	[129]		
	2011	1,887	33.3	29.0	(25.9, 32.2)	✗	[212]	cd	
	2016	914	28.7	—	(25.8, 31.7)	*	[137]	f	
LR Women	2006	4,346	30.7	26.8	(22.7, 28.7)	*	[129]	e	
	2011	9,843	38.2	30.8	(28.9, 32.8)	*	[212]	ce	
	2016	5,203	36.5	31.5	(30.0, 33.1)	*	[137]	e	
Non-LR Women	2006	72	53.0	—	(41.5, 64.3)	*	[129]	f	
	2011	373	54.5	48.1	(41.5, 54.8)	*	[212]	cd	
	2016	263	45.3	—	(39.3, 51.3)	*	[137]	f	
LR Men	2006	3,243	17.1	14.1	(6.5, 16.7)	*	[129]	e	
	2011	6,733	23.2	19.0	(18.0, 20.1)	*	[212]	ce	
	2016	2,684	25.1	16.9	(15.7, 18.1)	*	[137]	e	
Non-LR Men	2006	506	36.1	—	(32.0, 40.3)	*	[129]	f	
	2011	1,515	28.1	24.1	(21.4, 26.9)	*	[212]	cd	
	2016	651	22.8	—	(19.7, 26.1)	*	[137]	f	
FSW Overall	2011	328	70.3	60.5	(52.1, 69.0)	✓	[108]	g	
	2014	781	37.8	—	—	✗	[141]	h	
	2021	676	60.8	58.8	(53.9, 63.6)	✓	[108]	g	

^a LR: lower risk, reporting 0-1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; ^b 95% CI as reported from sampling adjustment; ^c adjusted from ages 18–49 to 15–49 (see § 3.3.2.1); ^d 95% CI expanded via inferred sampling adjustment; ^e adjusted for biased reporting of risk behaviours (see § 3.2.8 and § 3.3.2.1); ^f 95% CI inferred from N; ^g RDS-adjusted; ^h self-reported; * used within prevalence ratio only; all estimates used the BAB distribution.

Table 3.6: Estimated HIV prevalence ratios in Eswatini

Numerator ^a	Denominator ^a	Year	Ratio	(95% CI)	Used	Ref	Notes
Non-LR Women	LR Women	2006	2.02	(1.84, 2.34)	✓	[129]	b
		2011	1.54	(1.47, 1.66)	✓	[212]	b
		2016	1.42	(1.37, 1.51)	✓	[137]	b
Non-LR Men	LR Men	2006	2.57	(2.16, 5.28)	✓	[129]	b
		2011	1.24	(1.20, 1.34)	✓	[212]	b
		2016	1.32	(1.26, 1.45)	✓	[137]	b
FSW Overall	Women Overall	2011	2.16	(1.87, 2.50)	✓	[108, 212]	b
HR FSW	LR FSW	2011	1.46	(1.30, 1.63)	✓	[108]	c
		2014	2.30	(1.92, 2.75)	✗	[141]	cd

^a LR: lower risk, reporting 0–1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; HR/LR FSW: higher/lower risk FSW, as defined in § 3.2.7; ^b mean and 95% CI estimated via Monte Carlo sampling; ^c per analysis in § 3.2.7.3; ^d self-reported; see Table 3.5 for more notes on data sources and adjustments.

p6m, reported 2+) was representative of HIV prevalence among “unobserved” non-lower risk (had 2+, reported 0–1). Thus, HIV prevalence among the “true” lower risk (had 0–1, reported 0–1) can be estimated as:

$$H_{01} = \frac{H - H_{2+} W'_{2+}}{W'_{01}} \quad (3.18)$$

where H denotes HIV prevalence, and W' denotes the adjusted proportions calculated in § 3.2.8.

Age Range. The model aims to capture the Swati population aged 15–49. While the 2006 and 2016 surveys provide data for ages 15–49, the 2011 survey was limited to ages 18–49. Since HIV prevalence is much lower among ages 15–17, the 2011 estimates would be biased high. I therefore adjusted all 2011 HIV prevalence estimates in as follows. Drawing on age-stratified data in 2006 [129] and 2011 [212], I assumed that HIV prevalence among ages 15–17 was 5% among girls/women, 2% among boys/men, and 3.5% overall. Next, I estimated the fraction of women aged 15–17 among all women aged 15–49 (13.5%), and likewise for men (15.4%) and overall (14.4%) [107]. I then estimated HIV prevalence among women, men, and overall for ages 15–49 using a weighted average of the 15–17 and 18–49 estimates. Finally, I computed the resulting relative reduction in HIV prevalence for women overall, and applied this reduction equally to the HIV prevalence estimates for lower risk and non-lower risk women, and likewise for men and the population overall.

Since risk heterogeneity is a key determinant of epidemic dynamics, it is important to capture HIV prevalence ratios across risk groups. For this objective, directly specifying prevalence ratio targets is more efficient than using independent prevalence targets for lower risk and non-lower risk. Based on the available data, I defined the prevalence ratio targets in Table 3.6.

The raw (unadjusted) estimates suggest that HIV prevalence strongly peaked between 2006 and 2016. After adjustment for respondent ages, 2011 estimates remained highest, but the magnitude of differences with 2006 and 2016 was reduced substantially. The largest reduction in HIV prevalence via adjustment was among lower risk women in 2011: from 38.2% to 30.8%, due to the modelled “addition” of women/girls aged 15–17 (lower HIV prevalence), and “subtraction” of women with 2+ partners p6m (higher HIV prevalence).

Table 3.7: Estimates of HIV incidence in Eswatini

Population ^a	Year	N	Raw		Adjusted		Used	Ref	Notes
			%	(%)	(95% CI)				
Overall	2016	9,476	1.48	—	(0.96, 1.99)	✓	[137]	bc	
Women Overall	2011	5,486	3.1	2.94	(2.52, 3.47)	✓	[213]	de	
	2016	5,227	1.99	—	(1.16, 2.80)	✓	[137]	bc	
Men Overall	2011	5,746	1.7	1.50	(1.16, 1.84)	✓	[213]	de	
	2016	4,249	0.99	—	(0.39, 1.59)	✓	[137]	bc	
LR Women	2011	4,924	3.21	1.58	(0.40, 2.24)	*	[213]	def	
Non-LR Women	2011	93	10.10	9.62	(4.76, 18.29)	*	[213]	de	
LR Men	2011	3,855	1.64	0.76	(0.01, 1.17)	*	[213]	def	
Non-LR Men	2011	874	3.87	3.42	(2.21, 4.94)	*	[213]	de	
FSW Overall	2021	676	11.71	—	(8.31, 16.92)	✓	[109]	b	

^a LR: lower risk, reporting 0–1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; ^b via HIV-1 Limiting Antigen recency testing; ^c 95% CI as reported from sampling adjustment; ^d via 6 month cohort (94.4% follow-up); ^e adjusted from ages 18–49 to 15–49 (see § 3.3.2.1); ^f adjusted for biased reporting of risk behaviours (see § 3.2.8 and § 3.3.2.1); * used within incidence ratio only; all estimates used the skew normal distribution.

3.3.2.2 HIV Incidence

Population-level incidence was first measured in the 2011 Swaziland HIV Incidence Measurement Survey (SHIMS) via 6-month cohort (gold standard) [134, 213], in which 145 seroconversions were observed among 11,232 re-tested (LTFU was 5.6%). The follow-up SHIMS2 study in 2016–17 used the HIV-1 Limiting Antigen Enzyme Immunoassay (LAg EIA) “recency test”, which detects infections acquired within the past 141 days, 95%CI: (119, 160) [142]; this LAg EIA incidence measure was validated during SHIMS1 [134]. Recency testing was also recently integrated into Eswatini standard of care [138].

Table 3.7 summarizes the available HIV incidence data for Eswatini. Uncertainty around each estimate was modelled using a skewnormal or inverse gaussian distribution. As with prevalence, the 2011 estimates were adjusted for the missing 15–17 age range, this time assuming 2% and 0.4% annual incidence among girls/women and boys/men aged 15–17, respectively (extrapolating from age-stratified incidence estimates from [213]). The 2011 estimates for lower risk women and men were also adjusted for biased partner number reporting using the same approach as for HIV prevalence. Two incidence ratios were also defined (Table 3.8).

No study of FSW in Eswatini estimated incidence directly, but [109] reported that 30 of 676 prevalent HIV infections among FSW were identified as recent via LAg EIA per national guidelines [137, 138]. Using Eq. (3.2) with $\rho = 30/676 = 4.44\%$ and $T = 130$ days, I computed an incidence rate of $\lambda = 11.7\%$ per year. I further estimated uncertainty for this rate by combining the 95% CI from $\rho \sim \text{Binom}(p = 4.44\%, N = 676)$ and $T \in (118, 140)$, yielding 95% CI for λ of (8.3, 16.9).

3.3.2.3 HIV Cascade of Care

Table 3.9 summarizes the available data for the HIV cascade of care in Eswatini, including estimates stratified by risk group where possible. Both conditional (e.g., on ART among diagnosed, “90–90–90”) and

Table 3.8: Estimated HIV incidence ratios in Eswatini

Numerator ^a	Denominator ^a	Year	Ratio	(95% CI)	Used	Ref	Notes
Non-LR Women	LR Women	2011	5.74	(2.47, 22.26)	✓	[212]	b
Non-LR Men	LR Men	2011	4.16	(1.69, 23.09)	✓	[212]	b

^a LR: lower risk, reporting 0-1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; ^b mean and 95% CI estimated via Monte Carlo sampling; see Table 3.7 for more notes on data sources and adjustments.

unconditional (e.g., on ART among PLHIV, “90-81-73”) cascade data were included, which is redundant but may improve calibration quality. Unlike HIV prevalence and incidence calibration targets, no adjustments were applied to these data. A recent meta-analysis [335] suggested substantial under-reporting of known HIV+ status, including 9 (4, 15)% among the population overall (10 studies), and 32 (22, 44)% among FSW specifically (2 studies). However, data from SHIMS2 [137] suggested much lower under-reporting (2.2%) in Eswatini.

3.4 Results

This section presents the results of model calibration, including: the posterior distributions of calibrated parameters (see Table B.1 for definitions), and the modelled patterns of transmission among risk groups in Eswatini over time.

3.4.1 Posterior Parameter Distributions

Figure 3.8 illustrates the distributions of calibrated model parameters, stratified by prior (all samples) vs. posterior (top 1% by calibration likelihood). Many of the distributions do not significantly differ (Anderson-Darling Test [337]), indicating that calibration did not reduce uncertainty in these parameters. While more advanced model calibration techniques might improve parameter inference [333], the overall model fit was judged to be sufficient for the downstream research questions (i.e., § 1.4). A total of 20 parameters had highly significant differences ($p < 10^{-5}$) between prior and posterior distributions:

- **Mean increased:** aRbeta_gud_inf, aRbeta_gud_sus, beta_0, C12m_cas_wm, C12m_msp_xl, dur_acute, dur_cas, F_msp, P_gud_fsw_l, PF_ai, PX_w_fsw, PX_w_h, Rbeta_acute, RC_cas_cli.wm, RF_cas.msp,
- **Mean decreased:** dur_fsw_l, dx_wq_2011, Rdx_global, Rdx_m.wq_2011, revx_2010,

Such differences overwhelmingly tended towards increasing overall HIV transmission, suggesting that the set of prior distributions tended to underestimate transmission risk, despite several adjustments towards increasing transmission risk (§ 3.2). Indeed, the high HIV prevalence in Eswatini, and other generalized epidemics, has long been challenging to explain based on the available data [61, 118].

Figure 3.9 further illustrates bivariate rank correlations among posterior parameter values (subset of parameters with at least one correlation ± 0.1). Of these 18 parameters, 10 were subject to relational constraints (§ B.4.1) and 10 had highly significant differences between prior and posterior distributions. For example, condom use levels were positively correlated across regular and occasional sex work partnerships, including over time (PF_condom_sw*), as were the proportions of anal sex acts in sex work vs. non-sex

3.4 RESULTS

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Table 3.9: Estimated HIV cascade of care in Eswatini

Step ^a	Population ^a	Year	N	%	(95% CI)	Used	Ref	Notes	
Diagnosed among PLHIV	Overall	2011	5,807	62.6	(61.4, 63.8)	✓	[253]	bc	
		2016	2,417	86.1	(84.7, 87.6)	✓	[137]	e	
	Women overall	2011	3,810	69.1	(67.6, 70.6)	✓	[253]	b	
		2016	1,690	90.2	(88.6, 91.8)	✓	[137]	e	
	Men overall	2011	1,997	50.1	(47.9, 52.3)	✓	[253]	b	
		2016	727	77.3	(74.0, 80.6)	✓	[137]	e	
	FSW	2011	313	74.1	(61.7, 89.8)	✓	[336]	d	
		2021	411	88.3	(85.1, 91.2)	✓	[109]	bf	
	On ART among Diagnosed	Overall	2011	3,635	52.1	(50.5, 53.7)	✓	[253]	bcd
			2016	2,113	87.8	(86.0, 89.6)	✓	[137]	e
		Women overall	2011	2,633	48.0	(46.1, 49.9)	✓	[253]	bd
			2016	1,532	87.5	(85.4, 89.6)	✓	[137]	e
		Men overall	2011	1,002	62.7	(59.7, 65.7)	✓	[253]	bd
			2016	581	88.4	(85.2, 91.6)	✓	[137]	e
		FSW	2011	174	36.9	(30.1, 44.2)	✓	[336]	
			2021	363	97.5	(95.7, 98.9)	✓	[109]	bf
	On ART among PLHIV	Overall	2011	5,807	31.9	(30.7, 33.1)	✓	[253]	bc
			2016	2,417	75.6	(73.6, 77.5)	✓	[137]	e
		Women overall	2011	3,810	33.2	(31.7, 34.7)	✓	[253]	b
			2016	1,690	78.9	(76.8, 81.1)	✓	[137]	e
		Men overall	2011	1,997	31.4	(29.4, 33.4)	✓	[253]	b
			2016	727	68.3	(64.7, 72.0)	✓	[137]	e
		FSW	2011	313	27.4	(20.9, 35.7)	✓	[336]	d
			2021	411	86.1	(82.6, 89.3)	✓	[109]	bf
	VLS among On ART	Overall	2016	1,858	90.3	(89.0, 91.6)	✓	[137]	e
			2016	1,342	91.4	(89.9, 92.8)	✓	[137]	e
			2016	516	87.6	(84.4, 90.9)	✓	[137]	e
		Women overall	2016	2,417	68.2	(66.1, 70.4)	✓	[137]	e
			2016	1,690	72.1	(69.7, 74.5)	✓	[137]	e
			2016	727	59.9	(56.1, 63.7)	✓	[137]	e

^a PLHIV: people living with HIV; ART: antiretroviral therapy; VLS: HIV viral load suppressed, defined as ≤ 1000 RNA copies/mL in [137]; FSW: female sex worker; ^b 95% CI inferred from N; ^c estimated from combining women & men; ^d estimated from conditional steps, with 95% CI via simulation; ^e 95% CI as reported from sampling adjustment; ^f not RDS-adjusted; n.b. [129] did not provide any appropriate cascade data.

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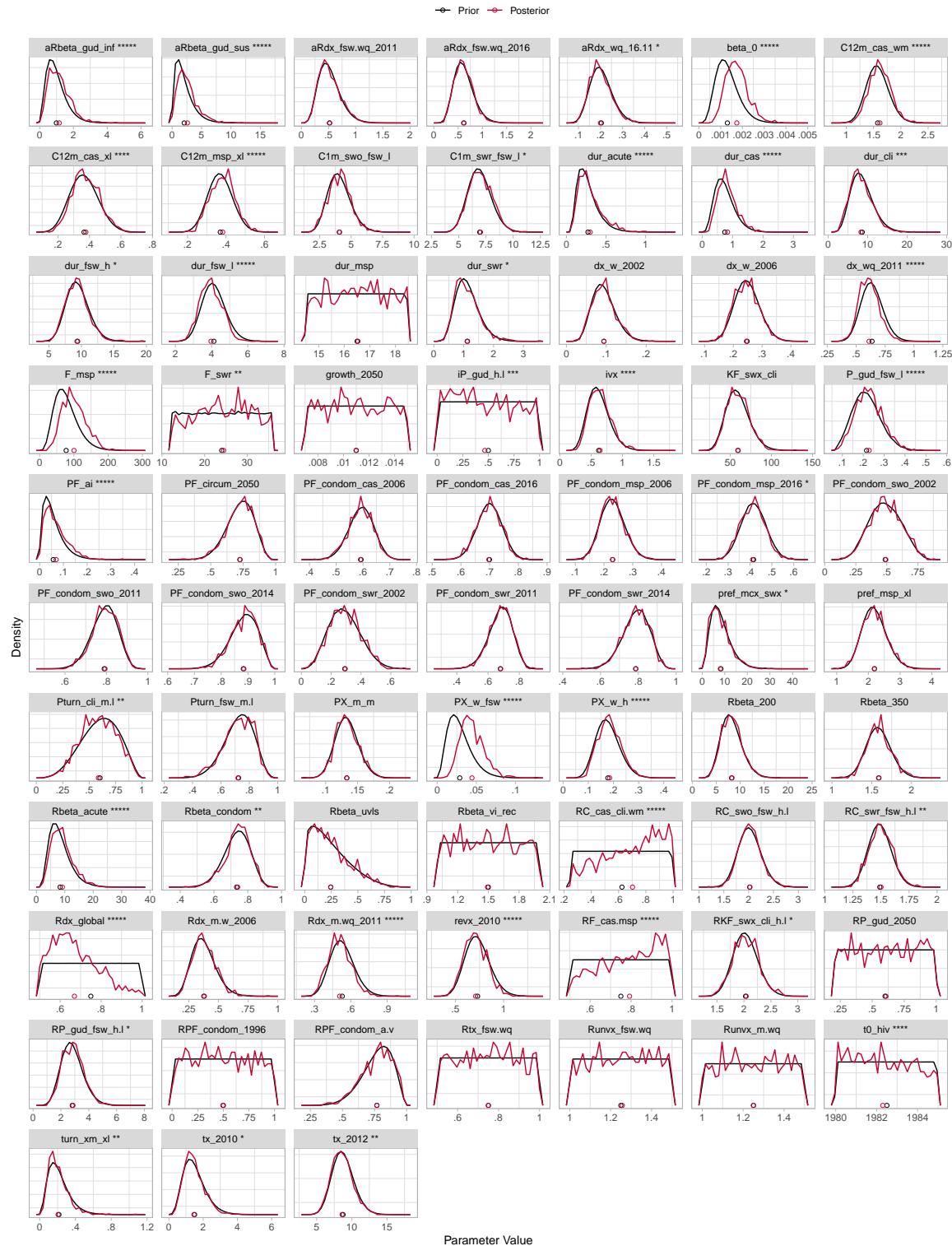


Figure 3.8: Distributions of calibrated model parameters, stratified by prior (all samples) vs. posterior (top 1% by calibration likelihood)

Asterisks denote significance of Anderson-Darling Test [337] for comparing distributions, where $p < 0.1$: *, $p < 0.01$: **, etc.; Table B.1 gives parameter definitions.

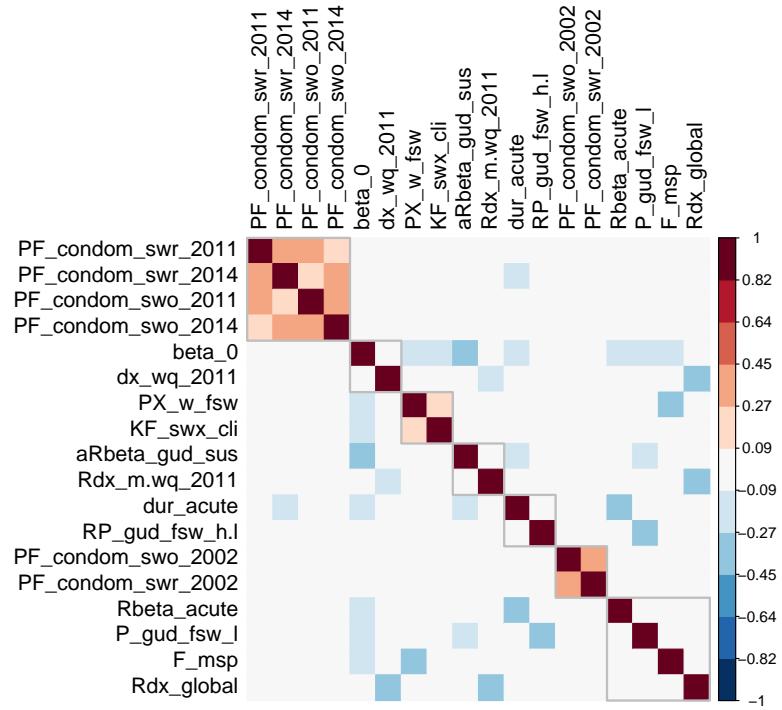


Figure 3.9: Rank correlations among selected posterior model parameters

Subset of parameters with at least one correlation ± 0.1 ; layout computed via hierarchical clustering using the Ward-2 criterion [339]; gray squares denote computed clusters; Table B.1 gives parameter definitions.

work partnerships (PF_ai_*). Multiple combinations of parameters with similar influence on transmission dynamics were *negatively* correlated, such as the baseline per-act probability of transmission (β_0) vs. relative susceptibility due to GUD ($aRbeta_gud_sus$), and diagnosis rates overall (Rdx_global) vs. among specific risk groups (dx_wq_2011 , $Rdx_m.wq_2011$).

These correlated parameters reflect challenges of non-identifiability [338], although no parameters in the model are perfectly non-identifiable. Thus, the variance of posterior distributions may be inflated for these parameters [338], but so long as the joint posterior maintains the observed correlations — i.e., individual parameter values are not permuted among posterior parameter sets — the resulting epidemic simulations should remain plausible.

3.4.2 Calibration

This section presents the estimates of key model outputs from the 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets), with comparison to the associated calibration targets. Additional results are given in § B.4.2, including: distribution of log-likelihoods (Figure B.8) total Eswatini population size aged 15–49 (Figure B.12), and condom use within each partnership type (Figure B.13).

3.4 RESULTS

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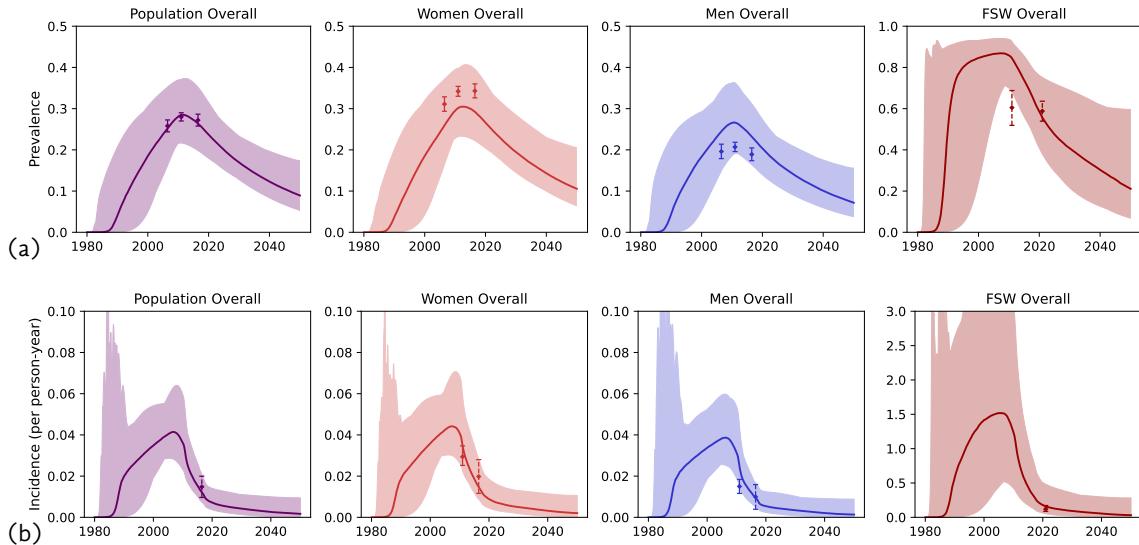


Figure 3.10: Modelled HIV prevalence and incidence among selected risk groups and associated calibration targets

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

3.4.2.1 HIV Prevalence & Incidence

Figure 3.10 illustrates the modelled HIV prevalence (a) and incidence (b) among selected risk groups. Figures B.9 and B.10 similarly illustrate HIV prevalence and incidence ratios, respectively. Overall, model estimates agree well with the available calibration targets, with the following shortcomings. Relative to the calibration targets, the model tends to underestimate HIV prevalence among women overall, but overestimate HIV prevalence among men overall, and among FSW prior to 2020. HIV prevalence and incidence ratios also tend to be overestimated by the model vs. the targets, with the exception of the prevalence ratio among higher vs. lower risk FSW, which is reduced towards 1 as prevalence saturates in both groups. These shortcomings could be explained by omission of age in the model (see § 3.5.2.1) or insufficient reporting bias adjustment for women's partners — despite substantial adjustment in § 3.2.8, only 18% of women were modelled to have 2+ partners in p12m, including FSW (Figures 3.4c and B.7). Thus, the model may struggle to reproduce high HIV prevalence among women overall, without high incidence and thus prevalent among FSW and medium activity women. Indeed, previous work has shown that HIV prevalence among lower risk groups can be partially driven by turnover of infected individuals from higher risk groups [10].

Few data are available to validate the modelled early epidemic dynamics. Modelled incidence among women and men peaked rapidly after introduction of HIV (Figure 3.10b), corresponding to rapid acquisition and saturation among higher risk FSW and clients. Modelled incidence and prevalence continued to increase approximately linearly over 1990–2010, reflecting a balance of would-be exponential epidemic growth and build-up of mitigating factors, such as increasing condom use, male circumcision, ART coverage, and accumulation of seroconcordant partnerships (see § 4.3.3). These trends can be compared with HIV prevalence from Eswatini antenatal care clinics over the same period (Figure B.11), which suggest

similar trends.²³ Decline of HIV incidence and prevalence after 2010 can likely be attributed to rapid ART scale-up (see § 3.4.2.2) and further increases in condom use (Figure B.13). Although modelled incidence declined rapidly, prevalence remained relatively higher due to increased survival of PLHIV with ART. In some model fits, prevalence among FSW declined faster than among women overall, likely due to high turnover of women in sex work.

3.4.2.2 ART Cascade

Figure 3.11 illustrates the modelled ART cascade among selected risk groups, including both conditional and unconditional cascade steps, and the associated calibration targets. The model estimates agree quite well with these targets, for all risk groups. The non-monotonic proportions virally suppressed among treated PLHIV reflect major changes in treatment eligibility (see § 3.2.6.2), which caused influxes of newly ART-eligible PLHIV to temporarily decrease the proportions virally suppressed among treated PLHIV.

3.4.3 Who Infected Whom

As further model validation, and to gain insights into the modelled networks of transmission, this section presents several summaries of “who infected whom” — i.e., distributions of yearly infections stratified by the transmitting group, acquiring group, and partnership type. Throughout the section, the numbers of yearly infections shown are obtained from the median value across all 1000 model fits.

Figure 3.12 illustrates the total numbers and proportions of modelled yearly infections transmitted from (a) and acquired among (b) modelled risk groups. Figure 3.13 then gives the *ratio* of yearly infections transmitted vs. acquired. Figure 3.14 stratifies yearly infections by partnership type, while Figure 3.15 illustrates the complete transmission network every 10 years from 1990.

Before 1990, most infections were transmitted between FSW and their clients, mainly via regular sex work partnerships. Indeed, throughout the epidemic, FSW, clients, and regular sex work partnerships were disproportionately involved in transmission. Higher risk FSW had the largest ratio of infections transmitted vs. acquired, suggesting that prevention efforts prioritizing these women would be highly efficient at reducing overall transmission. Interestingly, this ratio for lower risk FSW declined and remained below 1 by approximately 2013, suggesting that lower risk sex work could be seen as a net sink (vs. source) of new infections, though the risk of transmission after exiting sex work is not captured by this ratio. Also, the ratio for medium activity men was sometimes higher than for clients of FSW; two factors could contribute to this result: a greater proportion of sexual partners who are susceptible among medium activity men (i.e., not FSW), and greater overall sexual activity vs. lower risk clients in some model fits. Since many clients are highly mobile for work and thereby away from regular partners [305, 310, 340], it is not implausible that overall sexual activity could be lower among some clients vs. a “medium activity” group of men.

After 1990, lowest/medium activity women and men began to acquire and transmit a larger proportion of infections, mainly via casual partnerships, corresponding with the epidemic peak. While lowest/medium activity women transmitted similar proportions of infections vs. lowest/medium activity men, these

²³ Antenatal care data were not used as calibration targets because such data are known to overestimate HIV prevalence among women overall due to non-representative sampling [127, 128].

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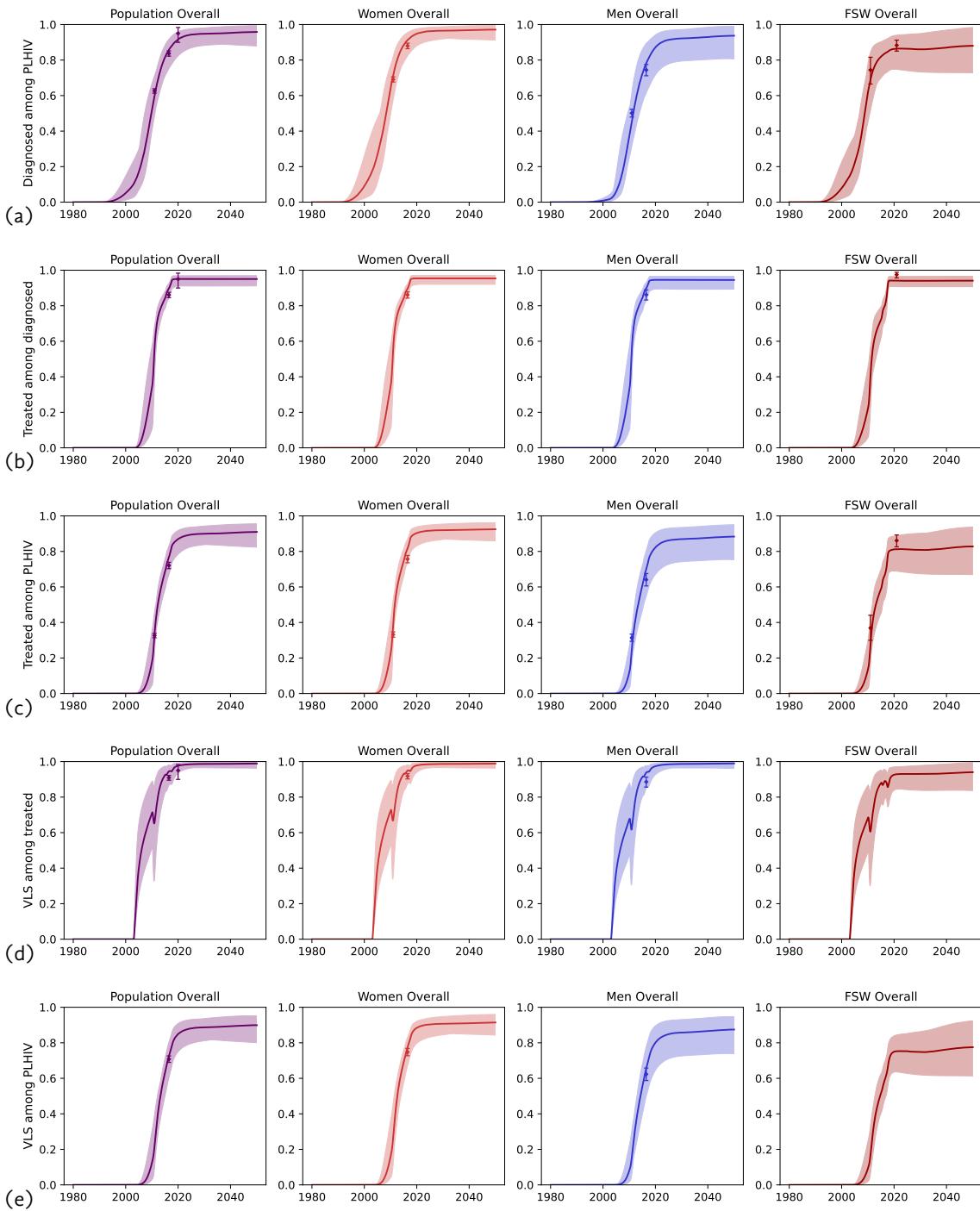


Figure 3.11: Modelled ART cascade among selected risk groups and associated calibration targets

PLHIV: people living with HIV; VLS: viral load unsuppressed; 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

3.5 DISCUSSION

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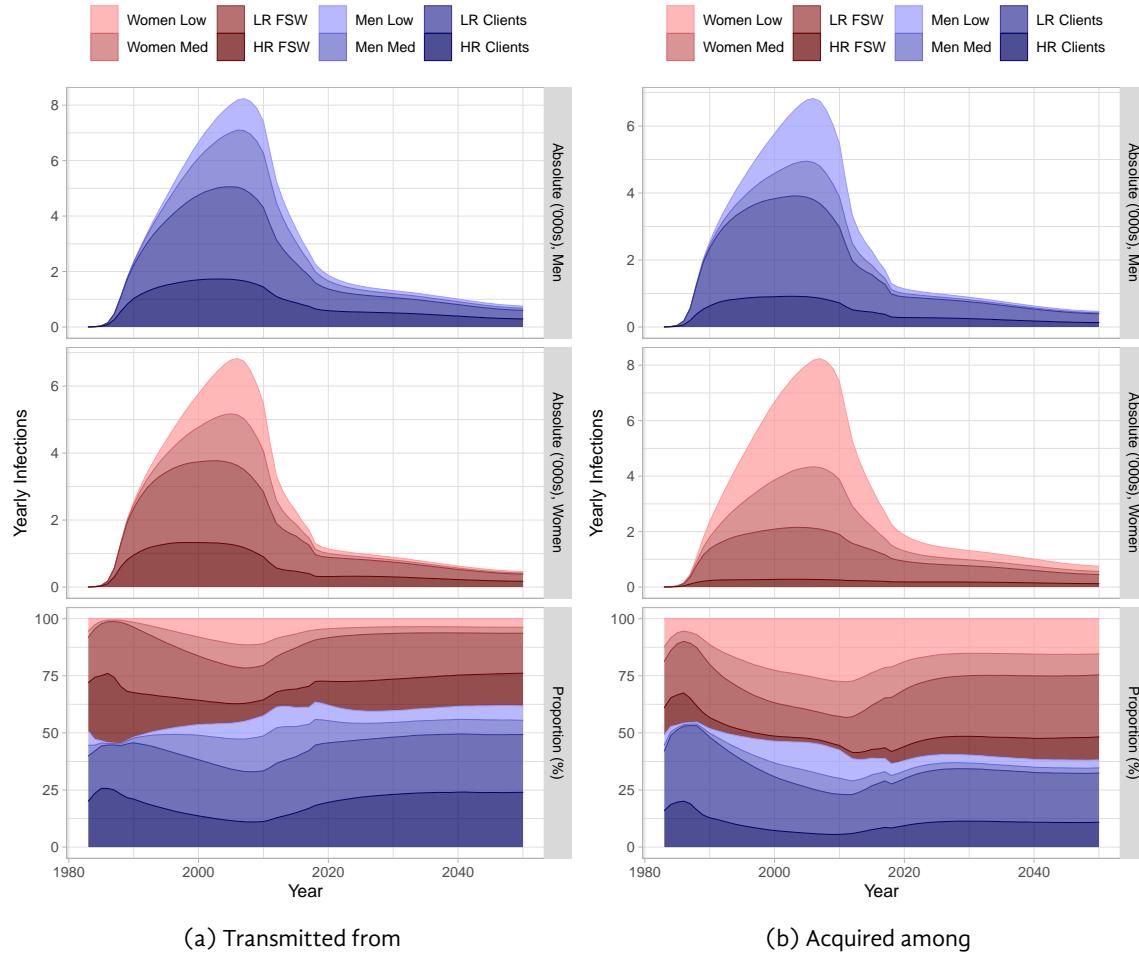


Figure 3.12: Absolute numbers and proportions of modelled yearly HIV infections (a) transmitted from and (b) acquired among risk groups in Eswatini

Low: lowest activity; Med: medium activity; LR/HR: lower/higher risk; FSW: female sex workers; Clients: of FSW; median numbers of infections across all model fits shown.

women *acquired* substantially more infections than the men, including projected infections beyond 2020. As incidence declined over 2010–2020 and beyond, new infections were modelled to become “re-concentrated” within sex work populations and partnerships. This re-concentration of HIV incidence among higher risk sexual networks is indeed anticipated across multiple declining epidemics [171, 203], and may undermine the anticipated prevention benefits of ART scale-up (as explored in Chapter 5) [64].

3.5 Discussion

Model design, parameterization, and calibration are key steps in applied transmission modelling, each step comprising numerous assumptions and analyses. As I illustrate throughout this thesis, these assumptions and analyses can be strong determinants of model outputs. Yet, the full details of these steps are often relegated to the supplementary materials of published articles — if available at all — with varying notation, terminology, and organization [174, 175]. It’s not clear whether these supplementary materials are

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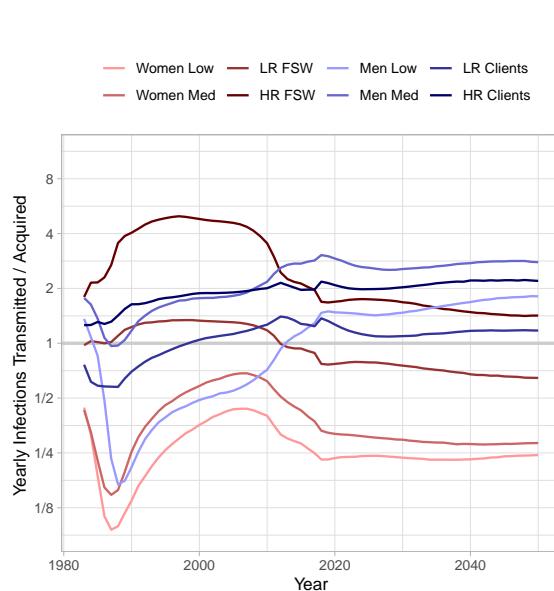


Figure 3.13: Ratio of modelled yearly infections transmitted from vs. acquired among risk groups in Eswatini

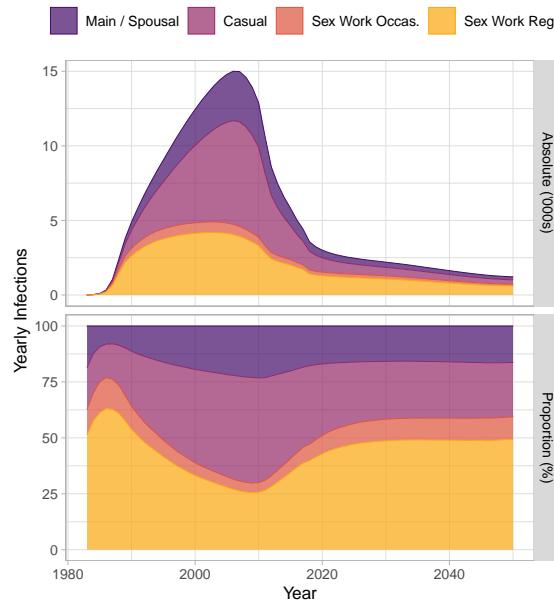


Figure 3.14: Absolute numbers and proportions of modelled yearly HIV infections transmitted via different partnership types in Eswatini

Low: lowest activity; Med: medium activity; LR/HR: lower/higher risk; FSW: female sex workers; Clients: of FSW; median numbers of infections across all model fits shown.

subject to the same level of peer review as the main text. This chapter gives the complete details of the Eswatini model development, which, in combination with the online code,¹ aims to provide full transparency and opportunity for peer review.

3.5.1 Methodological Contributions for Model Parameterization

The analyses required to support model parameterization depend heavily on the available data. Standardized approaches will likely remain less fruitful vs. careful consideration of the data at hand with respect to potential biases and precise interpretation. This chapter presents several novel methodologies for model parameterization, which may be useful to modellers, epidemiologists, and others.

3.5.1.1 Quantifying Sexual Behaviour

Quantifying sexual behaviour has long been challenging due to issues of representative sampling, non-response, recall bias, and reporting bias [341]. Such challenges may be magnified by the HIV epidemic itself, and intersect with issues of stigma and marginalization. Household-based face-to-face surveys, such as the demographic and health surveys [342] are typically one of few context-specific data sources for HIV transmission models; yet sexual behaviour data from these surveys have a high risk of bias. For example, household-based surveys likely miss populations at higher risk of HIV, including those who are highly mobile, homeless, or who live in institutions like brothels, prisons, and barracks [343–346]. As such, household-based surveys are generally not recommended to collect data on stigmatized behaviour and/or key populations [52, 53].

3.5 DISCUSSION

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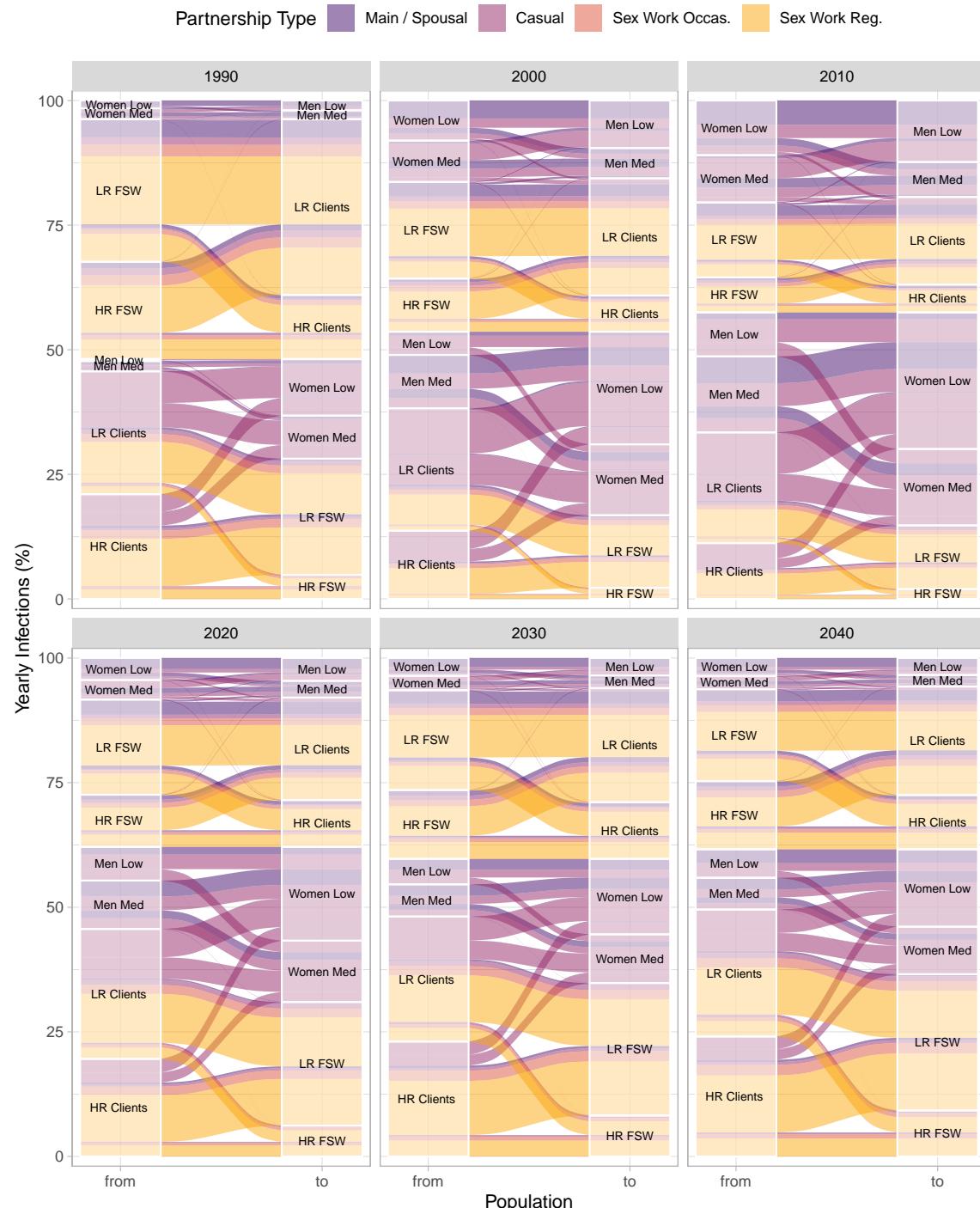


Figure 3.15: Alluvial diagram showing proportions of all yearly infections (ribbons) transmitted from (left) to (right) modelled risk groups, stratified by partnership type (color) and year (facets) in Eswatini

Low: lowest activity; Med: medium activity; LR/HR: lower/higher risk; FSW: female sex workers; Clients: of FSW; median numbers of infections across all model fits shown.

Moreover, comparison of survey delivery modes, including self-administered questionnaires, computer-assisted tools, and anonymous polling booth methods suggests that face-to-face surveys likely induce strong social desirability reporting bias [43, 44]. For example, reporting of extramarital sex in p12m among men and women was estimated via polling booth vs. face-to-face survey to be 3–7 times higher in Benin [238] and 6–8 times higher in India [44]; reporting of genital ulcers was likewise 2–5 and 14–35 times higher, respectively; buying and selling sex was similarly biased [44, 238]. Qualitative data from Eswatini [293–296] reinforce the possibility of prevalent unreported sexual partnerships.

Reporting Bias Adjustment. In § 3.2.8, I proposed a framework to incorporate reporting biases when estimating the proportions of women and/or men who report stigmatized behaviour — in this case, numbers of sexual partners. This framework formalizes ad hoc adjustments often made by modellers to reconcile relatively small numbers of reported partners with high levels of observed transmission, e.g., [161]. Unlike ad hoc adjustments, the proposed framework explicitly uses a specified ratio between adjusted vs. reported population proportions engaging in the behaviour, and further supports uncertainty in this ratio via Monte Carlo sampling. The framework also allows estimation of internally consistent population proportions (i.e., sum to 100%) for more than 2 strata through constructing and solving a system of constrained, nonlinear equations.

Recall Period Adjustment. A related issue concerns how to derive a partnership formation rate (or number of concurrent partners) from survey data. Sexual health surveys will typically ask questions like “*How many different people have you had sex with in the past 12 months?*” [342] or “*past 1 month*”, etc. [108, 122, 141]. Then, it’s not obvious whether the reported partner numbers should be interpreted as a rate per recall period, or simply a number of concurrent partners. Indeed, the former interpretation of these data has likely contributed to a common practice of capping modelled partnership durations at 1 year (see § 4.1.4), with notable influence on model outputs. In § 3.2.11.1, I showed that the correct interpretation is somewhere in between these extremes, and derived expressions for both the partnership formation rate Eq. (3.8) and numbers of concurrent partners Eq. (3.9), given a partnership duration. While partnership duration can also be challenging to measure [316], these expressions can help conceptualize survey responses and, at minimum, support more precise assumptions when analyzing the data. Future work should explore the influence of heterogeneous partnership duration on these equations.

3.5.1.2 Log-Linear Mixing

Mixing patterns — i.e., who contacts whom — are a well-established determinant of epidemic dynamics [4, 170, 324]. Like-with-like (“assortative”) mixing generally acts to compound the effects of risk heterogeneity: increasing the initial rate of epidemic growth (reproduction number) and decreasing the equilibrium prevalence [170]. Despite the recognized importance of mixing, there are surprisingly limited data to inform sexual mixing patterns among risk groups, and many compartmental HIV models continue to use a 1-parameter (ϵ) approach [174, 324].²⁴ This approach assumes that a minimum proportion of partners (ϵ) are guaranteed to be from the same risk group, and that this proportion is fixed and equal for all risk groups.

²⁴ Stratification of partnership types, where different risk groups form different numbers of each partnership type, also contributes to overall mixing patterns.

By contrast, the log-linear approach proposed in [327] provides greater flexibility in conceptualizing and implementing mixing via the *odds* of any two groups mixing vs. random mixing. However, [327] does not provide a method to maintain fixed partnership numbers / formation rates — which are typically assumed constant based on the available data — for arbitrary mixing patterns; I hypothesize that this limitation has prevented widespread adoption of the log-linear approach. In § 3.2.14.2, I developed a method to maintain fixed partnership formation rates for arbitrary mixing patterns using an iterative proportional fitting procedure [328]. This method therefore allows specification of more complex mixing patterns to reflect emerging data and/or modelling hypotheses, while maintaining fixed overall sexual activity. The log-linear approach also defines mixing patterns at the population-level (vs. partnerships per-person, or conditional probability of a given partnership), making it easy to verify and/or enforce that partnerships “balance”, as population-level mixing matrices should be symmetric [347].

3.5.1.3 Duration of Risk Exposure

In addition to risk heterogeneity and mixing, recent work has shown that “turnover” among risk groups, also called “episodic risk”, is another key determinant of epidemic dynamics and intervention impact [10, 200]. Risk group turnover acts to reduce risk heterogeneity via net movement of infections from higher risk groups into lower risk groups; thus, calibrating a model to a given prevalence ratio with vs. without turnover requires an even larger *incidence* ratio [10]. Turnover can be parameterized using, among other things, the average duration within a given risk group [10]. Within the model, these durations are implicitly assumed to be exponentially distributed, which appears reasonable for Swati FSWs [108, 141] (Figure B.6). However, such durations are often estimated from survey data using the difference between the respondent’s current age and the age they reported first selling sex. As discussed in § 3.2.10.2, this definition of sex work duration can be biased by up to three factors: right censoring, as FSW continue selling sex after the survey (duration underestimated); difficulties reaching new FSW [35] (duration overestimated); and intermittent engagement in sex work (duration overestimated). Although I have tried to explicitly account for such biases, future work could explore and compare alternate methods of estimating duration in sex work (or other epidemiologically relevant “states”) [196]. Indeed, in the absence of age stratification, the conceptualization and implementation of turnover in the current model is somewhat simplistic (see also § 3.5.2.1), ignoring unique vulnerabilities faced by young sex workers [35], and whether paid sex is driven by supply vs. demand [4, 348].

3.5.1.4 Within-Group Heterogeneity

Key populations are usually assumed to be homogeneous in compartmental models — i.e., heterogeneity *within* key populations is not considered. Yet, there is substantial variability in the structural, behavioural, and network-level HIV risk factors experienced by FSW, within and between epidemic contexts [29, 30, 271, 349]. The Eswatini model aims to represent this heterogeneity — albeit simply — by stratifying FSW into higher and lower risk groups. As explored in § 3.2.7, I parameterized these groups using individual-level data from FSW surveys in 2011 [108] and 2014 [141] in Eswatini. Although these data were not ideal for inferring mechanistic risk (see below), the data-driven stratification and parameterization of risk groups used — drawing on risk score methodology [349, 350] — may be useful elsewhere.

Unfortunately, these parameterization analyses are limited by the suitability of the available data, namely: the cross-sectional nature of both surveys, and the availability of only self-reported HIV status in 2014 [108, 141]. While cross-sectional data can be used to estimate associations of factors with HIV status, which may be directly useful for recommending HIV testing [351], the same factors may not be associated with HIV *acquisition* risk, since risk is dynamic but HIV status reflects cumulative risk. Factors associated with acquisition risk would be more useful as mechanistic model inputs, and can be estimated from longitudinal data, as in the case of risk scores used to support PrEP initiation [349, 350]. Regarding HIV status, self-reported status was historically considered unreliable due to low rates of HIV diagnosis and high rates of incidence among FSW [105, 185]; however, recent scale-up of HIV testing and incidence declines in Eswatini may render self-reported HIV status a reasonable proxy for serological HIV status [352].

3.5.2 Limitations of the Model

Despite the advancements in model parameterization described above, the model developed here still has several limitations. This section describes these limitation and their potential influence on model outputs.

3.5.2.1 Model Structure

The model structure includes $2 \times 4 \times (1 + 5 \times 5) = 208$ compartments in total, reflecting sex, activity level, and HIV / treatment dimensions, as well as four distinct partnership types, and vaginal vs. anal sex. Yet even these stratifications omit several important aspects of HIV epidemiology in Eswatini.

Men Who Have Sex with Men. Men who have sex with men (MSM) experience disproportionate HIV risk globally due to multiple factors, including increased probability of transmission via anal sex and differences in sexual network density [27, 353]. Pooled HIV prevalence among MSM is estimated to be 3–9 times higher vs. men overall in Sub-Saharan Africa (SSA); however, prevalence ratios are generally smaller in larger epidemics [353]. In fact, HIV prevalence among Swati MSM has been estimated to be similar to among men aged 15–49 overall (approximately 20%) [109, 137, 353], likely because Swati MSM tend to skew younger, while HIV prevalence increases with age [109, 137]. The population size of MSM in Eswatini is estimated to be 1–2% of men aged 15–49 [109, 141, 219]. Thus, although unmet needs of MSM in other SSA countries are estimated to drive overall transmission [154, 206], including via overlapping MSM and heterosexual networks [354], the same may be less true in the Eswatini due to high overall HIV prevalence. Therefore, the influence of omitting MSM on modelled HIV transmission dynamics would likely be relatively small in Eswatini vs. in contexts with lower overall HIV prevalence.

Age Stratification & Transactional Partnerships. HIV prevalence in Eswatini, as elsewhere, continues to be strongly associated with age, increasing from <5% at age 15 to approximately 50% between ages 30–50, and declining thereafter [129, 134, 137]. While HIV risk likely accumulates with age due to sexual activity, older generations would have experienced lower cumulative risk if their sexual activity peaked before widespread HIV transmission. The age of peak prevalence is also shifting older as incidence declines, suggesting that younger generations are experiencing lower cumulative risk by a given age vs. older generations; yet, prevalence continues to peak earlier among women vs. men, suggesting that women experience more risk earlier [129, 134, 137].

Indeed, adolescent girls and young women are increasingly recognized as another key population in the HIV epidemic response [208], whose vulnerabilities include: higher biological susceptibility, gender-based violence, food/economic insecurity, and transactional relationships — defined in [355] as: “*non-commercial, non-marital sexual relationships motivated by the implicit assumption that sex will be exchanged for material support or other benefits*” [33, 40, 208]. Qualitative data highlight the prevalence of such factors in Eswatini, with roots in patriarchal norms and broader social pressures [293–296, 356].

By omitting age stratification, and not explicitly modelling transactional relationships as distinct from casual partnerships, the model may fail to capture two key epidemiological phenomena: 1) declining incidence due to age-cohorting effects — since true overall age mixing is likely assortative with moderate age disparities [294, 296, 357] some infections can become “trapped” within age cohorts [358], whereas the model without age stratification implicitly assumes random age mixing throughout the population;²⁵ 2) mechanistic contributions of transactional partnerships and associated factors — the importance of transmission drivers that are not modelled evidently cannot be inferred, and may instead be mis-attributed to factors that *are* modelled, such as the relative susceptibility of women vs. men (see § 3.2.2.2).

3.5.2.2 Calibration

My goals for model parameterization and calibration were to: a) obtain parameter sets which yielded plausible HIV epidemic trajectories for Eswatini and/or Southern Africa in general; and b) favor additional uncertainty over assumption-driven parameter constraints. Thus, I opted to consider uncertainty in a large number of parameters ($N = 73$), despite having only a similar number of calibration targets ($N = 69$). I represented this uncertainty mainly via univariate parameter priors, which could permit implausible combinations of parameter values, although I enforced a few joint parameter constraints (§ B.4.1). Additionally, the calibration approach used (selecting the top 1% of 100,000 parameter sets by likelihood) was similar to prior approaches [360], but still relatively simple and ad hoc. As a result, my ability to infer model parameter values through calibration was limited, and many parameter posterior distributions did not differ significantly from their priors (Figure 3.9). The quality of parameter inference and model agreement with the calibration targets might be improved using more efficient calibration techniques [333], such as Sampling Importance Resampling (SIR) [361] or Incremental Mixture Importance Sampling (IMIS) [362]. However, the quality of model-based evidence likely depends more on appropriate specification of model structure and unbiased parameter priors, than on more efficient calibration techniques.

3.5.2.3 Evolving Context & Interventions

A final group of limitations relate to the evolving epidemic context and interventions which are not captured by the model, including the COVID-19 pandemic, growing civil unrest, and emerging interventions. These conditions have largely developed since 2018, and thus are unlikely to influence the retrospective modelling analyses of later chapters. Moreover, the model applications in Chapters 4 and 5 are mainly illustrative, rather than directly tied to specific policy questions for Eswatini.

²⁵The importance of age-disparate partnerships for prevention remains controversial [330, 357, 359].

COVID-19. Many health systems were disrupted by the COVID-19 pandemic, including in Eswatini [138]. Prevention programs were particularly impacted during 2020, including scale-up of pre-exposure prophylaxis (PrEP) and voluntary medical male circumcision (VMMC), as well as HIV and viral load testing services [138]. While rapid interventions designed to minimize ART interruption were largely successful, COVID-19 mortality was high among PLHIV in Eswatini [138]. Additionally, government restrictions aimed at reducing COVID-19 transmission — including closing bars, clubs, etc., imposing a nighttime curfew, and travel restrictions [109] — likely also reduced HIV incidence, especially among FSW [363].

Civil Unrest. As noted in § 1.2, democratic freedoms in Eswatini are severely limited by the absolute monarchy [110], and socioeconomic inequality remains high [114]. An ongoing financial crisis and frustration with the political conditions led to growing pro-democratic protests since 2018, which grew further with COVID-19 restrictions [110, 114]. Such protests have been met with violence, including the assassination of prominent human rights lawyer and activist Thulani Maseko in 2023 January [116]. The trajectory of this unrest is not clear [111], but the implications for HIV service delivery in the coming years could be substantial.

New Interventions. In 2017, Eswatini began a PrEP demonstration project in 6 rural primary care clinics [131, 364], and aims to expand PrEP access nationally in the coming years, with a focus on adolescent girls and young women (AGYW) and FSW [138]. An estimated 25% of FSW (N = 264) and 8% of MSM (N = 303) were on PrEP by 2021 [109]. The success of these efforts will likely be further improved with the addition of long-acting injectable PrEP options [365, 366]. Similar improvements in viral suppression may also be gained in the coming years via long-acting injectable ART [367]. Injectable PrEP and ART can help overcome many of the structural barriers associated with oral — i.e., daily pill — regimens, such as high population mobility and familial power structures [120, 249, 368, 369]. The current PrEP expansion is also part of the national roll-out of the DREAMS (Determined, Resilient, Empowered, AIDSFree, Mentored, and Safe) package, which aims to address multiple HIV vulnerabilities among AGYWs [138, 140]. The current model does not currently include any of these emerging interventions, but they should be feasible to integrate in the future.

Chapter 4

Modelling HIV Transmission via Sexual Partnerships: Equations and Assumptions

While developing the Eswatini model in Chapter 3, and examining the models reviewed in Chapter 2, I noticed that the “force of infection” equation — the rate at which susceptible individuals acquire infection — has previously been defined in several different ways. These differences were not due to differences in which risk groups, partnership types, and/or intervention were considered, but rather due to differences in which mathematical approximations of sexual partnership dynamics were used. It was not clear if or how such differences might influence overall model outputs. Thus, this chapter explores different mathematical approaches to modelling HIV transmission via sexual partnerships in compartmental models. Specifically, I review prior approaches (§ 4.1), develop a new approach (§ 4.2), and compare the influence of selected approaches on model outputs (§ 4.3).

First Principles & Post-Transmission Contacts. In the simplest compartmental transmission models — i.e., without any population stratification, repeated contacts, etc. — the force of infection λ is defined as:¹

$$\lambda = C\beta \frac{I}{N} \quad (4.1)$$

where: C is the average contact rate per-person; β is the average probability of transmission per contact; and I/N is the current prevalence of infection.

If the population is stratified into multiple groups i , the infection is stratified into multiple infectious stages h , and contacts are stratified into multiple types p , then Eq. (4.1) can be generalized to:

$$\lambda_i = \sum_{p,i',h'} C_{pii'} \beta_{ph'} \frac{I_{i'h'}}{N_{i'}} \quad (4.2)$$

where: $C_{pii'}$ is the average rate of type- p contacts per-person among group i with group i' , $\beta_{ph'}$ is the average probability of transmission per type- p contact given infection stage h' , and $I_{i'h'}/N_{i'}$ is the

¹ Eq. (4.1) also assumes frequency-dependent transmission vs. density-dependent transmission, which is almost always more appropriate for sexually-transmitted diseases [370].

prevalence of infection stage h' among group i' . Note that Eq. (4.2) implicitly assumes that contact rate and mixing by infection status/stage is random.

The force of infection equation is further complicated by repeated contacts with the same individuals, such as in sexual partnerships (also household contacts, and other social relationships), where each contact reflects a single “sex act”. With repeated vs. random contacts, individuals who recently acquired or transmitted infection will continue to contact the same person, resulting in “post-transmission contacts” (PTC) — sometimes called “wasted contacts” (in terms of transmission) — and slower infection spread through the contact/partnership network.² A major concern when modelling HIV transmission via sexual partnerships is therefore to account for these PTC.

4.1 Prior Approaches: Instantaneous Partnerships

The earliest HIV transmission models [148] were adapted from models of other sexually transmitted diseases, especially gonorrhea [166, 324, 371]. These early HIV transmission models did not explicitly model individual sex acts, but instead assumed an overall probability of transmission per partnership [146]. This assumption was initially justified via data suggesting that the probability of HIV transmission per partnership increased quickly and then saturated [372]. Such data were later explained by heterogeneity in infectiousness (e.g., due to infection stage, etc.) and/or susceptibility (e.g., due to genital ulcer disease, etc.) [18, 235, 373]. As this heterogeneity was quantified [235] and incorporated into HIV transmission models [374], the probability of transmission was increasingly parameterized per act vs. per partnership.

The shift to per-act vs. per-partnership parameterization highlighted a fundamental limitation of compartmental models (see § 4.1.5): compartmental models cannot model individual partnerships, because each “compartment” reflects a group of individuals whose characteristics are assumed to be homogeneous and memoryless [375]. Therefore, the dynamics of sexual partnerships must be modelled using average rates of partnership change and average characteristics of those partnerships. As a result, partnerships are effectively modelled as instantaneous, such that the cumulative risk of transmission per partnership is applied at the moment of partnership change [376]. This cumulative risk can be defined in terms of the average total numbers of sex acts per partnership, but the timing of specific sex acts or other events within partnerships cannot be captured in compartmental models. Further implications of the “instantaneous partnership assumption” and alternate modelling frameworks which avoid this assumption are discussed in § 4.1.5, 4.1.6, and 4.2.

Thus, over the years, different force of infection equations have been designed for compartmental models which explicitly aggregate the risk of transmission across different numbers and types of sex acts, and likewise across different numbers and types of sexual partners/partnerships. The remainder of this section reviews these equations and their assumptions in detail.

² Other conceptions of “post-transmission contacts” include: “within-partnership competing risks” and HIV seroconcordance.

4.1.1 Aggregating Sex Acts within a Partnership

To account for PTC due to repeated sex acts with the same partner, the per-partnership probability of transmission B was conceptualized as follows [377]. Let A denote the total number of sex acts in the partnership, and β denote the probability of transmission per act. For now, β is assumed to be equal (constant) for all acts. With equal β , the theoretical probability of n transmissions after A acts can be described by a binomial distribution:

$$p(n) = \binom{A}{n} \beta^n (1 - \beta)^{A-n} \quad (4.3)$$

Since transmission of HIV can actually only occur once, the per-partnership probability of transmission B is defined via the probability of “escaping” infection after all A acts:³

$$\begin{aligned} B &= 1 - p(n=0) \\ &= 1 - \binom{A}{0} \beta^0 (1 - \beta)^A \\ &= 1 - (1 - \beta)^A \end{aligned} \quad (4.4)$$

Although $B(A)$ is monotonic increasing, the effective probability of transmission per act B/A decreases as the number of acts A increases because, on average, more and more acts are PTC — i.e., occur after transmission. Figure 4.1a illustrates the shape of $B(A)$ (red) and the corresponding effective probabilities of transmission per act B/A (tangent slopes) for a shorter (blue, fewer sex acts) vs. longer (green, more sex acts) partnership. The average proportion of sex acts that occur after transmission also increases with the per-act probability of transmission β , according to:

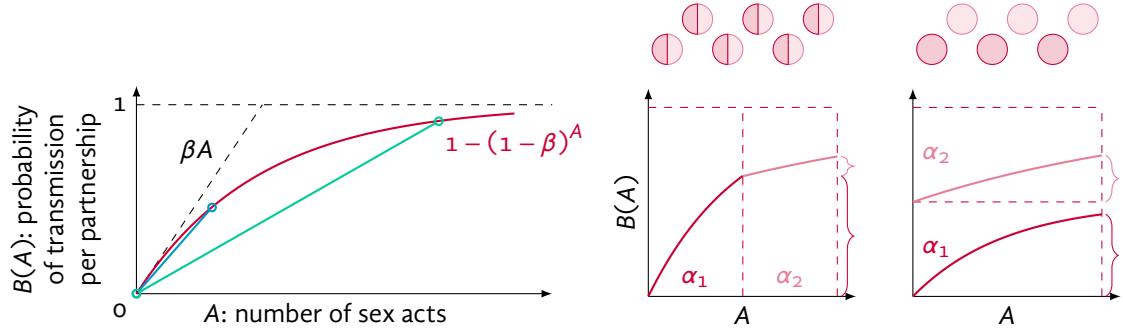
$$P_{PTC} = 1 - \frac{B(A)}{\beta A} \quad (4.5)$$

4.1.2 Heterogeneity in the Per-Act Probability of Transmission

As noted above, the per-act probability of transmission β is heterogeneous, varying with factors like: HIV infection stage, genital ulcer disease, condom use, etc. [18, 228]. The next step in developing a force of infection equation is to extend Eq. (4.4) to allow heterogeneity in β [377]. Let β_f denote the probability of transmission associated with a particular factor (or combination of factors) f ; and let α_f denote the proportion of acts A in an average partnership having transmission probability β_f (thus $\sum_f \alpha_f = 1$). There are two main approaches to aggregating β_f , reflecting different interpretations of α_f :⁴

³ Eq. (4.4) can also be reasonably approximated via the Poisson distribution $B = 1 - e^{-\beta A}$ for small β .

⁴ In most compartmental models without repeated contacts (partnerships), this distinction is not possible or necessary, because all contacts (sex acts) between two compartments (risk groups) are assumed to be independent.



(a) Probability of transmission per partnership B vs. number of sex acts A , comparing shorter (blue) vs. longer (green) partnerships
(b) Average accumulation of transmission probability for within-partnership heterogeneity (left) vs. between-partnership heterogeneity (right)

Figure 4.1: Per-partnership probability of transmission vs. number of acts

B : probability of transmission per partnership; β : probability of transmission per act; A : total acts per partnership; α : fraction of total acts (within or between partnerships).

- **Within-Partnership Heterogeneity (WPH):** modelled partnerships are identical, but comprise heterogeneous acts — α_f denotes a proportion of acts in each partnership (Figure 4.1b left).

$$B_{\text{WPH}} = 1 - \prod_f (1 - \beta_f)^{A\alpha_f} \quad (4.6)$$

- **Between-Partnership Heterogeneity (BPH):** modelled partnerships are different, but each comprise identical acts — α_f denotes a proportion of partnerships (Figure 4.1b right).

$$B_{\text{BPH}} = 1 - \sum_f \alpha_f (1 - \beta_f)^A \quad (4.7)$$

Figure 4.1b illustrates these approaches for a simple case with two factors. For WPH (left), each factor f marginally contributes to the probability of escaping infection in every partnership. For BPH (right), the overall probability of escaping infection is modelled as a weighted average across partnerships, each affected by a single factor f . Both approaches guarantee $B < 1$, but we can show that $B_{\text{WPH}} \geq B_{\text{BPH}}$ by the (weighted) AM-GM inequality (see § C.1) [378]. Intuitively, this inequality arises because any large probability of transmission β_f has disproportionate influence in Eq. (4.6), even for a small proportion of acts affected α_f , whereas this influence is bounded by α_f in Eq. (4.7), as shown in Figure 4.1b.

The decision to use WPH vs. BPH for aggregating specific types of heterogeneity in β should be driven by the factor(s) in question. To this end, it is possible to combine Eq. (4.6) and Eq. (4.7) as follows to aggregate both types of factors simultaneously:

$$B_{\text{XPH}} = 1 - \sum_g \gamma_g \prod_f (1 - \beta_{fg})^{A\alpha_{fg}} \quad (4.8)$$

where: f denotes WPH factor(s); g denotes BPH factor(s); and γ_g replaces α_f for BPH factors. Then, for example, if it is known or assumed that “50% condom use” reflects 50% condom use in 100% of partnerships, sex acts with condoms vs. without condoms should be aggregated as WPH, with $\alpha_f = 0.5$.

By contrast, heterogeneity in individual-level factors like infection stage or treatment status should be aggregated as BPH,⁵ with γ_g as the conditional prevalence of each stage/status g among infected partners. In fact, aggregating infection stage and treatment status is often deferred to the full incidence equation (see § 4.1.3) using an equivalent form, but where γ_g is replaced by the unconditional prevalence of stage/status g among *all* partners.

4.1.3 Aggregating Partnerships

Although we considered between-partnership heterogeneity in § 4.1.2, the modelled per-partnership probability of transmission B still corresponds to a single average partnership. Some population groups may have multiple partners per unit time (usually year), possibly including different types of partnerships, or less than one partnership per year, on average. Thus, the second step in constructing the incidence equation is to aggregate transmission risk across these various partnerships / exposures [377].

As in § 4.1.2, there are two main approaches to aggregating partnerships — indeed having similar equations to Eqs. (4.6) and (4.7):

- **Incidence Rate:** instantaneous rate of infection among susceptible individuals — transmission risks are additive; can have $\lambda_i > 1$.

$$\lambda_i^{\text{IR}} = \sum_{pi'h'} Q_{pii'} B_{pii'h'} \frac{l_{i'h'}}{N_{i'}} \quad (4.9)$$

- **Incidence Proportion:** cumulative proportion of susceptible individuals infected over a period Δ_t — transmission risks are competing; can only have $\lambda_i \leq 1$.

$$\lambda_i^{\text{IP}} = 1 - \prod_{pi'h'} \left(1 - B_{pii'h'} \frac{l_{i'h'}}{N_{i'}} \right)^{Q_{pii'} \Delta_t} \quad (4.10)$$

where: $Q_{pii'}$ is the rate of type- p partnership formation between groups i and i' ,⁶ $B_{pii'h'}$ is the average per-partnership probability of transmission from group/infection stage $i'h'$ to group i' via partnership type p , and $l_{i'h'}/N_{i'}$ is the prevalence of infection stage h' among group i' . Similar to within- vs. between-partnership heterogeneity, we can show that $\lambda^{\text{IR}} \geq \lambda^{\text{IP}}$ (see § C.1).

The force of infection is a rate by definition [190]. Yet, in principle, incidence proportion could be more precise than incidence rate *over a given time period* Δ_t . Since most models are now solved computationally, this period Δ_t could be matched to the timestep of the numerical solver.⁷ However, the added precision may be insignificant, because such timesteps should already be small.⁸ Moreover, some applications of incidence proportion have used a period of $\Delta_t = 1$ year in the equation, but then applied the result as a rate over smaller timesteps. Such applications erroneously reduce transmission within each *current* timestep

⁵ Individual-level factors should be aggregated as BPH because a given partner has exactly one current infection stage or treatment status; of course, this stage/status could evolve over the course of the partnership, but this future trajectory is not explicitly modelled — which only serves to highlight the limitations of either approach to aggregating heterogeneity in β .

⁶ This fully stratified partnership formation rate $Q_{pii'}$ is often broken down into a per-person partnership formation rate Q_{pi} and a mixing matrix $\rho_{pii'}$, as in § 3.2.14.1.

⁷ Popular numerical solvers include: `scipy.integrate.odeint` in Python, `deSolve::lsoda` in R, and `ode45` in MATLAB. These solvers can use adaptive timesteps for precision, but only pass the current time t , not the timestep, to the derivative computing function.

⁸ If the timestep must remain large due to computational constraints, then modellers should consider whether *all* rates should be similarly adjusted for the timestep — e.g., via Eq. (3.2).

in anticipation of competing risks between partnerships across *future* timesteps. These competing risks are already captured via loss of susceptibles to infection over successive timesteps. For example, if we compute $\lambda^{IP} = 0.2$ using $\Delta_t = 1$ year, but we apply this incidence using a timestep of 1 month, then the newly infected proportion after 1 year would be modelled as: $1 - (1 - \lambda^{IP}/12)^{12} = 0.18 < 0.20$. While $\Delta_t = 1$ year may be chosen to match common reporting periods for sexual behaviour data, this choice remains mathematically arbitrary, and often coincides with negligence of partnership dynamics beyond 1 year, as discussed below in § 4.1.4. In sum, unless the period Δ_t can be matched to the numerical solver timestep, incidence rate Eq. (4.9) is preferred over incidence proportion Eq. (4.10).

4.1.4 Revisiting Partnership Duration

A final issue in constructing the force of infection equation relates to parameterization. In Eqs. (4.3)–(4.10), partnership durations δ are not explicitly modelled, but implied by the total numbers of sex acts per partnership A , and a presumed frequency of sex per partnership F , such that $A = F\delta$. By contrast, the partnership formation rate Q is often directly informed by survey questions like “*How many different people have you had sex with in the past 12 months?*” (see also § 3.2.11.1). As such, the lowest possible value among sexually active individuals could naively be taken as $Q = 1$ (per year). Then, if $Q \geq 1$ is used in the model, the total sex acts per partnership can (and should) be reduced to reflect up to one year — i.e., $A \leq F$, or effectively $\delta \leq 1$ year. This change vs. $Q < 1, A > F$ can substantially reduce the proportions of sex acts which are modelled as PTC, and thus increases transmission via what would be longer ($\delta > 1$ year) partnerships. On the other hand, using the true $Q < 1, A > F$ can effectively delay early transmission in longer partnerships, such that modelled HIV prevalence could lag behind true HIV prevalence. These dynamics are further explored in simulation experiments (§ 4.3.3).

Lastly, it is worth noting that partnership duration δ is further related to the average partnership formation rate Q and the average number of concurrent partners K by $Q = K/\delta$. Thus, an alternate parameterization could specify the number of concurrent partners K and the frequency of sex with each partner F . The overall rate of sex would be the same: $QA = KF$, since $A = F\delta$. In some ways, this KF parameterization is more intuitive, and it will be useful later, in the new force of infection approach (§ 4.2).

4.1.5 Limitations of Prior Approaches

Overall, prior approaches to modelling HIV transmission via sexual partnerships have several limitations (see also [375]). These limitations, and their implications for existing model-based evidence, can be summarized as follows.

Instantaneous Partnerships. Eqs. (4.9) and (4.10) both include the current HIV prevalence I/N directly in the force of infection. Thus, newly infected individuals are modelled to be immediately at risk of onward transmission, including via the exact same partnership by which they were infected. Similarly, individuals who recently transmitted to a given partner are also modelled to be at risk of transmitting (again) to the same partner, albeit with a small absolute rate reduction due to the smaller susceptible population. This modelling assumption acts to increase the modelled rate of transmission vs. “reality”, especially for longer partnerships. As a result, the contribution of longer partnerships to overall transmission could be overestimated, while the contribution of shorter partnerships could be underestimated.

Aggregating Past/Future Sex Acts. The instantaneous partnerships assumption is in fact directly related to the PTC issue, because the delay in onward transmission risk that is missing under instantaneous partnerships reflects the same post-transmission period within partnerships wherein additional sex acts cannot result in more infections. The prevailing solution to this issue is to define the per-partnership probability of transmission B by aggregating competing risks from each sex act within a given partnership via Eq. (4.4) et al. However, as described in § 4.1.4, this approach introduces a trade off between capturing the true proportion of PTC in longer partnerships (using the true partnership duration δ) vs. capturing the true magnitude of early transmission within partnerships (using $\delta \leq 1$). These two options would then underestimate or overestimate the contribution of longer partnerships to overall transmission, respectively. Moreover, the sex acts aggregated within each partnership via Eq. (4.4) et al. are parameterized to reflect current conditions — i.e., HIV stage, treatment status, condom use, etc. — even though such conditions almost certainly evolve over the course of partnerships, especially longer partnerships. Again, we can see the direct connection to the instantaneous partnerships assumption. This issue parallels limitations of cross-sectional risk factor analyses (e.g., § 3.2.7.3), where risk factors are modelled as static, but true risk accumulates via cumulative exposure to dynamic risk factors. The implications of aggregating these past/future sex acts are not immediately obvious, and likely depend on numerous factors and conditions.

Incidence Proportion. Risk from multiple partnerships is sometimes aggregated as incidence proportion λ^{IP} via Eq. (4.10). As described in § 4.1.3, this approach is not inherently wrong, but the specification of time period $\Delta_t = 1$ often is. This Δ_t should be matched to the timestep of the numerical solver, but $\Delta_t = 1$ year is often used, and the resulting incidence applied as a rate over smaller timesteps, reducing transmission. Since λ^{IP} saturates at 1 — similar to $B(A)$ in Figure 4.1a — transmission to higher risk groups is disproportionately reduced.

Within vs. Between Partnership Heterogeneity. The final limitation of prior approaches is the apparent lack of distinction between within- vs. between-partnership heterogeneity when computing the average per-partnership probability of transmission B . Both WPH and BPH — i.e., Eqs. (4.6) and (4.7) — and combinations thereof, have been used to model modified transmission risk in a proportion of sex acts due to HIV stage, treatment status, PrEP use, condom use, STI co-infection, circumcision, and more, but the choice of aggregation model is almost never explicitly justified. For some factors, there may be no “correct” choice, but modellers should be aware of the assumptions implied by their choice. The implications of model choice for transmission dynamics mainly derive from the fact that $B_{WPH} \geq B_{BPH}$, but even then the differences are often small (see § 4.3.1).

4.1.6 Alternate Modelling Frameworks

Recognizing the limitations of compartmental models in simulating infectious disease transmission via sexual partnerships, two main alternate modelling frameworks have been developed. These frameworks are illustrated in Figure 4.2. Modelling frameworks are further classified Appendix 1 of [8].

Pair-Based Models. Pair-based models, also known as pair-formation models, were developed as early as 1988, with the explicit motivation to overcome limitations of classic compartmental models of STI transmission [376]. In pair-based models, the fundamental population stratification reflects different partnership configurations and health states [379], such as: susceptible and single, a susceptible/infected pair in a long-term partnership, etc. (Figure 4.2b). Such models can therefore track the numbers of

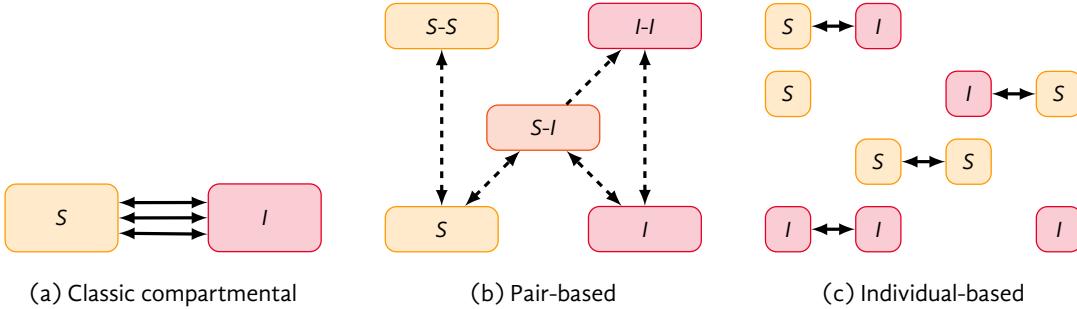


Figure 4.2: Representations of health states and sexual partnerships under three different STI modelling frameworks

S: susceptible; I: infectious; solid arrows: partnerships; dashed arrows: state transitions.

partnerships where transmission is vs. is not possible, thereby avoiding the instantaneous partnership assumption. Pair-based models have been applied to a variety of STIs [379]. However, the numbers of compartments required to reflect all possible partnership configurations *and* all possible health states among connected partners quickly become impractical [375, 379]. For example, a classic compartmental model with 2 risk groups and 2 health states would require $2 \times 2 = 4$ compartments; whereas even a first-order pair-based model (i.e., without “triples”) would require 2×2 (singles) + $(2 \times 2)^2$ (pairs) = 20 compartments; a second-order pair-based model would require $4 + 4^2 + 4^3 = 84$ compartments. Thus, pair-based models are especially limited in their ability to model partnership concurrency — the role of which in HIV epidemiology remains controversial [380]. As such, pair-based models have seen little widespread adoption for STI or HIV transmission modelling [375].

Individual-Based Models. Individual-based models, also known as agent-based, network-based, or microsimulation models, explicitly simulate unique individuals (Figure 4.2c). They represent a fundamental change in the model unit from groups of individuals — i.e., the “compartments” of compartmental models [375]. Individual-based models can therefore model unique partnerships, and track them over time. Such individuals and partnerships can then be parameterized in fundamentally different ways vs. compartmental models, including with continuous valued features like infection age and sex frequency, vs. predetermined categories like infection stages and partnership types [375, 381]. Parameters for each individual and partnership are thus sampled randomly and/or dynamically, allowing more complete and nuanced representations of risk heterogeneity and partnership dynamics. Such nuances can in fact be key determinants of epidemic dynamics and intervention impact [7, 8]. Evidently, many of the limitations of compartmental and pair-based models do not apply to individual-based models [375]. Yet these limitations are replaced with new challenges, especially related to implementing, parameterizing, and calibrating these powerful models [375, 381, 382]. For example, much effort has been dedicated to formalizing the statistical properties of dynamic networks via temporal exponential family random graph models (tERGM) [383] or latent order logistic models (LOLOG) [384], so that dynamic networks can be generated which are consistent with observed data. Although individual-based models have seen greater use than pair-based models, these challenges still prevent universal adoption over classic compartmental models [375]. It’s worth noting that not all individual-based models are transmission models, as individual-based models can also be used for simulation and inference for non-infectious diseases [385].

4.2 Proposed Approach: Effective Partnerships Adjustment⁹

Considering the potential drawbacks of pair-based and individual-based models outlined above in § 4.1.6, an improved approach to modelling HIV transmission via sexual partnerships within the compartmental framework would be useful. In this section, I propose such an approach — the *Effective Partnerships Adjustment*. That is, the proposed approach overcomes the limitations of prior approaches described in § 4.1.5, without the need to change modelling frameworks.

4.2.1 Illustrative Scenario

Consider the moment of one transmission event in a population of 16 monogamous partnerships, with 25% infection prevalence and random mixing by infection status (Figure 4.3a). Initially, infection prevalence is equal among partners of susceptible *S* and infectious *I* individuals: 6/24 and 2/8, respectively. Immediately after transmission, prevalence decreases to 5/23 among partners of *S* but increases to 4/9 among partners of *I*, decreasing the population-level transmission risk. Next, three events are possible:

- (a) another transmission occurs among the remaining *S-I* partnerships, yielding 4/22 prevalence among partners of *S*, and 6/10 among partners of *I*; population-level transmission risk decreases further
- (b) the partnership from the original transmission ends, and both individuals form new partnerships (assumed at random), yielding, on average, 9/32 prevalence among partners of both *S* and *I*; population-level transmission risk increases *above* the initial level ($9/32 > 6/24$)
- (c) any other partnership ends, and both individuals form new partnerships (assumed at random); infection prevalence among *S* and *I*, and population-level transmission risk all remain unchanged, on average

Prior compartmental models have effectively assumed that event (b) always occurs before (a) — i.e., the “instantaneous partnership assumption”. This assumption is reflected in Figure 4.3b, where the frequentist approximation does not explicitly model any individual partnerships. This assumption is evidently worse for longer partnerships.

4.2.2 Conceptual Development

The illustrative scenario highlights how any partnership where transmission has occurred are “transmission ineffective” — i.e., seroconcordant — and should be removed from the force of infection. In a compartmental (non-pair-based) model, these partnerships can be tracked as proportions of individuals: namely, all individuals who recently acquired infection *and* all individuals who recently transmitted infection. Here, I use “recent” to mean “before individuals change partners”. If some individuals have multiple concurrent partnerships ($K > 1$), then these individuals should not be removed entirely, but their numbers of “effective partnerships” should be reduced by 1. If multiple types of partners are considered, then only the partnership type involved in the transmission should be reduced. This adjustment to “effective partnerships” can then be applied until these individuals change partners — at a rate inversely related

⁹ A preliminary version of this approach was presented in [386].

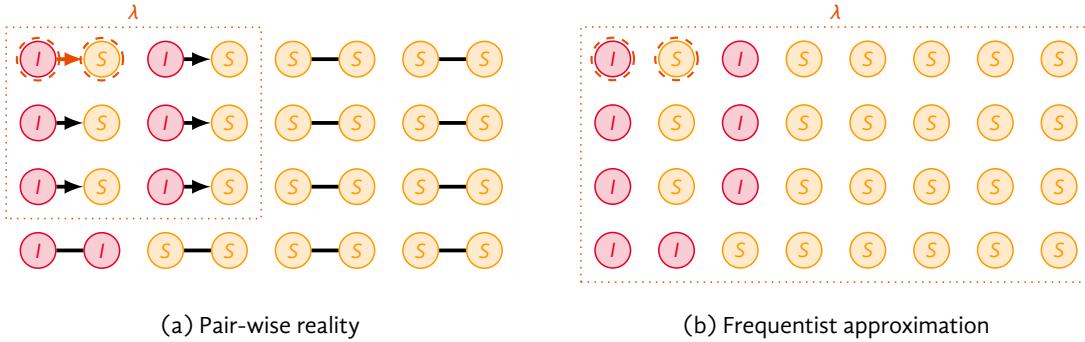


Figure 4.3: Comparison of pair-based reality and frequentist approximation for a population of 16 pairs with 25% infection prevalence, at the moment of one transmission event

S : susceptible; I : infectious; λ : force of infection; dashed circles: individuals involved in transmission event.

to partnership duration: δ^{-1} . However, during this period, these individuals should still be modelled to progress as usual through different stages of infection, activity group turnover, etc.

Using this conceptual basis, I propose a new stratification of the modelled infected population, denoted \bar{p} . The stratum $\bar{p} = 0$ corresponds to no recent transmission, or all “new” (potentially discordant) partnerships. Other strata $\bar{p} \neq 0$ correspond to recent transmission via (to or from) partnership type \bar{p} . Figure 4.4 illustrates the new stratification together with the existing HIV infection stratification (Figure 3.1b). Following infection, all individuals enter a stratum $\bar{p} \neq 0$ corresponding to the partnership type p by which they were infected. Thus, the rate of entry to this stratum from S_i is defined by the incidence rate without aggregating across partnership types: λ_{ip} . Individuals may then transition from $\bar{p} \neq 0$ to $\bar{p} = 0$ upon forming a new partnership, at a rate δ_p^{-1} . Finally, individuals may re-enter any stratum $\bar{p} \neq 0$ if they transmit infection via partnership type p . I denote the corresponding rate as λ'_{ip} , representing the per-person rate of *transmission*, not *acquisition* as in λ_{ip} . This rate λ'_{ip} is not defined or needed in prior models (§ 4.1) but I develop the necessary equations below in § 4.2.3. The issue of transmission via multiple partnerships is discussed in § 4.2.4.

4.2.3 Equations¹⁰

Since partnership duration is now considered separately and explicitly, I do not define any per-partnership probability of transmission B . Rather, I define the force of infection to directly include the frequency of sex per partnership F and probability of transmission per sex act β . However, the mixing is now slightly more complicated, since the number of “effective partnerships” depends on infection status. In addition, these partnerships are now defined as numbers of concurrent partners K , rather than partnership formation rates Q .

Let $M_{pi'i'}$ be the total (population-level, not per-person) number of type- p partnerships between group i and group i' . As described § 3.2.14, this “mixing matrix” $M_{pi'i'}$ can be defined in several ways, based on the total numbers of “effective partnerships” among each group: M_{pi} , $M_{pi'}$, plus some parameter(s) specifying mixing patterns (e.g., Φ). Working backwards, I start by defining M_{pi} (and likewise $M_{pi'}$) via

¹⁰“Enough talk. Show me the \$” — LATEX users.

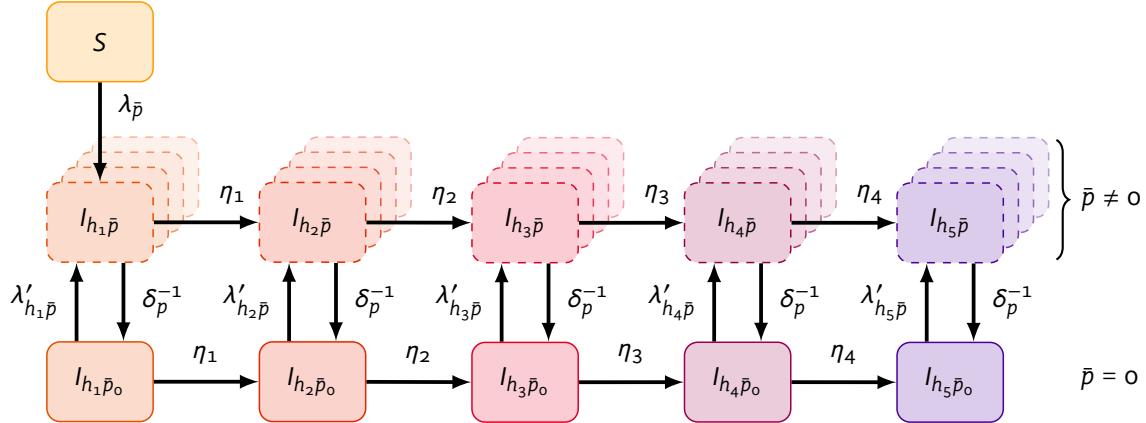


Figure 4.4: Modelled states and transitions related to HIV infection, and a new stratification \bar{p} to track the proportions of individuals in partnerships where transmission already occurred

S : susceptible; I_h : infectious in stage h ; p : partnership type; \bar{p} : new stratification, where $\bar{p} = 0$ reflects no recent transmission (all new partnerships), and $\bar{p} \neq 0$ reflects recent transmission via a type- p partnership; λ : force of infection per susceptible; λ' : force of infection per infectious; η : rate of progression between infection stages; δ : partnership duration.

the sum across health statuses — i.e., susceptible, and different stages of infection h :

$$M_{pi} = M_{S,pi} + \sum_h M_{I,pih} \quad (4.11)$$

I then define the total numbers of partnerships among susceptible individuals as:

$$M_{S,pi} = S_i K_{pi} \quad (4.12)$$

and likewise for individuals in infection stage h :

$$M_{I,pih} = I_{ih,\bar{p}=p}(K_{pi} - 1) + \sum_{\bar{p} \neq p} I_{ih\bar{p}} K_{pi} \quad (4.13)$$

Eq. (4.13) is the key equation whereby the numbers of “effective type- p partnerships” among individuals in stratum \bar{p} are reduced by 1. This reduction is then propagated through the mixing patterns when defining $M_{pii'}$. Thus, we are now ready to construct the overall force of infection equation as follows. I define the total (population-level, not per-person) rate of transmission from group i' and infection stage h' to group i via type- p partnerships as:

$$\Lambda_{pii'h'} = F_p \beta_{pii'h'} M_{pii'} \left(\frac{M_{S,pi}}{M_{pi}} \right) \left(\frac{M_{I,pi'h'}}{M_{pi'}} \right) \quad (4.14)$$

where the two fractions represent the proportions of all partnerships $M_{pii'}$ formed between susceptible individuals from group i ($M_{S,pi}$) and infectious individuals in group/infection stage $i'h'$ ($M_{I,pi'h'}$). The

per-person transmission rates to group i , and from group $i'h'$ can then be defined as:

$$\lambda_{pi} = \sum_{i'h'} \Lambda_{pii'h'} S_i^{-1} \quad (4.15)$$

$$\lambda'_{pi'h'} = \sum_i \Lambda_{pii'h'} I_{i'h'}^{-1} \quad (4.16)$$

For the purposes of solving the model, we can skip division by S_i and $I_{i'h'}$ in Eqs. (4.15) and (4.16), since λ'_{pi} and $\lambda'_{pi'h'}$ are immediately multiplied by S_i and $I_{i'h'}$, respectively, in the system of differential equations.

Finally, and to reiterate from above, infected individuals in stratum $I_{ih\bar{p}}$ are assumed to form new partnerships at a rate δ_p^{-1} , and thereby transition to stratum $I_{ih\bar{p}_0}$ ("all new partners"); and otherwise transition between infection stages, cascade of care, activity groups, etc. as usual, as illustrated in Figure 4.4.

4.2.4 Transmission via Multiple Partnerships

In the proposed *Effective Partnerships Adjustment* approach, I do not explicitly model the proportions of infected individuals who recently acquired and/or transmitted infection via two different partnership types, or two partnerships of the same type. To do so, the required size of the new dimension \bar{p} would be at least 2^P , not $P + 1$, where P is the number of different types of partnerships modelled. For transmission via three different partnerships, the required size would be at least 3^P , etc. Indeed, this exponential relationship is related to the challenge of specifying all possible combinations of partnership states in pair-based models [379]. However, under frequentist assumptions, we can equivalently model two transmissions by one individual as one transmission each by two individuals. Thus, we can transfer two individuals from $I_{ih\bar{p}_0}$ to $I_{ih\bar{p}_1}$ and $I_{ih\bar{p}_2}$ (one each) under the $P+1$ stratification, instead of just one individual from $I_{ih\bar{p}_0}$ to " $I_{ih\bar{p}_{12}}$ " under one of the exponential x^P stratifications.

In fact, $I_{ih\bar{p}_0}$ can be negative (but only for $\bar{p} = 0$), because the dimension \bar{p} is only relevant to Eq. (4.13); in all other contexts and equations, we use $I_{ih} = \sum_{\bar{p}} I_{ih\bar{p}}$, which must be positive as usual. Moreover, we can also have $I_{ih\bar{p}} > I_{ih}$, provided that:

$$I_{ih\bar{p}} \leq I_{ih} K_{pi} \quad (4.17)$$

reflecting the situation where 100% of I_{ih} have recently acquired and/or transmitted infection via at least one type- p partnership, or 50% via at least two partnerships, etc. This situation can therefore only arise in the context of multiple concurrent type- p partnerships: $K_{pi} > 1$. If $I_{ih\bar{p}} > I_{ih}$, then $I_{ih\bar{p}_0}$ must be negative, but we can show that Eq. (4.13) still yields the correct value of $M_{I,p,i}$. With this perspective, the constraint in Eq. (4.17) may be more intuitive: we cannot "remove" more than the total number of partnerships. This constraint should also be easy to guarantee for a small enough timestep, because $M_{I,p,i}$ approaches zero as $I_{ih\bar{p}}$ approaches $I_{ih} K_{pi}$ — i.e. all type- p partnerships become HIV+ seroconcordant, and no more transmission can occur via these partnerships until partners change.

4.3 Experiments

In this section, I describe some experiments (methods and results) to highlight differences in the various equations and approaches to modelling HIV transmission via sexual partnerships. Specifically: § 4.3.1 and 4.3.2 examine how the calculated per-partnership probability of transmission B differs under assumptions of: within- vs. between-partnership heterogeneity in the per-act probability of transmission β , and 1-year vs. complete partnership durations δ ; then § 4.3.3 explores differences in key transmission model outputs among the force of infection equations from § 4.1 and 4.2. In many transmission models, a justification for choosing each specific approach is rarely given. Thus, this section aims to illustrate potential implications of these choices.

4.3.1 Within- vs. Between-Partnership Heterogeneity

For computing an average per-partnership probability of transmission B , § 4.1.2 clarified the interpretations of Eq. (4.6) vs. Eq. (4.7) as modelling within-partnership heterogeneity (WPH) vs. between-partnership heterogeneity (BPH), respectively. As shown in § C.1 (proof), $B_{\text{WPH}} \geq B_{\text{BPH}}$. Here I explore under what conditions the ratio $B_{\text{WPH}} / B_{\text{BPH}}$ is maximized — i.e., when does the choice of approach matter most. For simplicity, I considered a single illustrative factor f affecting $\alpha_f \in [0, 1]$ proportion of sex acts ($1 - \alpha_f$ are unaffected), with relative probability of transmission $R_f \in [0.01, 10]$. I then computed B_{WPH} and B_{BPH} for $A \in [1, 1000]$ total sex acts, using a base per-act probability of transmission $\beta = 0.34\%$ as a representative value for HIV [18].

Figure 4.5 illustrates four 2-dimensional cross sections of $B(R, \alpha, A)$ under WPH vs. BPH, and the ratio $B_{\text{WPH}}/B_{\text{BPH}}$; the cross sections were at: $A = 32$, $\alpha = 0.5$, $R = 0.1$, and $R = 5$. Based on these results, the difference between approaches can be summarized as:

- negligible for $A < 10$, and small for $A < 100$
- increasing as R gets farther from 1 ($R \rightarrow 0$ or $R \rightarrow \infty$)
- maximized by specific values of (α, A) for a given R , including $\alpha > \frac{1}{2}$ for $R < 1$, and $\alpha < \frac{1}{2}$ for $R > 1$

The specific values of (α, A) which maximize the difference between approaches for a given R and β create a continuous curve (Figure 4.6), which slowly tends towards $\alpha \rightarrow 1, A \rightarrow \infty$ as $R \rightarrow 0$, and $\alpha \rightarrow 0, A \rightarrow 0$ as $R \rightarrow \infty$. The curve is sigmoidal for log-transformed A , and shifts left with increasing β . I did not derive an analytical expression, but it should be possible to do so. In the context of HIV, the difference between approaches would be larger for protective factors (e.g., condoms) affecting most of a large number of sex acts ($\alpha > 1000$); and likewise larger for risk-increasing factors (e.g., anal sex) affecting a minority of a moderate number of sex acts ($\alpha \approx 100$).

4.3.2 Partnership Durations

As described in § 4.1.3, multiple prior models have implicitly assumed a maximum partnership duration $\delta \leq 1$ year. As such, the adjustment for PTC Eq. (4.4) would have less effect. This reduced effect can be quantified via the effective probability of transmission per sex act β' — i.e., tangent slopes in Figure 4.1a

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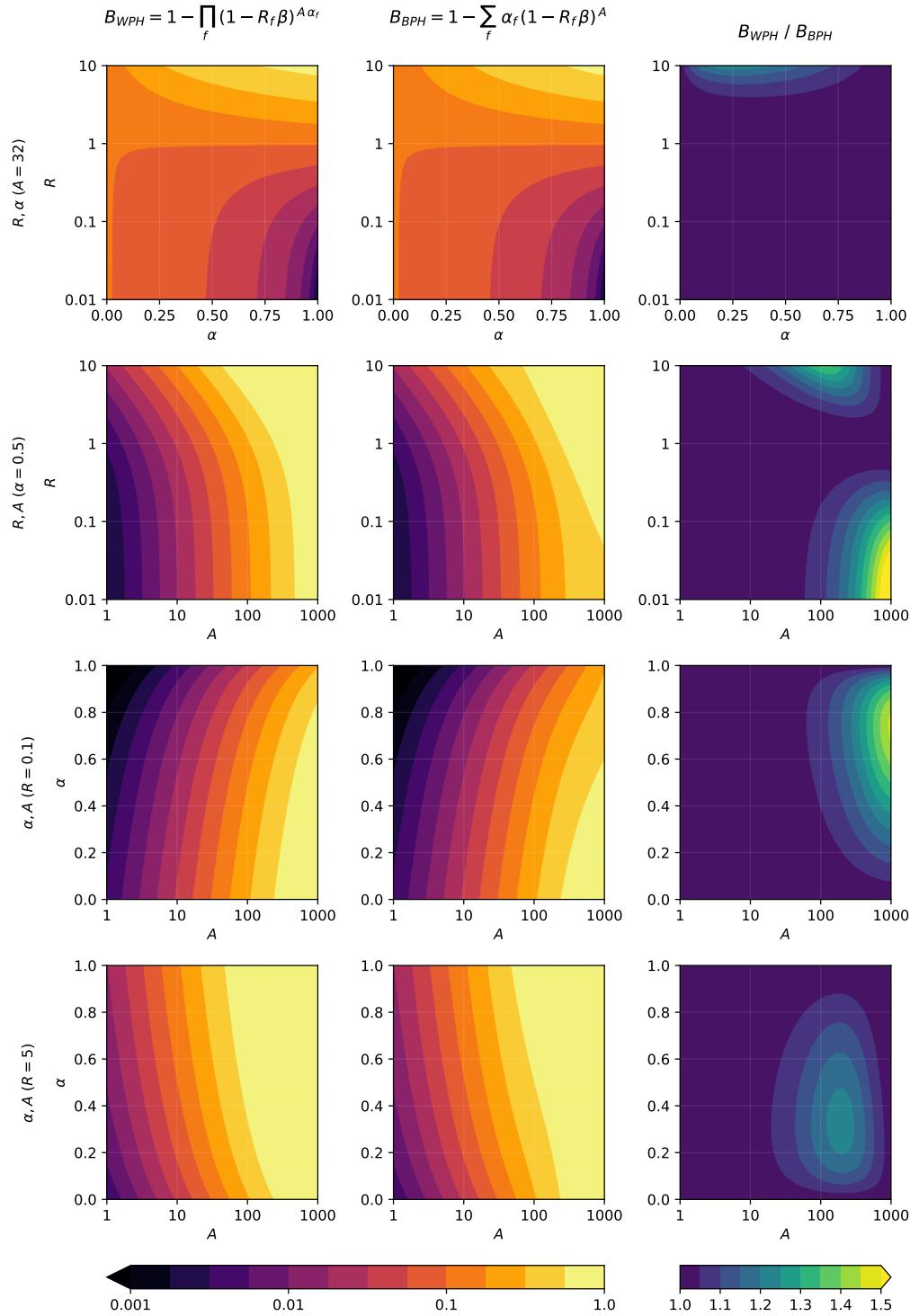


Figure 4.5: Average per-partnership probability of transmission B given heterogeneity in the per-act probability of transmission β within vs. between partnerships

B : probability of transmission per partnership (log scale colourmap); $\beta = 0.34\%$: probability of transmission per sex act (fixed) [18]; A : total sex acts per partnership (log scale); α_f : proportion of sex acts affected by factor f (linear scale); R_f : relative β given factor f (log scale); WPH: within-partnership heterogeneity; BPH: between-partnership heterogeneity.

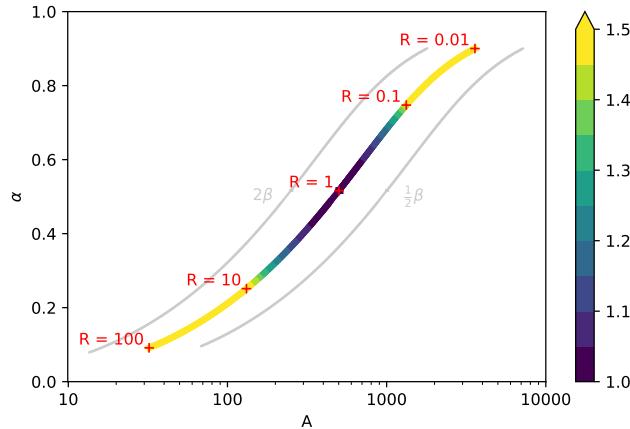


Figure 4.6: Parameter values (α, A) which maximize the difference between the average per-partnership probability of transmission given within- vs. between-partnership heterogeneity

$B_{\text{WPH}} / B_{\text{BPH}}$: line colour; $\beta = 0.34\%$: probability of transmission per sex act (fixed) [18]; A : total sex acts per partnership (log scale); α_f : proportion of sex acts affected by factor f (linear scale); R_f : relative β given factor f (log scale); gray lines denote equivalent contours for 2β and $\frac{1}{2}\beta$.

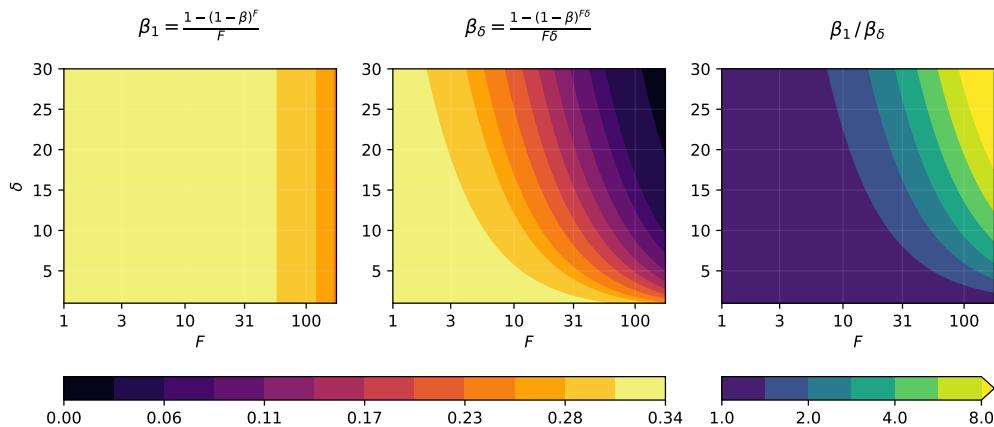


Figure 4.7: Effective probability of transmission per sex act over 1 year vs. total partnership duration

$\beta = 0.34\%$: probability of transmission per sex act (fixed) [18]; F : frequency of sex per partnership (per year, log scale); δ : partnership duration (years, linear scale); β_1, β_δ : effective probability of transmission per sex act, for 1 year vs. total partnership duration, respectively.

— defined as:

$$\beta' = \frac{B}{A} = \frac{1 - (1 - \beta)^A}{A} \quad (4.18)$$

Figure 4.7 illustrates the 1-year β'_1 vs. true-duration β'_δ , for different partnership durations $\delta \in [1, 30]$ and sex frequencies $F \in [1, 180]$ per year. Assuming $\delta \leq 1$ can considerably increase the modelled rate of transmission for partnerships with $F \geq 52$ (i.e., weekly) and a true duration $\delta \geq 5$ years, including up to 8-fold difference with $F \approx 100$ and $\delta \approx 30$. Thus, prior models using $\delta \leq 1$ may have substantially overestimated the relative contribution of longer partnerships with frequent sex — including main/spousal partnerships — to overall transmission.

4.3.3 Comparing Approaches in the Eswatini Model

Next, I sought to explore how different approaches to modelling and parameterizing the force of infection equation influence key outputs from a complete model. For this analysis, I focused on two aspects of prior approaches: whether or not partnership durations are effectively capped at 1 year (§ 4.1.4), and whether incidence is aggregated across partnerships as a rate vs. proportion (§ 4.1.3). Thus, I considered 3 prior approaches, plus the *Effective Partnerships Adjustment* approach from § 4.2 (Table 4.1). I integrated each approach within the model from Chapter 3.¹¹

Table 4.1: Compared approaches to modelling HIV transmission via sexual partnerships

ID	Name	Key Eqs.	Key Parameters
EPA	Effective Partnerships Reduction	(4.11)–(4.16)	K, F, δ
IRD	Instantaneous Rate-Duration	(4.7), (4.9)	A, Q
IRY	Instantaneous Rate-1-Year	(4.7), (4.9)	A_1, Q_1
IPY	Instantaneous Proportion-1-Year	(4.7), (4.10)	A_1, Q_1

K : number of concurrent partners; F : frequency of sex per partnership; δ : partnership duration; $A = F\delta$: total sex acts per partnership; $Q = K/\delta$: partnership formation rate; $A_1 = F\delta_1$, $Q_1 = K/\delta_1$, where $\delta_1 = \min(\delta, 1)$.

I then explored selected model outputs under each of the 4 approaches, with the aim of characterizing:

1. fundamental differences in transmission dynamics under each approach
2. differences in the model-estimated prevention priorities under each approach

For aim 1, I compared HIV incidence (overall and group-specific) using *equal* model parameters across approaches. While the specific parameters required by each approach are slightly different, I derived these parameters from a consistent set of “upstream” data as described below in § 4.3.3.1 and illustrated in Figure 4.8. For aim 2, I compared the transmission population attributable fraction (TPAF, details in § 4.3.3.3) of several transmission pathways, using *recalibrated* model parameters (i.e., approach-specific). A transmission pathway could reflect a given partnership type, or infections acquired among and/or transmitted from a given risk group, etc. Since applied models are usually calibrated to a given context, aim 2 thus provides a realistic comparison of how prevention priorities could differ when informed by distinct models using each approach.

4.3.3.1 Equal & Recalibrated Parameters

The *Effective Partnerships Adjustment* (EPA) approach uses the numbers of concurrent partnerships K , frequency of sex per partnership F , and partnership duration δ , while the prior approaches use the total numbers of sex acts per-partnership A , and partnership formation rate Q . For *equal* model parameters, I used model fits (parameter sets) from EPA (see § 3.4.1), and converted $A = F\delta$ and $Q = K/\delta$ for all 3 prior approaches (IRD, IRY, IPY), with the additional adjustment $\delta_1 = \min(\delta, 1)$ for the 1-year approaches (IRY, IPY). For *recalibrated* parameters, I repeated the methods in § 3.3, yielding 1000 unique model fits (parameter sets) for each prior approach.

¹¹ See: github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/foi.py

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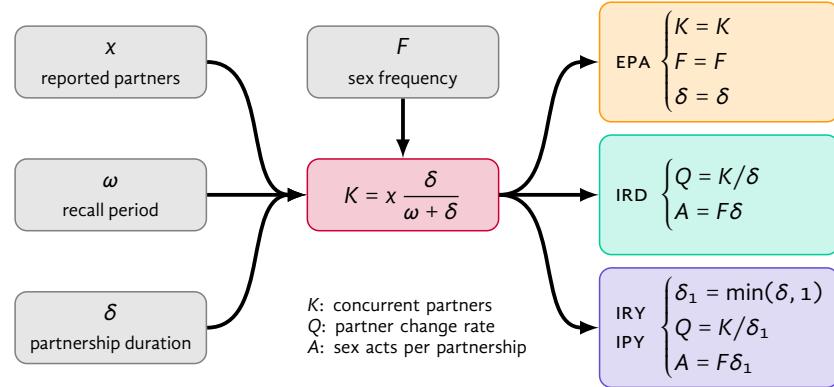


Figure 4.8: Flow chart for deriving model parameters for each force of infection approach from a consistent set of upstream data

Table 4.1 gives approach definitions.

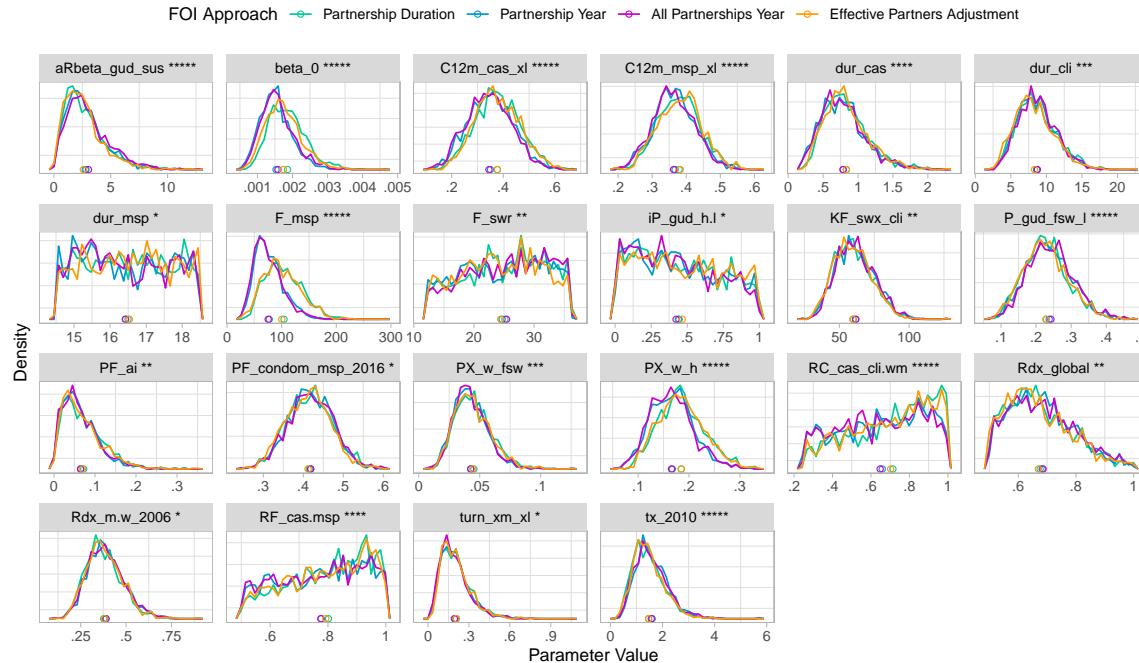


Figure 4.9: Posterior distributions of model parameters (top 1% by likelihood among 100,000 sampled parameter sets) under different force of infection approaches (colours)

Asterisks denote significance of Anderson-Darling Test [337] for comparing distributions, where $p < 0.1$: *, $p < 0.01$: **, etc.; subset of parameters with $p \leq 0.1$; Table B.1 gives parameter definitions; Table 4.1 gives approach definitions.

Figure 4.9 illustrates the posterior distributions of calibrated parameters under each approach (subset of parameters with significant differences via Anderson-Darling Test [337]). Figures C.1–C.4 illustrate model-estimated HIV prevalence, incidence, and ratios thereof vs. calibration targets under each approach.

4.3.3.2 Transmission Dynamics using Equal Parameters

Figure 4.10 illustrates HIV incidence under each approach among FSW, clients, and everybody else (“lower risk”). Specifically, Figure 4.10a illustrates incidence per person-year (EPA repeated for comparison) and Figure 4.10b illustrates relative differences vs. the EPA approach.¹² I made the following observations, drawing on the complete network of modelled transmission under EPA (Figure 3.15):

- Incidence among lower risk was generally much higher under 1-year approaches (IRY , IPY) — underestimation of PTC under these approaches disproportionately increases transmission via main/spousal partnerships, allowing more transmission to/from lower risk individuals, including a positive feedback loop via increasing HIV prevalence given like-with-like mixing (see § 3.2.14.3).
- Incidence differences between the 1-year approaches (IRY , IPY) vs. EPA grew over time — EPA explicitly models the accumulation of seroconcordant partnerships wherein sex acts are PTC, or “partnership-level herd effects” [386]; thus, by underestimating PTC throughout the epidemic, the 1-year approaches are initially less biased vs. EPA , but later overestimate incidence.
- Incidence among all risk groups was lower under the full-duration approach (IRD) — complete and instantaneous accounting of PTC under this approach effectively delays transmission in all partnership types, and contributes to a lower HIV prevalence feedback loop.
- Incidence among FSW and clients was lower under the “incidence proportion” approach (IPY) — incidence proportion Eq. (4.10) treats all transmission risks as competing, and notably forces incidence $\lambda^{IP} \leq 1$, disproportionately reducing incidence among those at highest risk.
- Incidence among FSW and clients under IRY approximately matched EPA — competing biases due to underestimation of some PTC (delays transmission), but not all PTC (overestimates transmission) coincidentally yielded incidence roughly matching EPA .

Overall, IRD resulted in the most *consistent* bias vs. EPA across groups and over time.

Figure 4.11 further illustrates the proportions of modelled yearly HIV infections transmitted via different partnership types under each approach using equal parameters (top) and recalibrated parameters for comparison (bottom). As hypothesized above, for equal parameters, the 1-year approaches (IRY , IPY) featured the greatest proportions of transmission via main/spousal partnerships, and the least via sex work. By contrast, the full-duration approach (IRD) featured the smallest proportions transmitted via main/spousal partnerships, and the most via sex work. The distribution under the proposed approach (EPA) was in between these two extremes. Interestingly, there were minimal differences in Figure 4.11 between 1-year incidence rate (IRY) vs. incidence proportion (IPY) approaches.

4.3.3.3 Prevention Priorities using Recalibrated Parameters

Many models applied to assess HIV prevention priorities explicitly model specific intervention scenarios, often with a cost dimension [48, 161, 162]. However, these context-specific intervention and cost details require additional analyses and/or assumptions, and only explore a subset of the modelled transmission pathways. By contrast, the TPAF reflects an “intervention agnostic” measure of how any given transmission pathway contributes to transmission overall.

¹² Relative differences were “paired” according to each parameter set k , and computed as $(ixx_k - EPA_k)/EPA_k$.

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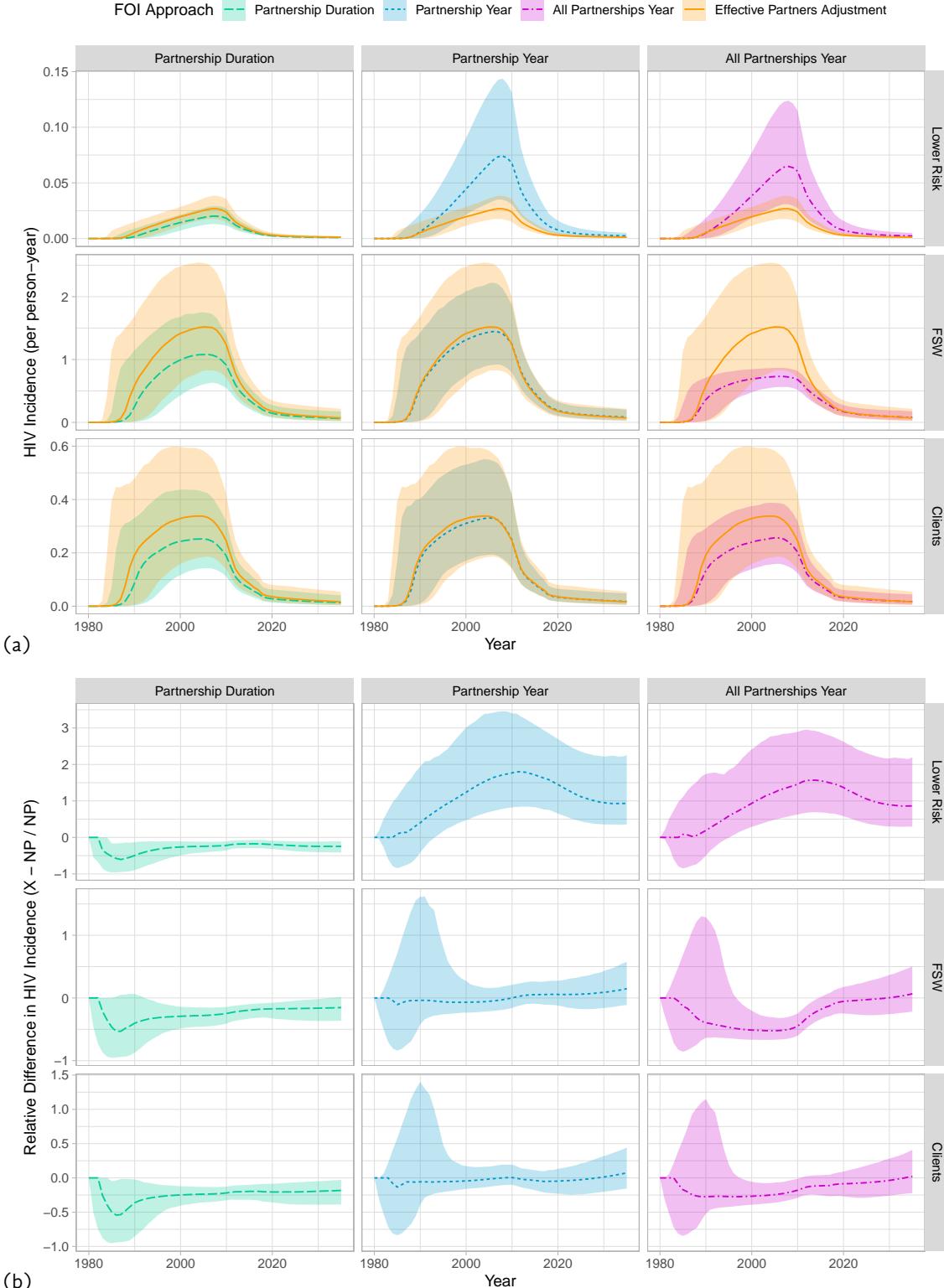


Figure 4.10: HIV incidence among selected risk groups, estimated under different prior force of infection approaches (colours) vs. the *Effective Partnerships Adjustment* approach using equal model parameters

Table 4.1 gives approach definitions; (a) absolute incidence; (b) relative differences: $(ixx_k - EPA_k)/EPA_k$; Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW; ribbon and curve: range and median of model fits.

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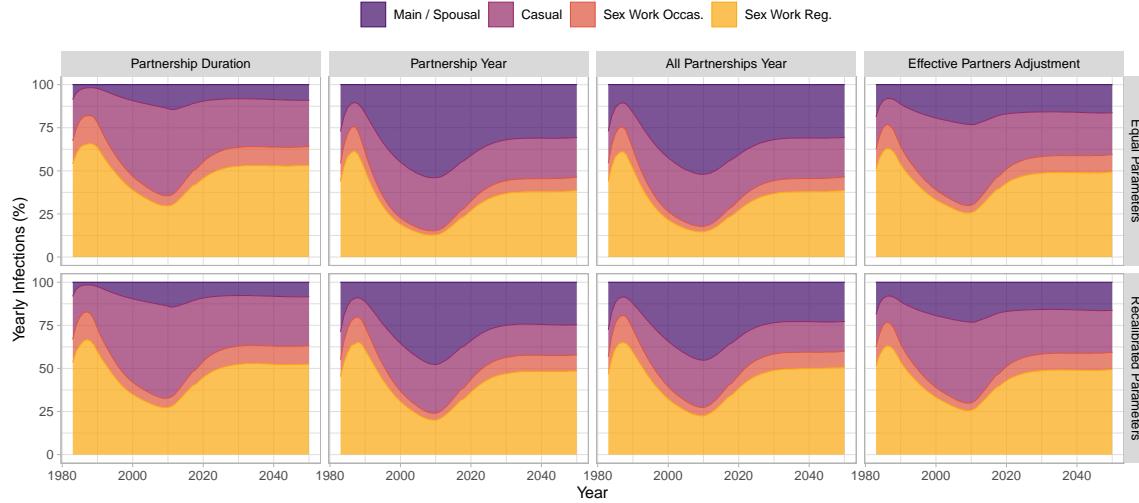


Figure 4.11: Proportions of modelled yearly HIV infections transmitted via different partnership types in Eswatini estimated under different force of infection approaches (horizontal facets) with equal vs. recalibrated parameters (vertical facets)

Table 4.1 gives approach definitions; median numbers of infections across all model fits shown.

Transmission Population Attributable Fractions (TPAFs). Classic PAFs aim to quantify the relative contribution of a specific factor to a given outcome at the population level, by comparing the number of outcomes with vs. without the factor [387, 388]. However, classic PAFs are not well-suited for infectious diseases, especially over longer time horizons, because they fail to capture the nonlinear dynamics of indirect transmission [389]. In some cases, preventing one transmission event could avert numerous downstream infections; in other cases, preventing one transmission event might only delay infection a short time for an individual at high risk. The TPAF for infectious diseases was developed as a better measure of the contribution of different transmission pathways to overall transmission [6, 390, 391].

The TPAF among population j of transmission pathway k is defined as the relative difference in cumulative infections Ω among j since a given time t_0 with vs. without transmission via k :

$$\text{TPAF}_{jk}(t) = \frac{\Omega_j(t) - \Omega_{jk}(t)}{\Omega_j(t)}, \quad \Omega_{jk}(t) = \int_{t_0}^t \Lambda_{j,M_k=0}(\tau) d\tau, \quad t = t_0 + \Delta_t \quad (4.19)$$

Thus, TPAFs reflect hypothetical interventions with perfect prevention, ignoring practical implementation challenges associated with any real intervention. Like classic PAFs, TPAFs can sum to more than 100% [172, 392].

I computed TPAFs for the following transmission pathways: main/spousal, casual, and sex work (occasional and regular combined) partnership types; and transmission from FSW, clients, and everybody else (“lower risk”). I computed these TPAFs under each of the 5 force of infection approaches, over $\Delta_t = 1, 3$, and 10-year time horizons, starting in $t_0 = 1990, 2000$, and 2010 (270 total TPAFs). I implemented scenarios without transmission via pathway k using a boolean “mask” applied to the mixing matrix $M_{pii'}$, after resolving the values per § 3.2.14, such that mixing patterns were not affected.

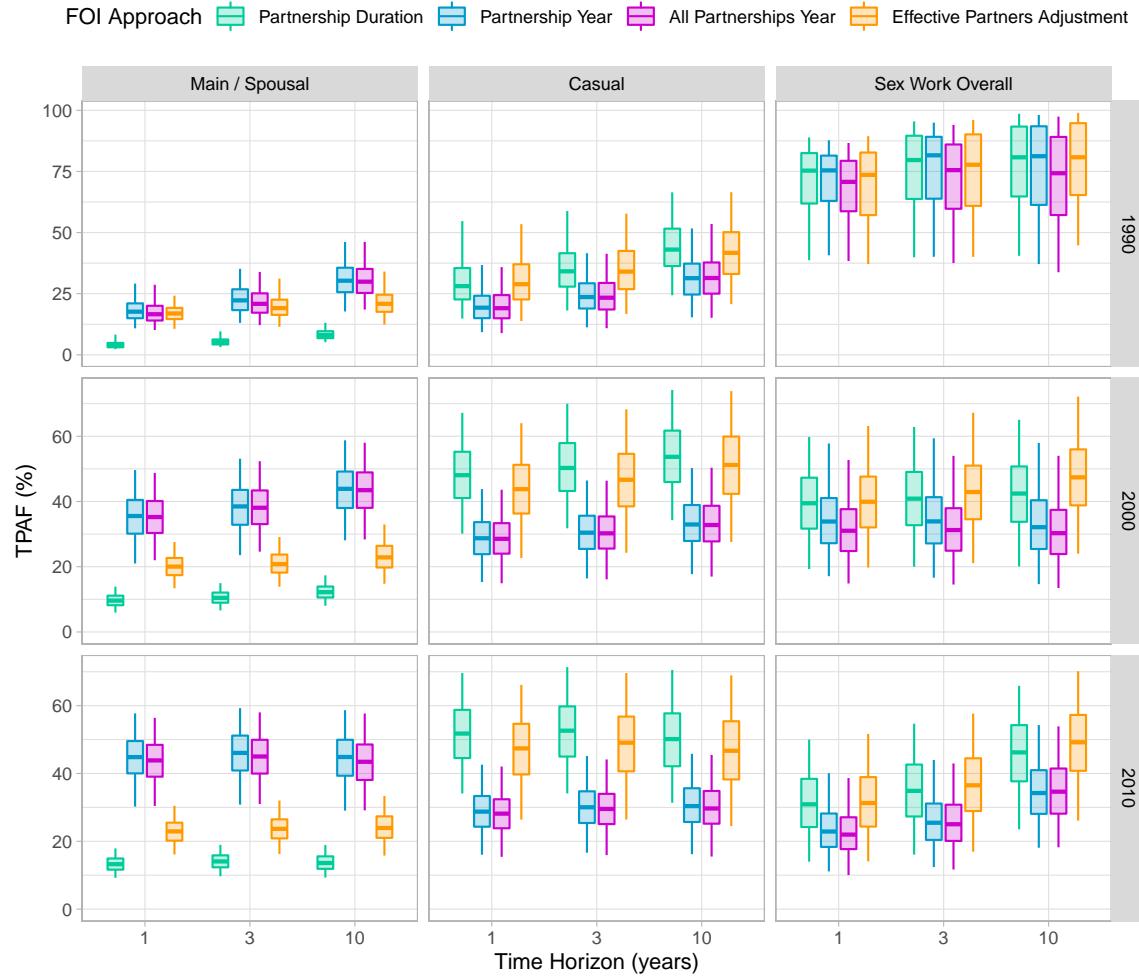


Figure 4.12: TPAF of transmission via different partnership types (horizontal facets), starting from different t_0 (vertical facets), estimated under different force of infection approaches (colours)

Table 4.1 gives approach definitions; TPAF: transmission population attributable fraction, § 4.3.3.3; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

TPAFs of Partnership Types. Figure 4.12 illustrates the TPAFs for partnership types. TPAFs generally increased over longer time horizons Δ_t , increased with calendar year t_0 for non-sex work partnerships, and decreased with t_0 for sex work (n.b. vertical scales). Such trends are consistent with prior work showing that TPAFs of key populations are typically large at first and decrease as epidemics become more widespread [25, 393, 394].

TPAF differences across force of infection approaches were largest for main/spousal partnerships, with 1-year approaches (**IRY**, **IPY**) significantly larger than the full-duration approach (**IRD**). Main/spousal TPAFs under **EPA** were similar to **IRY** and **IPY** from 1990 over short time horizons, beyond which TPAFs under **EPA** were more similar to **IRD**; similar to incidence differences in § 4.3.3.2, these findings reflect reduced transmission via longer partnerships over time due to the accumulation of seroconcordant partnerships, which are only captured under **EPA**. Relative differences in casual partnership TPAFs across approaches were exactly opposite (but less pronounced) vs. differences in main/spousal partnership TPAFs. As such, casual TPAFs were always greater than main/spousal TPAFs under **IRD**, while main/spousal TPAFs were



Figure 4.13: TPAF of transmission from different risk groups (horizontal facets), starting from different t_0 (vertical facets), estimated under different force of infection approaches (colours)

Table 4.1 gives approach definitions; TPAF: transmission population attributable fraction, § 4.3.3.3; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

almost always greater than casual TPAFs under [IRY](#) and [IPY](#). There were minimal differences in TPAFs for main/spousal or casual partnerships *between* 1-year approaches ([IRY](#) vs. [IPY](#)).

Interestingly, differences in sex work TPAFs across force of infection approaches were less pronounced vs. for other partnership types. These smaller differences could be explained by two factors. First, HIV prevalence in Eswatini may saturate among FSW and their clients, such that the rate of new infections is mainly influenced by “supply” of susceptible individuals via risk group turnover, and less by differences between force of infection approaches. Second, modelled regular sex work partnership durations were not especially long or short, with posterior distribution spanning 0.5–2.0 years (see § 3.2.13 and Figure 3.8). By 2010, clearer differences across approaches in sex work TPAFs emerged, which were similar to differences for casual partnerships.

TPAFs of Risk Groups. Figure 4.13 illustrates the TPAFs for transmission from selected risk groups, which can be related to the goal of perfect viral suppression via ART. In 1990, the TPAFs of FSW and clients were

largest and overall similar to TPAFs of sex work partnerships. In 2000 and 2010, the TPAFs of FSW and clients remained similar to sex work partnerships, but TPAFs for clients vs. FSW grew larger and with more pronounced differences between force of infection approaches. Such results reflect the greater onward transmission potential of clients vs. FSW due to their larger population size and greater number of casual partnerships (e.g., Figure 3.15). TPAFs of lower risk groups (not engaged in sex work) had differences across approaches that were similar to those for main/spousal partnerships but less pronounced. These differences reflect the strong influence of the 1-year partners duration assumption (i.e., approaches [IRY](#), [IPY](#)) on the contribution of lower risk groups to overall transmission.

4.4 Discussion

In this chapter, I have critically reviewed key assumptions and differences among various existing approaches to modelling HIV transmission via sexual partnerships in compartmental models. I formalized distinctions between: within- vs. between-partnership heterogeneity when calculating the average probability of transmission per partnership; per partnership-year vs. per partnership-duration when adjusting for “post-transmission contacts” (PTC); and incidence rate vs. incidence proportion when aggregating risk across multiple partnerships. I also proposed a new approach: the *Effective Partnerships Adjustment*, which can overcome some of the key limitations of prior approaches. Finally, through comparison with the new approach in the Eswatini model, I found that two popular prior approaches may overestimate the relative contribution of longer vs. shorter partnerships to overall transmission, even after recalibrating the model under each approach.

4.4.1 Insights for Transmission Modelling

The critical review and experiment results in this chapter offer new insights for modelling transmission of HIV, and possibly other infectious diseases. This section discusses these insights and draws connections to several prior model comparison studies.

4.4.1.1 Average Probabilities of Transmission per Partnership

Models with instantaneous partnerships must compute average probabilities of transmission per partnership. The choice of averaging equation implies either “within-partnership heterogeneity” or “between-partnership heterogeneity” in the probability of transmission per act. While I have shown that these two cases are mathematically related by an inequality, I only found notable differences (e.g., > 10%) in the context of large cumulative risk — e.g., a high volume of sex and/or risk-increasing transmission modifiers. Indeed, approximations in HIV force of infection equations are often justified by noting that the probabilities of transmission are typically small [[162](#)]. Thus, the distinction between within- vs. between-partnership heterogeneity may be of little practical consequence. Moreover, “correct” interpretations of data on transmission modifiers are not always obvious. For example, levels of condom use are often derived from questions like “*Did you use a condom the last time you had sex?*” — but this does not distinguish between 50% condom use in 100% partnerships vs. 100% condom use in 50% partnerships.

On the other hand, two major challenges remain for calculating average probabilities of transmission per partnership. First, relative risks associated with transmission modifiers are typically quantified at the per act (vs. per partnership) level, using exposure-stratified individual-level data [18, 222, 235, 395]. Yet, these relative risks have been directly applied to average probabilities of transmission per partnership in several models. This approach would then underestimate the impact of risk-reducing modifiers (e.g., condoms) and overestimate the impact of risk-increasing modifiers (e.g., GUD).¹³ Second, it's not clear how *dynamic* transmission modifiers (e.g., condom use, infection stage) should be modelled when aggregating sex acts across many years within longer partnerships.

4.4.1.2 Accumulation of Seroconcordance

The concept of “post-transmission contacts” (PTC) is directly related to seroconcordance, because transmission naturally generates seroconcordant (*I-I*) partnerships, wherein “post-transmission contacts” occur. Seroconcordant partnerships thus accumulate during an epidemic, which decouples incidence from prevalence, as shown in § 4.2.1 and 4.3.3.2. An earlier version of this work [386] therefore described the accumulation of seroconcordant partnerships as “*partnership level herd effects*”, while Eames and Keeling [396] describe this accumulation in a network model as “*correlation of infection statuses of neighboring individuals*”. There are two main implications of this seroconcordance perspective. First, an alternate adjustment for “post-transmission contacts” in compartmental models could make use of data on seroconcordant and/or serodiscordant partnerships. Such an adjustment should consider potential biases in these data, and be applied mainly over shorter time horizons due to the dynamic nature of the seroconcordant proportion. Second, efforts to quantify serosorting — preferential selection of sexual partners with matching (perceived) HIV serostatus [397] — may need to focus on new partnerships or longitudinal data [398], since it may not be possible to distinguish intentional seroconcordance from transmission-driven seroconcordance in cross-sectional data [399, 400].

4.4.1.3 Influence of Instantaneous Partnerships on Epidemic Growth

Prior model comparisons of instantaneous partnerships with pair-based models [396, 401, 402] and with a stochastic dynamic network model [8] have shown that instantaneous partnerships can overestimate the initial epidemic growth rate and equilibrium prevalence. Such findings seem intuitive. However, in § 4.3.3 (Figure 4.10), I showed how the epidemic growth rate under instantaneous partnerships depends on the effective partnership duration used for the PTC adjustment — if such an adjustment is applied at all. That is, when durations were capped at 1 year (approaches IRY, IPY), this adjustment likely had little effect, and modelled incidence was indeed overestimated relative to the EPA approach; by contrast, when full partnership durations were used (approach IRD), this adjustment reduced transmission immediately in anticipation of future PTC, and modelled incidence was *underestimated* relative to the EPA approach. No PTC adjustments were described in [396, 402], and the PTC adjustments in [8] did not consider full partnership durations,¹⁴ similar to the former 1-year case.

¹³ Modifying the transmission probability via R — per-act: $B_a = (1 - (1 - R\beta)^A)$ vs. per-partnership: $B_p = R(1 - (1 - \beta)^A)$; thus: $B_a > B_p$ if $R < 1$, and $B_a < B_p$ if $R > 1$.

¹⁴ The PTC adjustments in [8] considered 1 month for main/spousal, 6 months for casual, and nothing for sex work partnerships; thus, repeated sex work contacts were not considered.

4.4.1.4 Partnership Types vs. Risk Groups

The results in § 4.3.3.3 suggest that models ignoring or underestimating PTC have the potential to systematically overestimate the relative contribution of longer vs. shorter partnerships to overall transmission. Such results then extend to various risk groups, depending on the average numbers and types of partnerships among each group. These results are corroborated by Johnson and Geffen [8], who concluded:¹⁵ “*Frequency-dependent models are likely to underestimate the importance of interventions that are targeted at high-risk groups, while overestimating the impact of interventions targeted at low-risk groups.*” While higher risk groups typically have more shorter partnerships, higher risk is not necessarily synonymous with shorter partnerships. Indeed, the Eswatini model includes both shorter (casual) partnerships among the lowest risk groups and longer (regular sex work) partnerships among the highest risk groups. This distinction between risk groups and partnership types is therefore important to keep in mind when interpreting these results and their potential implications.

4.4.2 Implications for Existing Model-Based Evidence

The majority of existing compartmental HIV transmission models have used an instantaneous partnerships approach, with adjustments for PTC considering 1 year or less. As noted above, it is possible that these models have systematically overestimated the relative contribution of longer vs. shorter partnerships to overall transmission, and thus, the relative impact of some prevention strategies vs. others. I have illustrated these potential biases in the context of the high-prevalence epidemic in Eswatini, but these biases and implications could be different and possibly greater elsewhere. Below I further discuss two specific models, chosen due to their widespread use in numerous countries, usually for the explicit purpose of guiding resource allocation.

Optima HIV Model. [47, 162, 403, 404] The Optima model allows for flexible definitions of demographic/risk groups, which usually include key populations. Within the model, the force of infection is defined as an incidence proportion, wherein all sex acts over a given time period (default $\Delta_t = 0.2$ years)¹⁶ are modelled as competing risks. Thus, partnership durations are not considered. While Optima results have often recommended increased resources for key populations over country-specific current spending, these recommendations may still undervalue prevention in shorter partnerships and among highest risk groups due to overestimation of transmission in longer partnerships.

Goals Risk-Structured Model. [405, 406] The Goals Model includes 11 total risk groups, including FSW, their clients, MSM, and PWID, without age stratification [405].¹⁷ As in the Optima model, the force of infection is defined as an incidence proportion, this time with $\Delta_t = 1$ year, and a default partnership change rate of at least 1 per year among all risk groups. Thus, for the same reasons as Optima, the relative impact of prioritizing shorter partnerships and key populations for prevention have likely been underestimated by the Goals Model.

¹⁵ The term “frequency-dependent” in [8] is synonymous with “instantaneous partnerships” here.

¹⁶ From: github.com/optimamodel/optima/blob/master/optima/parameters.py

¹⁷ An age stratified variant of Goals was recently developed for “generalized” epidemics, which subsumes key populations as proportions of age strata; the new model is called the Goals “Age-Stratified Model” (ASM), whereas the original model is now called the Goals “Risk-Stratified Model” (RSM) [406]. To confuse matters further, a Goals “Age-Risk-Stratified Model” is also being developed.

4.4.3 Outlook & Future Work

The 2021 review by Rao et al. [375] summarizes frameworks that have been used to simulate partnership dynamics for modelling sexually transmitted infections (see also § 4.1.6 and Appendix 1 of [8]). Besides pair-based models, the review does not identify another approach which has extended the compartmental modelling framework beyond instantaneous partnerships. However, several hybrid models have been developed [407, 408] wherein long-term pairs are explicitly modelled, but additional “one-off” partnerships are modelled as instantaneous. When long-term partnership concurrency is low, such hybrid approaches may offer substantial improvements over fully instantaneous partnerships [396, 401, 402]. However, the high number of *regular* clients reported by Swati FSW (§ 3.2.7) reflects precisely the kind of dense, persistent sexual network — i.e., high concurrency — which is difficult to model using a pair-based approach.¹⁸ Thus, the *Effective Partnerships Adjustment* represents an alternative to hybrid / pair-based models for such contexts, and a new solution to a longstanding modelling challenge [376].

Future Work. In considering potential integration of the *Effective Partnerships Adjustment* approach into new and existing models, four key areas for future work should be considered. First, it would be helpful to explore in more detail which of the Eswatini model parameters “adjusted” during model recalibration under each approach, in order to fit the same calibration targets. Second, while I developed the approach in the context of the Eswatini model, examining this approach in a simpler model — e.g., with 2 risk groups and 2 partnerships types — may allow a more precise understanding of potential biases and mechanisms involved. A simpler model may also be more practical as an example implementation of the approach — e.g., as a reference for other modellers.¹⁹ Third, the approach should be compared and validated against “gold standard” individual-based models, similar to experiments in [8]. Finally, while I developed the proposed approach in the context of HIV, accurate simulation of partnership dynamics is also relevant for models of other sexually transmitted infections. However, the approach should be carefully adapted for infections with recovery and/or re-infection, as I have not considered how transitions out of the newly proposed infected strata should be conceptualized and parameterized.

¹⁸The importance of partnership concurrency in HIV transmission has been debated extensively [380, 409–412].

¹⁹The main implementation of this approach in the Eswatini model is in:

github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/foi.py, where `foi_mode='base'`.

Chapter 5

Modelling Intersections of Differential Risk and ART Coverage

5.1 Introduction

Early HIV treatment via antiretroviral therapy (ART) offers numerous individual-level health benefits [1, 85, 89, 90], and can prevent transmission in serodiscordant partnerships [93–95]. As such, immediate initiation of ART has been recommended by WHO since 2016 [20]. Alongside expanding ART eligibility, interest has grown in the potential population-level prevention impacts of ART, motivating numerous modelling studies [3, 96, 174, 413] and several large community-based trials [97–99, 414] of ART scale-up as “treatment as prevention”, especially across Sub-Saharan Africa. In general, the prevention impacts estimated via these trials have not met expectations from modelling, prompting questions about the potential influence of modelling assumptions on predictions [64].

Within these modelling studies, ART prevention impacts are usually quantified as incidence rate reduction or cumulative infections averted in scenarios with higher cascade attainment vs. scenarios with lower attainment [174]. Modelled populations are often stratified by risk, including key populations like FSW and their clients, to capture important epidemic dynamics related to risk heterogeneity [149, 167, 168]. However, these studies almost always assume that cascade attainment (i.e., proportions of PLHIV who are diagnosed, treated, and virally suppressed) or progression (i.e., rates of diagnosis, treatment initiation, and treatment failure/discontinuation) are equal across modelled risk groups. For example, among the modelling studies reviewed in Chapter 2, key populations were usually assumed to have “average” cascade progression, or “above average” progression in some scenarios, but never “below average”, as compared to the population overall.

Yet, there is growing evidence of differential ART cascade across population strata, including age, gender, mobility, and risk [105, 106]. These differences can be driven by unique barriers to engagement in care faced by vulnerable populations, which intersect with drivers of HIV risk [415–417]. Moreover, the lowest cascades likely remain unmeasured [105, 418]. These intersections of risk and cascade heterogeneity could potentially undercut the prevention impacts of ART scale-up anticipated from model-based evidence [64]. Therefore, I sought to examine the following questions in an illustrative modelling analysis:

1. How are projections of ART prevention impacts influenced by differences in ART cascade across risk groups?
2. Under which epidemic conditions do such differences have the largest influence?

I examined these questions using the Eswatini model from Chapter 3, focusing on differential risk related to sex work. Eswatini has recently achieved outstanding cascade gains, surpassing 95-95-95 (see § 3.2.6) [12, 139]. As such, I used observed ART scale-up in Eswatini as a *base case* reflecting evidently attainable scale-up, and explored *counterfactual* scenarios in which scale-up was slower, and where specific risk groups could have been “left behind”.

5.2 Methods

This section briefly reviews the transmission model used, and outlines the analyses conducted to answer the research questions outlined above.

5.2.1 Model

The complete details of model structure, parameterization, and calibration are given in Chapter 3. The proposed force of infection approach from Chapter 4 was used throughout. Briefly, the deterministic compartmental model features 8 risk groups, including higher and lower risk FSW and clients, and 4 partnership types, including regular and occasional sex work (Figure 3.1a). Risk heterogeneity is captured through group-level factors, including group sizes, turnover, GUD prevalence, and different numbers/types of partnerships; as well as partnership-level factors, including mixing patterns, partnership durations, frequency of vaginal and anal sex, and levels of condom use. Modelled HIV natural history includes acute infection and stages defined by CD4 count, which determine differences in infectiousness, HIV-attributable mortality, and historical ART eligibility. I obtained $N_f = 1000$ plausible model fits via calibration.

5.2.2 Scenarios & Analyses

5.2.2.1 Objective 1: Influence of cascade differences between risk groups

For Objective 1, I defined the *base case* scenario to reflect observed cascade scale-up in Eswatini, reaching 95-95-95 by 2020 [12]. Next, I defined 4 *counterfactual* scenarios in which overall viral suppression was lower, such that the population overall reached 80-80-90 by 2020, reflecting approximate trends in SSA cascades prior to universal ART [12]. In these counterfactual scenarios, I reduced cascade progression among specific risk groups in different combinations: FSW, clients, and/or the remaining population (“lower risk”). I reduced cascade progression by calibrating and applying a constant relative scaling factor “R” to group-specific rates of: diagnosis ($R_d \in [0, 1]$), treatment initiation ($R_t \in [0, 1]$), and treatment failure / discontinuation ($R_u \in [1, 20]$). When FSW and/or clients had reduced cascade, I calibrated their Rs so that these populations achieved approximately 60-40-80 by 2020. By contrast, I calibrated Rs for the lower risk population so that the Swati population *overall* achieved 80-80-90 in all 4 counterfactual scenarios, thus ensuring that a consistent proportion of the population overall experienced reduced viral suppression. Table 5.1 summarizes these scenarios, while Figure D.1 plots the modelled cascades over

Table 5.1: Modelling scenarios for Objective 1 defined by 2020 calibration targets

Scenario	ART cascade in 2020 ^a			Re-scaled cascade rates ^b		
	FSW	Clients	Overall	FSW	Clients	Lower Risk
Base Case	95-95-95	—	95-95-95	—	—	—
Leave Behind: FSW	60-40-80	—	80-80-90	✓	✗	✓
Leave Behind: Clients	—	60-40-80	80-80-90	✗	✓	✓
Leave Behind: FSW & Clients	60-40-80	60-40-80	80-80-90	✓	✓	✓
Leave Behind: Neither	—	—	80-80-90	✗	✗	✓

^a Cascade: % diagnosed among PLHIV; % on ART among diagnosed; % virally suppressed among on ART; ^b Rates of: diagnosis; ART initiation; treatment failure; Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW. Figure D.1 plots the modelled cascades over time.

time. When cascade rates among FSW and/or clients were unchanged from the base case, the cascade these groups achieved could be lower than 95-95-95 due to risk group turnover and higher incidence. All cascades continued to increase beyond 2020 due to assumed fixed rates of diagnosis, treatment initiation, and treatment failure / discontinuation thereafter.

I quantified ART prevention impacts via relative cumulative additional infections (CAI) and additional incidence rate (AIR) in the counterfactual scenarios (k) vs. the base case (o), over multiple time horizons up to 2030, starting from $t_0 = 2000$:

$$\text{CAI, AIR}(t) = \frac{\Omega_k(t) - \Omega_o(t)}{\Omega_o(t)}, \quad \Omega(t) = \begin{cases} \int_{t_0}^t \Lambda(\tau) d\tau & \text{CAI} \\ \lambda(t) & \text{AIR} \end{cases} \quad (5.1)$$

where: Λ denotes absolute numbers of infections per year, and λ denotes incidence rate per susceptible per year. For each scenario, I computed these outcomes (CAI and AIR) for each model fit j , and reported median (95% CI) values across model fits, reflecting uncertainty.

5.2.2.2 Objective 2: Conditions that maximize the influence of cascade differences

For Objective 2, I estimated via regression: the effects of lower cascade among certain risk groups on relative CAI and AIR, plus potential effect modification by epidemic conditions. The hypothesized causal effets are illustrated as a directed acyclic graph in Figure 5.1, and the synthetic data generation processes and variable definitions are as follows.

For this regression analysis, I obtained 10,000 samples. I explored a wider range of counterfactual scenarios vs. Objective 1 by randomly sampling the relative rates for diagnosis and treatment initiation $R_d, R_t \sim \text{Beta}(\alpha = 3.5, \beta = 1.9)$ and treatment failure $R_u \sim \text{Gamma}(\alpha = 3.4, \beta = 1.9)$ for each of: FSW, clients, and the remaining lower risk population (9 total values). These sampling distributions had 95% CI: (0.25, 0.95) and (1.5, 15), respectively, and were chosen to obtain cascades in 2020 spanning approximately 60-60-90 through 90-90-95 (Figure D.4). For each of $N_f = 1000$ model fits, I generated $N_k = 10$ counterfactual scenarios per fit via random relative rates “ R ” via Latin hypercube sampling, yielding $N_f N_k = 10,000$ total counterfactual samples for the regression.

For each of these 10,000 samples, I defined relative CAI and AIR by 2030 vs. the base case, as in Objective 1. For each sample, I further defined U_{fki} for risk groups $i \in \{1: \text{FSW}, 2: \text{clients}, *: \text{overall}\}$ as the proportions

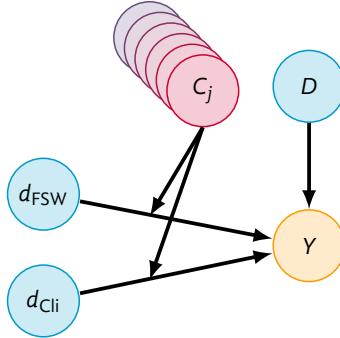


Figure 5.1: Directed acyclic graph (DAG) for inferring the epidemic conditions under which differential viral suppression across risk groups matters most

Y : cumulative additional infections (CAI) or additional incidence rate (AIR) by 2030; D : difference in population-overall viral unsuppression in counterfactual vs. base case scenario; d_i : difference in group- i -specific viral unsuppression vs. population overall within counterfactual scenario; C_j : epidemic conditions (effect modifiers of d_i).

virally unsuppressed among people living with HIV by 2020, reflecting a summary measure of ART cascade gaps. Using U_{fki} , I defined the main regression predictors as: $D_{fk} = U_{fk*} - U_{fo*} > 0$, reflecting differences in *population-overall* viral unsuppression in sample $k \in [1, 10]$ vs. the base case (denoted $k = 0$); and $d_{fki} = U_{fki} - U_{fk*} \leq 0$, reflecting differences in *group-i-specific* viral unsuppression in sample k vs. the population overall in sample k — i.e., disproportionate unsuppression.

Next, I defined the following measures of epidemic conditions (C_{fj}) related to sex work, as hypothesized modifiers of the effect of disproportionate unsuppression on relative CAI and RAI: FSW and client population sizes (% of population overall); average rate of turnover among FSW and clients (per year, reciprocal of duration selling / buying sex); and HIV incidence ratios in the year 2000 among FSW vs. other women, and among clients vs. other men. For these measures, I combined higher and lower risk FSW, and likewise higher and lower risk clients. I used HIV incidence ratios in 2000 to reflect summary measures of risk heterogeneity prior to ART, as compared to including all modelled risk factors for HIV acquisition (e.g., Table 2.1), which could lead to overfitting and improper inference due to effect mediation.

Finally, I defined a general linear model for each outcome (CAI, AIR) as:

$$\text{CAI, AIR} = \beta_0 D + \sum_i \beta_i d_i + \sum_{ij} \beta_{ij} d_i C_j \quad (5.2)$$

such that each outcome is modelled as a sum of the effects of: differential population-level unsuppression in the counterfactual vs. the base scenario (D); differential unsuppression among FSW and clients vs. the population overall within the counterfactual scenario (d_i); and effect modification of d_i by epidemic conditions (C_j). The model does not include an intercept because if $D = d_i = 0$, then we expect CAI = AIR = 0. I fitted this model for each outcome using generalized estimating equations [419] to control for repeated use of each model fit f . I standardized all model variables (D, d_i, C_j) via $\hat{x} = (x - \text{mean}(x))/\text{SD}(x)$ to avoid issues of different variable scales and collinearity in interaction terms. This standardization does not imply that regression coefficient magnitudes can be compared to indicate variable “importance”, because the standardization applied to each variable is driven by the variance before standardization — in

this case reflecting arbitrary ranges (D, d_i) or uncertainty in calibration (C_j).¹ Rather, effect sizes can be interpreted as: the expected change in outcome per standard deviation change in the variable.

5.3 Results

Results of model calibration and inferred dynamics of heterosexual HIV transmission in Eswatini are given in § 3.4 and B.4.2. This section focuses on results of scenarios and analyses outlined in § 5.2.2.

5.3.1 Objective 1: Influence of cascade differences between risk groups

Figure D.1 illustrates cascade attainment over time in each of the four counterfactual scenarios (80-80-90 overall by 2020), plus the base case (95-95-95 overall by 2020). Figure D.2 illustrates overall HIV incidence in each scenario. Figure 5.2 then illustrates cumulative additional infections (CAI) and additional incidence rate (AIR) in each counterfactual scenario vs. the base case. Leaving behind both FSW and clients resulted the most additional infections: median [IQR] 28.8 [17.5, 46.2] % more than the base case by 2030. By contrast, leaving behind neither FSW nor clients resulted in the fewest additional infections: 13.0 [6.1, 25.6] % more than the base case by 2030 — a 54.2 [30.3, 73.2] % reduction. Leaving behind either FSW or clients resulted in a similar number of additional infections: 21.8 [12.5, 36.7] % and 20.4 [11.8, 34.7] %, respectively. Relative differences were similar for additional incidence rate. Which risk groups acquired additional infections differed across scenarios (Figure D.3c), with more additional infections among clients when FSW were left behind, vs. among lower risk risk women when clients were left behind. The majority of additional infections were transmitted via casual partnerships in all scenarios (Figure D.3a).

5.3.2 Objective 2: Conditions that maximize the influence of cascade differences

The fitted regression models Eq. (5.2) indicated that population-overall viral unsuppression (D) and group-specific unsuppression among FSW and clients (d_i) were each strongly and positively associated with the 2030 CAI and AIR outcomes ($p < 10^{-5}$). These associations support the results of Objective 1. Figure 5.3 plots the estimated effects of group-specific unsuppression d_i , and effect modification by epidemic conditions C_j . The effect of unsuppression among FSW on CAI and AIR increased with: FSW and client population sizes, client turnover, and HIV incidence ratio among FSW vs. other women. The effect on AIR also decreased with: HIV incidence ratio among clients vs. other men. The effect of unsuppression among clients on CAI and AIR increased with: FSW and client population sizes and FSW turnover. The effect on AIR also modestly with: HIV incidence ratio among FSW vs. other women and client turnover.

¹ I verified that results were qualitatively the same using $\hat{x} = (x - \text{median}(x))/\text{IQR}(x)$. For further discussion on interpretation of standardized regression coefficients, see also: stats.stackexchange.com/questions/29781 and links therein.

5.4 DISCUSSION

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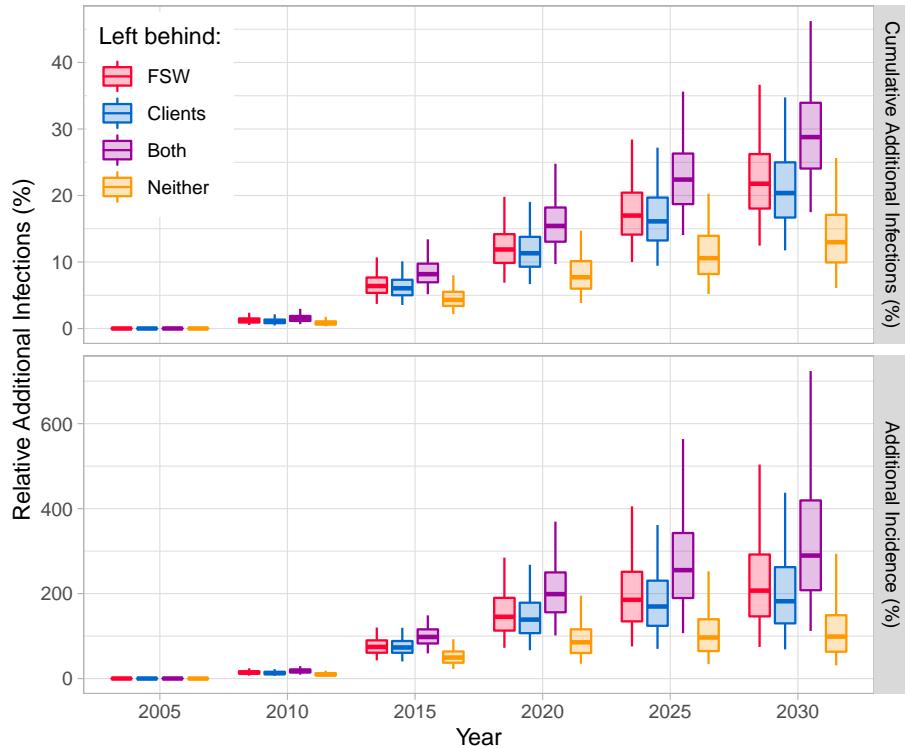


Figure 5.2: Relative additional infections under counterfactual scenarios vs. the base case

Base case: 95-95-95 by 2020; “left behind” counterfactual scenarios: 80-80-90 overall by 2020, with reduced cascade (60-40-80) among FSW, clients of FSW, both, or neither; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

5.4 Discussion

I sought to explore how intersections of risk heterogeneity and differential ART coverage may influence model-estimated prevention impacts of ART. I found that ART scale-up that “leaves behind” higher risk groups, such as female sex workers (FSW) and their clients, can result in substantially more HIV infections, even for the same population-overall coverage. I also found that the transmission impact of leaving behind higher risk groups generally increased with: the size of the risk group, the size of their predominant partner group (i.e., clients for FSW and FSW for clients), and the rate of turnover among their predominant partner group.

Although my analysis only considered Eswatini, my findings are likely generalizable to other epidemic contexts. In fact, HIV prevalence ratios between key populations and the population overall are relatively low in Eswatini vs. elsewhere [28, 353]; thus, the transmission impact of cascade gaps among key populations in other contexts would likely be even greater than I found for Eswatini. Moreover, as HIV incidence declines in many settings, epidemics may become re-concentrated among key populations [171, 420], further magnifying the transmission impact of cascade disparities.

To my knowledge, this study is the first to explore the transmission impact of heterogeneity in ART coverage across risk groups, within consistent population-overall coverage. In my review of mathematical modelling of ART scale-up in Sub-Saharan Africa (Chapter 2), I found that few studies have considered any cascade differences by risk group, but that such differences likely mediate ART prevention impacts [174].

Cascade gaps have been observed among men vs. women [106, 181], younger vs. older populations [106, 421], key populations vs. the population overall [105], and within key populations themselves [422, 423]. Moreover, unmeasured cascades — such as among populations who have not been reached by programs and interventions — are likely lowest [105, 418]. Consistent integration of these data going forward could improve the quality of model-based evidence for HIV resource prioritization.

Global ART scale-up has many benefits, including for individual-level health outcomes [85, 89], prevention in serodiscordant relationships [94], and contributing to population-level incidence declines [101]. However, efforts to maximize cascade coverage should not overlook populations that may be harder to reach, where barriers to engagement in HIV care often intersect with drivers of HIV risk [64, 415–417]. Such populations can be reached effectively through tailored services to meet their unique needs [55], services which can be designed and refined with ongoing community engagement [57, 180, 424]. As I have shown, an equity-focused approach to ART scale-up can maximize prevention impacts, and accelerate the end of the HIV epidemic.

My analysis above has three major strengths. First, drawing on my conceptual framework for risk heterogeneity (Table 2.1) and multiple sources of context-specific data [108, 129, 134, 141, 213], I captured several dimensions of risk heterogeneity, including: heterosexual anal sex, four types of sexual partnerships, sub-stratification of FSW and clients into higher and lower risk, and risk group turnover. Second, whereas most modelling studies of ART scale-up project hypothetical future scenarios which may not be achievable, my base case scenario reflects observed scale-up in Eswatini. Finally, my analytic approach to objective 2, in which epidemic conditions are conceptualized as potential effect modifiers, represents a unique methodological contribution to the HIV modelling literature.

My analysis above has three main limitations. First, I only considered heterosexual HIV transmission in Eswatini, and mainly explored risk heterogeneity related to sex work. However, my findings would likely generalize to other transmission networks and determinants of risk heterogeneity, including risk groups not always recognized as key populations, such as mobile populations and young women [35, 207]. Second, I did not consider transmitted drug resistance. Drug resistance is more likely to emerge in the context of barriers to viral suppression [425]; thus, cascade gaps among those at higher risk would likely accelerate emergence of transmitted drug resistance, and amplify impacts of such gaps. Third, even among the top 1% of model fits, substantial uncertainty remained in the values of inferred parameters, yielding wide confidence intervals in the outputs of interest (additional infections and incidence). In the absence of additional data, such intervals reflect true uncertainty in the magnitude of these outputs, though more advanced calibration techniques could potentially improve precision.

In conclusion, HIV prevention efforts should be rooted in context-specific understandings of prevention gaps. In the “treatment as prevention” era, prevention gaps include cascade gaps. Thus, differential cascades within and between populations at higher risk of HIV must be described, modelled, and ultimately addressed to fully realize the anticipated prevention impacts of ART.

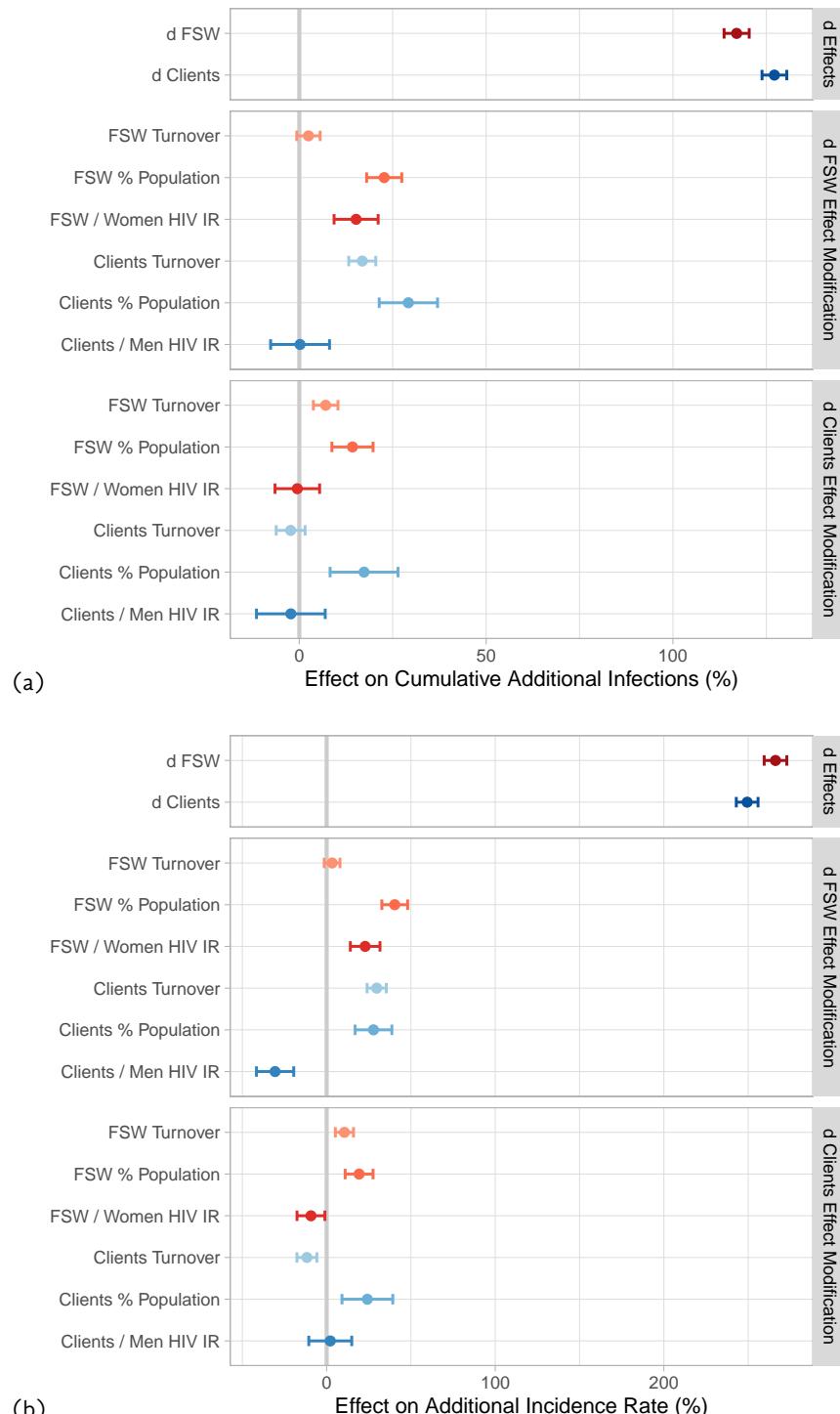


Figure 5.3: Estimated effects on relative additional infections of disproportionate viral unsuppression (d) among FSW and clients vs. population overall, plus effect modification by epidemic conditions

(a) cumulative additional infections, (b) additional incidence rate by 2030 vs. base case; FSW: female sex workers; Clients: of FSW; IR: incidence ratio in 2000; d_i : difference in group- i -specific viral unsuppression vs. population overall within counterfactual scenario; points and error bars: mean and 95% CI for each effect estimated via Eq. (5.2).

Chapter 6

Conclusion

Compartmental models of HIV transmission continue to guide epidemic response in numerous ways and at multiple scales [163, 406, 426]. Such models must make simplifying assumptions due to time and data constraints. However, prior work has shown that these simplifying assumptions can sometimes influence key model outputs [7, 8, 10, 11]. Thus, this thesis sought to explore the overarching research question:

How do modelling assumptions influence outputs of compartmental HIV transmission models?

Modelling assumptions were conceptualized to include: the design of model structure, such as which risk groups are explicitly represented; the parameterization of model inputs, such as how potential biases in data are adjusted; and the implementation of the model, such as which equations are used to define the force of infection.

I explored these assumptions in the context of heterosexual HIV transmission within Eswatini, focusing on assumptions related to sex work. The key results of each chapter can be summarized as follows:

Chapter 2: Scoping Review of Risk Heterogeneity in Compartmental Models of ART as Prevention. Among 94 compartmental HIV transmission models applied to assess ART prevention impacts: (2.1) Approximately 2/3 and 2/5 stratified the modelled population by sexual activity and key populations, respectively, while approximately 1/3 and 1/4 considered any turnover and differential ART cascade among risk groups, respectively. (2.2) Model-estimated ART prevention impacts were generally lower when risk group turnover was considered, and higher when one or more cascade steps were prioritized to key populations. (2.3) No models considered reduced cascade among key populations.

Chapter 3: Model Structure, Parameterization, & Calibration. (3.1) I developed and calibrated a model of heterosexual HIV transmission in Eswatini that can be applied to downstream research questions. (3.2) While developing the model, I proposed several incremental changes to conventional parameterization steps, including: a data-driven approach to stratifying higher vs. lower risk female sex workers (FSW), an adjustment for reporting bias in partner numbers data using polling booth data, an adjustment for bias due to partnership duration in partner numbers data, an adjustment for censoring in risk group turnover/duration data, and a balancing approach to support more flexible “log-linear” mixing patterns.

Chapter 4: Modelling HIV Transmission via Sexual Partnerships: Equations and Assumptions. (4.1) Using first principles, I critically reviewed existing approaches to modelling HIV transmission via sexual partnerships within compartmental models, including their implicit assumptions, data needs, strengths, and limitations. (4.2) I developed a new approach — the *Effective Partnerships Adjustment* — which can overcome some of the key limitations of existing approaches. (4.3) Through comparison with the new approach, I inferred that some existing approaches might be systematically overestimating the impact of prevention in longer partnerships, and underestimating the impact of prevention in shorter partnerships.

Chapter 5: Modelling Intersections of Differential Risk and ART Coverage. (5.1) I found that ART prevention impacts could be substantially reduced if higher risk groups are “left behind” during scale-up — filling the research gap identified in (2.3). (5.2) I also found that this reduction increases with the higher risk group population size, relative incidence, and turnover among their predominant partner group.

Taken together, these results suggest that existing compartmental HIV transmission models may underestimate the importance of prioritizing resources to populations at highest risk of HIV acquisition and/or transmission. Such populations include classically defined key populations like female sex workers, but also emergent reconceptualizations of “higher risk” contexts and periods, such as transactional sex among young women [33, 35], and highly mobile populations [100]. Indeed, as HIV treatment and prevention programs increasingly meet the needs of well-studied populations, efforts to characterize and address residual risks at the peripheries of program reach will be needed to fully prevent *all* new infections.

This chapter aims to place these results in context with respect to broader trends in HIV epidemiology and response, and offer specific recommendations for future work.

6.1 Results in Context

Global HIV incidence has been declining since the late 1990s, with the largest reductions coming across Sub-Saharan Africa (SSA) [12, 427]. Global HIV prevalence has simultaneously plateaued, as PLHIV continue to live longer with advances in ART and clinical care [12]. Yet, these trends are not consistent within or between contexts, and service gaps threaten to prolong the epidemic and sustain health inequities [12, 100, 203, 427–429]. These realities underscore the importance of identifying, understanding, and ultimately addressing differences in HIV risk, including through models with precise assumptions.

Growing & Shrinking Epidemics. While HIV incidence is decreasing across much of SSA, new infections are estimated to be increasing in the Middle East, North Africa, Eastern Europe, and Central Asia [12]. Several modelling studies have highlighted how prioritizing resources to populations at highest risk of HIV is most efficient at reducing infections, especially during periods of epidemic growth [154, 206, 430]. Results throughout this thesis further support this conclusion. Thus, the ability of models to accurately reflect these populations and quantify the relative impact of their unmet needs will be essential for guiding efficient response within these growing epidemics. Moreover, in contexts with decreasing overall transmission, new infections are expected to “re-concentrate” among populations at highest risk [100, 203, 427, 429] — reflecting analogous conditions to growing epidemics. Thus, within declining epidemics too, modelling assumptions must explicitly reflect pockets of residual risk, and remain responsive to emerging data on prevention gaps.

Treatment as Prevention. The additional role of ART in preventing HIV transmission offers numerous benefits at the individual, partnership, and community levels. However, the results of major trials and recent model validation studies suggest that anticipated community-level prevention benefits of ART have potentially been overestimated [64, 101, 152]. Chapters 2 and 5 offer evidence that this overestimation could arise from failure to consider intersections of HIV risk and barriers to care. Such intersections may derive from upstream structural factors [27, 30, 73, 431], but also from inherent limitations of treatment as prevention vs. other prevention tools. For example, short delays in HIV diagnosis, ART initiation, and viral suppression may be inevitable, during which time some risk of onward transmission remains, notably in the context of acute infection [77]. Thus, rates of HIV testing and movement along the ART cascade will need to remain high — especially among populations at highest risk of onward transmission — in order to maximize ART prevention benefits. These efforts should then be complemented by continued investment in prevention tools, including condom provision, risk communication, structural interventions, and multiple PrEP options [15].

HIV in Eswatini. Efforts to maximize ART prevention impacts could be guided by the highly successful *MaxART* programs in Eswatini, which featured comprehensive and community-led initiatives to reach all populations, especially youth and men, whose cascades are often lower [106, 135, 136]. Notably, these and/or other programs appear to have reached Swati FSW and MSM living with HIV too [109] — whose ART cascades might now be among the highest in the world [12]. Alongside *MaxART*, Eswatini has also expanded the number and coverage of prevention tools available [130, 131], informed by context-specific epidemiological drivers of transmission, including multiple structural factors and unmet prevention needs among key populations.¹ As a result, HIV incidence in Eswatini is estimated to have declined substantially in recent years [12, 134, 137]. I am hopeful that these efforts will continue to rapidly and equitably end the HIV epidemic in Eswatini and around the world.

6.2 Recommendations & Future Work

This thesis contributes new insights about the influence of several common modelling assumptions, as well as methods to facilitate alternate assumptions which can be more plausible and/or flexible. These contributions can therefore support development of best practices for HIV transmission modelling, while also opening new avenues of research to validate and further explore the alternate assumptions.

6.2.1 Validation & Model Comparison

Chapter 3 presents several incremental variations on existing methods for model design and parameterization, but does not explore the influence on model outputs of each variation vs. conventional methods. Similarly, Chapter 4 includes preliminary comparison of different force of infection approaches, but the proposed *Effective Partnerships Adjustment* approach should be further validated. This section offers hypotheses about the potential influence of these incremental model developments, and an outline of potential analyses to test these hypotheses.

¹ Though sex work, same-sex sex, and possessing drugs regrettably remain illegal [121].

Substratified Key Populations. The Eswatini model substratified FSW and clients into higher vs. lower risk, whereas FSW and clients are each typically modelled as a single risk group. This additional substratification is then expected to more fully capture effects of risk heterogeneity (see § 1.3.3). Future work could compare models with vs. without this substratification — plus different definitions of substrata — across different epidemic contexts and model applications, similar to analyses in [7, 9, 11]. These results could then guide the design of new models and model updates, especially for multi-context/multi-purpose models such as Goals [405], Optima [162], and the like.

Partnership Types. Similar work could explore the influence of defining partnership types by the risk groups involved vs. as overlapping types (e.g., whether main/spousal partnerships can form between FSW and clients), and which partnership types are considered (e.g., whether repeat vs. one-off sex work partnerships are distinguished). Failure to model main/spousal partnerships between FSW and clients could underestimate core group dynamics, while failure to distinguish repeat vs. one-off sex work partnerships could have varied effects, since repeat sex work partnerships are likely to have lower condom use but more post-transmission sex acts. Future work should also explore explicit representations of transactional sex — and different typologies thereof [294] — given the hypothesized importance of these partnerships for HIV transmission in SSA [33].

Force of Infection. As noted above and in § 4.4.3, there are several potential areas of future work to better understand and validate the proposed *Effective Partnerships Adjustment* approach. These areas broadly include to: integrate the approach into a simpler model in order to precisely understand modelled transmission dynamics and sensitivity to particular parameters; identify changes to parameter inference under the new vs. existing approaches; and validate the proposed approach against a “gold standard” individual-based model.

6.2.2 Data Considerations

Measuring sexual behaviour is notoriously difficult due to sampling, participation, recall, and reporting biases [341], as well as intricacies in the interpretation of responses. Yet, because sexual behaviour data are often mechanistically incorporated into HIV transmission models, accurate estimation and interpretation of these data remains a critical step in model development.

Data Sources. In many contexts, household-based surveys, such as Demographic and Health Surveys (DHS) [342] and Population-based HIV Impact Assessment (PHIA) surveys [432], are the main source of HIV epidemiological data to support transmission modelling. Such surveys are likely to underestimate the sizes of communities and prevalence of behaviours that are stigmatized and/or criminalized [44, 238, 341, 344]. While unique sampling methods have helped reach conventional key populations with tailored surveys [52, 433], additional surveys are likely needed among other priority populations, including mobile populations and young women [34, 35, 100]. Simultaneously, complementary general population surveys with alternate delivery modes — e.g., polling booth designs [44, 238] and others [43] — could help quantify potential biases associated with household-based survey data.

Dynamic Risk. Adding to previous work [10, 200], this thesis highlights the importance of modelling activity group “turnover” — i.e., dynamic individual-level risk. However, the conceptualization of turnover in the Eswatini model is limited by the lack of age stratification, particularly considering the growing data on unique HIV vulnerabilities among young women [33, 35, 202]. Therefore, future models could

explore age-related trajectories of sexual risk for key and priority populations, similar to modelling of MSM in [434, 435]. Such models could also help quantify, for example, the proportions of prevalent infections among lower activity groups that were actually acquired during periods of higher activity. Data to support these models could be obtained from cohort studies and/or cross-sectional surveys with appropriate questions [280, 436, 437]. Such data could also allow improved analysis of HIV risk factors beyond associations with prevalent infection as in § 3.2.7.

Duration Data. This thesis also highlights the importance of quantifying “durations” — for both activity groups and sexual partnerships. As noted in § 3.2.10.2 and 3.2.11.1, quantifying these durations requires careful design of survey questions and interpretation of responses, to account for: left censoring (e.g., whether a partnership started before the recall period), right censoring (e.g., whether a partnership is ongoing), and possible “gaps” within reported durations (e.g., whether a respondent ever stopped selling sex, for how long, etc.). Burington et al. [316] review considerations for estimating sexual partnership durations, while Fazito et al. [196] review similar considerations for key populations.

6.2.3 Model Design & Parameterization vs. Calibration

It has been argued that model calibration can overcome suboptimal model structure and/or parameterization, implying that many of the considerations above may be inconsequential. A related argument is that models should avoid “non-identifiability” among parameters, whereby multiple parameters have similar roles, such that changes in one parameter can be compensated by opposite changes in another parameter, and inference on parameter values becomes difficult.² That is, a simple calibrated model with a few generic parameters is desirable. In the context of HIV transmission modelling, I respectfully dispute these arguments for the following three reasons.

First, the number of available HIV calibration targets is typically small, and often similar to the number of uncertain model parameters — i.e., much smaller than the “15:1” rule for classic statistical inference [438]. Moreover, the majority of calibration targets, including HIV prevalence and cascade data, reflect cumulative measures for recent years, which could be reproduced by a wide range of simulations. Indeed, prior work has shown how diverse model structures can fit the same data similarly well, but yield varied model outputs [7, 9, 11, 152].³ Thus, the ability of a model to reproduce these limited data is often a necessary but not sufficient condition for a plausible model.

Second, uncertainty in model outputs due to non-identifiability of parameters can be desirable for transparency. Unless the goal of model calibration is to infer *individual* parameter values, it is often sufficient to identify *combinations* of parameter values which yield plausible epidemics. Selecting parameters to combine and/or fix may reduce the spread of model outputs, but this can imply a false degree of certainty. That is, simpler models may make “fewer” assumptions, but each assumption is often “bigger”. For example, a model may include no risk stratification and a single partnership type, reflecting two (big) assumptions; whereas another model may include 8 risk groups and 4 partnership types, each with unique parameters, reflecting numerous (smaller) assumptions. Additional model complexity is often added based on the particular research question using new data or expert knowledge. Thus, I would argue that *simplifying* assumptions should require stronger justification than *complicating* assumptions.

² An analogous problem in statistical models is collinearity [438].

³ Although sensitivity analyses are often used to quantify the influence of specific model parameters on model outputs [158, 159], it could be interesting to similarly quantify the influence of specific calibration targets on inferred parameter values.

Third, I and others have shown how modelling assumptions can cause hidden biases in model outputs which may/not be addressed via model calibration [7–10]. Such biases are most likely to affect the relative contributions of various transmission pathways, for which fewer calibration targets are often available. For example, there may be estimates of overall HIV prevalence, but not HIV prevalence ratios among groups. The risk of bias is amplified when a model designed for one research question is repurposed to answer other questions, without necessarily updating the model structure and parameterization. Thus, models exploring a range of intervention strategies should aim to validate the relative contributions of each affected transmission pathway before comparing strategies, or else *ensure uncertainty* in these contributions during model calibration.

6.3 Conclusion

Compartmental HIV transmission models continue to guide the policy and programmatic response to HIV at global, national, and local scales. These models provide indispensable insights through mechanistic inference of epidemiological variables and uncertainty-informed comparison of intervention scenarios. The utility of these models is therefore rooted in their ability to reflect — via modelling assumptions — the best available knowledge of current epidemic drivers and prevention gaps. Thus, routine and rigorous reexamination of modelling assumptions should remain a pillar of applied modelling, while the potential harms of flawed assumptions should be kept top-of-mind.

Appendix A

Supplement to Chapter 2

These materials are copied verbatim from the appendix of [174].

A.1 Search Strategy

We designed our search strategy with guidance from an information specialist at the University of Toronto Library.

A.1.1 Search Terms

Our search strategy and step-wise results are as follows (Table A.1), where term/ denotes a MeSH term, and .mp searches the main text fields, including title, abstract, and heading words. We searched MEDLINE and EMBASE via Ovid on 2020 March 20. Duplicate studies were removed automatically by Ovid and by Covidence; four additional duplicates with subtly different titles were later identified and removed manually.

Table A.1: Systematic review search terms and hits

Term	Hits
M1	238,076
M2	334,921
M3	302,802
M4	196,814
M5	67,459
M6	32,801
M7	455,312
M8	1,369,153
H1	290,863
H2	651,624
H3	753,274
H4	369,182

continued ...

A.1 SEARCH STRATEGY

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... continued

Term	Hits	
H5	538,214	(human immun*deficiency virus OR human immun* deficiency virus).mp
H6	216,228	exp Acquired Immunodeficiency Syndrome/
H7	235,971	(acquired immun*deficiency syndrome OR acquired immun* deficiency syndrome).mp
H8	954,470	OR/ H1-H7
G1	3,512	Angola/ OR Angola.mp
G2	9,273	Benin/ OR Benin.mp
G3	5,809	Botswana/ OR Botswana.mp
G4	9,983	Burkina Faso/ OR Burkina Faso.mp
G5	2,055	Burundi/ OR Burundi.mp
G6	16,822	Cameroon/ OR Cameroon.mp
G7	1,196	Cape Verde/ OR Cape Verde.mp
G8	15,416	Central African Republic/ OR Central African Republic.mp OR CAR.ti.
G9	3,075	Chad/ OR Chad.mp
G10	995	Comoros/ OR Comoros.mp
G11	13,737	Democratic Republic of the Congo/ OR Democratic Republic of the Congo.mp OR DRC.mp
G12	959	Djibouti/ OR Djibouti.mp
G13	1,131	Equatorial Guinea/ OR Equatorial Guinea.mp
G14	1,437	Eritrea/ OR Eritrea.mp
G15	35,959	Ethiopia/ OR Ethiopia.mp
G16	4,500	Gabon/ OR Gabon.mp
G17	6,626	Gambia/ OR Gambia.mp
G18	25,213	Ghana/ OR Ghana.mp
G19	360,920	Guinea/ OR Guinea.mp
G20	2,625	Guinea-Bissau/ OR Guinea-Bissau.mp
G21	9,730	Cote d'Ivoire/ OR Cote d'Ivoire.mp OR Ivory Coast.mp
G22	46,917	Kenya/ OR Kenya.mp
G23	1,649	Lesotho/ OR Lesotho.mp
G24	4,239	Liberia/ OR Liberia.mp
G25	11,386	Madagascar/ OR Madagascar.mp
G26	16,367	Malawi/ OR Malawi.mp
G27	9,111	Mali/ OR Mali.mp
G28	1,573	Mauritania/ OR Mauritania.mp
G29	2,373	Mauritius/ OR Mauritius.mp
G30	8,502	Mozambique/ OR Mozambique.mp
G31	3,818	Namibia/ OR Namibia.mp
G32	35,455	Niger/ OR Niger.mp
G33	82,192	Nigeria/ OR Nigeria.mp
G34	13,547	Republic of the Congo/ OR Republic of the Congo.mp OR Congo-Brazzaville.mp
G35	1,545	Reunion/
G36	7,597	Rwanda/ OR Rwanda.mp
G37	342	"Sao Tome and Principe"/ OR "Sao Tome and Principe".mp
G38	16,674	Senegal/ OR Senegal.mp
G39	1,566	Seychelles/ OR Seychelles.mp
G40	5,456	Sierra Leone/ OR Sierra Leone.mp
G41	4,667	Somalia/ OR Somalia.mp
G42	114,536	South Africa/ OR South Africa.mp
G43	1,193	South Sudan/ OR South Sudan.mp
G44	21,680	Sudan/ OR Sudan.mp
G45	2,409	Swaziland/ OR Swaziland.mp OR Eswatini/ OR Eswatini.mp
G46	32,442	Tanzania/ OR Tanzania.mp
G47	3,749	Togo/ OR Togo.mp
G48	37,399	Uganda/ OR Uganda.mp
G49	13,506	Zambia/ OR Zambia.mp
G50	15,755	Zimbabwe/ OR Zimbabwe.mp
G51	482,060	exp africa south of the sahara/ OR sub-saharan.mp OR south of the sahara.mp
G52	982,505	OR/ G1-G51
X1	2,190	M8 AND H8 AND G52
X2	2,160	X1 NOT animal/
X3	2,155	limit X2 to english language
X4	2,125	limit X3 to yr="1860 - 2019"
X5	1,384	remove duplicates from X4

A.1.2 Inclusion/Exclusion Criteria

Table A.2: Systematic review criteria for inclusion and exclusion

Include	Exclude
Publication Type	
<ul style="list-style-type: none"> • English language • published before 2020 • peer-reviewed journal article 	<ul style="list-style-type: none"> • non-English language • published in or after 2020 • non-peer-reviewed article • review article¹ • textbook, grey literature • opinions, comments, correspondence • conference abstracts and proceedings • model comparison study
Mathematical Modelling of HIV Transmission	
<ul style="list-style-type: none"> • sexual HIV transmission model • non-linear HIV transmission model² • population-level dynamics • compartmental model³ 	<ul style="list-style-type: none"> • no sexual HIV transmission modelled • HIV transmission model is linear • only within-host/cellular/protein modelling • individual-based model
Context & Objectives	
<ul style="list-style-type: none"> • any region in Sub-Saharan Africa (SSA)⁴ • assess prevention impact of ART scale-up for all⁵ 	<ul style="list-style-type: none"> • only regions outside SSA modelled • only theoretical context modelled • only individual-level benefits of ART modelled • only prevention benefits of other interventions • no base-case scenario reflecting status quo* • only ART-combination interventions* • only ART intervention targeted to some risk groups* • only ART prevention impacts reported for some risk groups* • ART prevention impacts not reported^{5*}

¹ Review articles were included if they also presented new HIV transmission modelling results fitting our criteria. ² We defined a *non-linear model* as one where the number of infections projected at time t is an iterative function of the number of infections previously projected by the model before time t . ³ We defined a *compartmental model* as one where the system variables represent the numbers of individuals in each state, rather than unique individuals. ⁴ SSA was defined based on the countries in the UN regions of East, South, Central, and West Africa, plus South Sudan (see Table A.1 for full country list). Studies were included if the model was parameterized/calibrated to reflect at least one context within SSA. Only model parameters & outcomes for SSA contexts were extracted. ⁵ Articles reporting HIV incidence reduction and/or cumulative HIV infections averted among the whole population due to increased coverage or initiation rate of ART for the whole population. * Used to define Dataset B only.

A.1.3 Included Studies

A.1.3.1 Dataset B

- [439] 2005 Salomon et al.
- [440] 2006 Abbas, Anderson, and Mellors
- [96] 2009 Granich et al.
- [441] 2009 Hallett et al.
- [442] 2010 Bacaer, Pretorius, and Auvert
- [443] 2010 Pretorius et al.
- [444] 2011 Metzger, Lloyd-Smith, and Weinberger
- [445] 2012 Yusuf and Benyah
- [446] 2012 Andrews et al.
- [447] 2012 Granich et al.
- [448] 2012 Wagner and Blower
- [449] 2013 Abbas et al.
- [450] 2013 Long and Stavert
- [326] 2013 Cremin et al.
- [451] 2013 Alsallaq et al.
- [452] 2014 Nichols et al.
- [453] 2014 Nichols et al.
- [454] 2014 Alistar, Grant, and Bendavid
- [150] 2014 Eaton and Hallett
- [455] 2015 Ying et al.
- [273] 2015 Low et al.
- [456] 2015 Khademi, Anand, and Potts
- [457] 2015 Gilbert et al.
- [458] 2015 Heaton et al.
- [459] 2016 Rahman, Vaidya, and Zou
- [460] 2016 Gilbert et al.
- [461] 2016 Blaizot et al.
- [462] 2016 Ying et al.
- [463] 2016 Barnighausen, Bloom, and Humair
- [464] 2016 Heffernan et al.
- [465] 2017 Maheu-Giroux et al.
- [157] 2017 Maheu-Giroux et al.
- [466] 2017 Volz et al.
- [467] 2017 Blaizot et al.
- [153] 2018 Mukandavire et al.
- [468] 2018 Guillou
- [469] 2018 Akudibillah, Pandey, and Medlock
- [47] 2018 Stuart et al.
- [470] 2018 de Montigny et al.
- [264] 2019 Hauser et al.

A.1.3.2 Dataset A less B

- [471] 2006 Johnson and Dorrington
- [472] 2006 Baggaley, Garnett, and Ferguson
- [473] 2006 Wilson, Kahn, and Blower
- [474] 2008 Bacaer et al.
- [475] 2009 Chigidi and Lungu
- [476] 2010 Williams et al.
- [477] 2011 Nyabadza and Mukandavire
- [478] 2012 Barnighausen, Bloom, and Humair
- [479] 2013 Wagner, Coburn, and Blower
- [480] 2013 Decker et al.
- [481] 2013 Wirtz et al.
- [482] 2014 Shafer et al.
- [483] 2014 Hove-Musekwa et al.
- [484] 2014 Braithwaite et al.
- [485] 2014 Nichols et al.
- [486] 2014 Abu-Raddad and Awad
- [161] 2014 Anderson et al.
- [487] 2014 Alistar et al.
- [160] 2014 Cori et al.
- [405] 2014 Stover et al.
- [488] 2014 Wirtz et al.
- [489] 2015 Korenromp et al.
- [490] 2015 Knight et al.
- [162] 2015 Kerr et al.
- [491] 2015 Fraser et al.
- [492] 2015 Kassa and Ouhinou
- [205] 2015 Bekker et al.
- [30] 2015 Shannon et al.
- [493] 2015 Blaizot et al.
- [494] 2016 Smith et al.
- [495] 2016 Atun et al.
- [496] 2016 Shattock et al.
- [497] 2016 McGillen et al.
- [159] 2016 Johnson et al.
- [498] 2016 Sharma et al.
- [499] 2017 Akudibillah, Pandey, and Medlock
- [500] 2017 Alsallaq et al.
- [501] 2017 Anderson et al.
- [502] 2017 Chiu et al.
- [503] 2017 Johnson et al.
- [504] 2017 Stuart et al.
- [505] 2017 McGillen et al.
- [272] 2017 Cremin et al.
- [506] 2018 Ross et al.
- [507] 2018 Anderson et al.
- [508] 2018 Anderson et al.
- [509] 2018 Omondi, Mbogo, and Luboobi
- [510] 2018 Woods et al.

- [511] 2018 Stevens et al.
- [512] 2019 Stopard et al.
- [513] 2019 Beacroft and Hallett
- [514] 2019 Reidy et al.
- [515] 2019 Omondi, Mbogo, and Luboobi
- [48] 2019 Maheu-Giroux et al.

A.2 Definitions & Extraction

Data were obtained from (in order of precedence): article text; article tables; article figures; appendix text; appendix tables; appendix figures; and likewise for articles cited like “the model is previously described elsewhere”. Data were assessed from figures with the help of a graphical measurement tool.¹

Fitted Parameters. For the values of fitted parameters, we used the posterior value as reported, including the mean or median of the posterior distribution, or the best fitting value. If the posterior was not reported, we used the mean or median of the prior distribution, including the midpoint of uniform sampling ranges.

A.2.1 Epidemic Context

Let t_0 be the time of ART scale-up/scenario divergence in the model.

HIV Prevalence. As reported in the context overall at t_0 : *Low*: <1%; *Medium*: 1–10%; *High*: >10%.

Epidemic Phase. As projected in the base-case scenario in the context overall between t_0 and roughly $t_0 + 10$ years: *Increasing* (linear or exponential); *Increasing but stabilizing*; *Stable*; *Decreasing but stabilizing*; *Decreasing* (linear or exponential).

Geographic Scale. For studies of one geographic context, scale was defined as one of: *regional*: multiple countries; *national*: one country; *sub-national*: smaller than a country but greater than a city; *city*: one city or less. For studies that consider multiple geographic contexts, scale was defined as *multi-x*, where x is the smallest geographically homogeneous scale considered from the list above.

Country. The countries counted were: *Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, The Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Côte d'Ivoire, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Republic of the Congo, Reunion, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe*. See Table A.1 for related search terms. If a study modelled multiple countries at a national scale or smaller, the counter for each country was incremented.

A.2.2 Risk Heterogeneity

A.2.2.1 Key Populations

Female Sex Workers. Any female activity group meeting 3 criteria: representing <5% of the female population; and being $<1/3 \times$ the size of client population or highest non-MSM male activity group; and

¹ WebPlotDigitizer: apps.automeris.io/wpd/

having $>50 \times$ the partners of the lowest sexually active female activity group [29, 193, 310]. We also noted whether the authors described any activity groups as FSW. If it was not possible to evaluate any criteria due to lack of data, then we assumed the criteria was satisfied.

Clients of FSW. Any male activity group meeting 2 criteria: described as representing clients of FSW; being $>3 \times$ the size of the FSW population [310]. If group sizes were not reported, then we assumed an activity group described as clients met the size criterion. We also noted whether clients were described as comprising a proportion of another male activity group.

Men who have Sex with Men. Any male activity group(s) described by the authors as MSM.

Transgender People. Any activity group(s) described by the authors as transgender.

People who Inject Drugs. Any activity group(s) described by the authors as PWID.

Prisoners. Any activity group(s) described by the authors as prisoners.

A.2.2.2 Activity Groups

Activity groups were defined as any stratification based on sex/gender and the number and/or types of partnerships formed, including key populations, but excluding stratifications by age.

Count. We counted the number of modelled activity groups in total, and separately for women who have sex with men, men who have sex with women, and MSM.

Highest Risk Group Size. The proportion of men and women in the highest risk group.

Turnover. Turnover refers to movement of individuals between activity groups and/or key populations reflecting sexual life course. We defined four classifications of turnover if activity groups were modelled: *None*: no movement between activity groups; *High-Activity*: only movement between one high activity group or key population and other activity group(s); *Multiple*: movement between multiple pairs of risk groups; *Replacement*: only movement from low to high activity to maintain high activity group size(s) against disproportionate HIV mortality.

A.2.2.3 Partnerships

Approaches. How studies defined partnerships, classified into one of three approaches: *Generic*: all partnerships are equal; *By-Group*: partnership types are defined only by the activity groups involved; *Overlapping*: multiple partnership types can be formed by the same pair of activity groups. Within *By-Group*, we classified how the parameters of the partnership were defined, as based on either: the *susceptible* partner; the *lower activity* partner; the *higher activity* partner; or some consideration of *both partners*.

Characteristics. Whether any of the following varied between different partnership types: *Condom Use*: proportion of sex acts protected; *Total Sex*: total number of sex acts, possibly defined by differences in partnership duration and/or frequency of sex.

Mixing. Mixing by activity group was classified as either: *Proportionate*: proportionate to the total number of partnerships offered by each risk group; *Assortative*: any degree of preferential partnership formation between individuals of the same or similar risk groups.

A.2.2.4 Age Groups

Count. The number of age groups considered in the model.

Risk. Whether age groups differed in any characteristic that conferred transmission risk (binary).

Mixing. We classified whether partnership formation between age groups was assumed to be: *Proportionate*: proportionate to the number of partnerships offered by each age group; *Strictly Assortative*: any degree of preferential partnership formation between individuals of the same or similar age groups that is equal for both sexes. *Off-Diagonal*: any degree of preferential partnership formation between younger women and older men.

A.2.3 HIV Natural History

Count. The number of states of HIV infection considered in the model, excluding stratifications related to treatment. If states were defined by both CD4 and viral load, then the count considers all unique combinations.

Acute Infection. Whether any state represented increased infectiousness associated with acute infection (binary).

Late-Stage Infection. Whether any state(s) considered increased infectiousness associated with late-stage infection (binary).

HIV Morbidity. Whether any state(s) considered decreased sexual activity associated with late-stage disease (binary), and how that decreased was modelled: *Inactive*: complete cessation of sexual activity; *Partners*: decreased rate of partnership formation; *Sex Acts per Partnership*: decreased frequency of sex per partnership; and/or *Generic*: representative decreased probability of transmission.

A.2.4 Antiretroviral Therapy

A.2.4.1 Transmission

Transmission Reduction due to ART. The relative reduction in probability of transmission (0 is perfect prevention, 1 is no effect) among individuals who are virally suppressed; if viral suppression was not explicitly modelled, then the relative reduction among individuals who are on treatment was used.

Transmitted Resistance. Any consideration of 1+ strains of HIV which are transmitted and for which ART had reduced benefits. We did not document the number of resistant strains, or characteristics of resistance and transmissibility.

A.2.4.2 Treatment Cascade States

Forward Cascade. We extracted whether each of the following states were included (binary): *Diagnosed*: aware of their HIV+ status, but have not yet started ART; *Not Yet Virally Suppressed*: started ART, but are not yet virally suppressed; *Virally Suppressed*: on ART and achieved viral suppression; and *Generic On ART*: simplifications of any/all of the above.

Stopping ART. We extracted whether individuals stopped ART, either due to: *Treatment Failure*: ART is no longer efficacious due to resistance; or *ART Cessation*: ART is discontinued for other reasons, such as barriers to access or side effects. We also extracted whether individuals stopping ART for either reason were tracked separately, or whether they re-entered a generic ART-naïve state, such as “Diagnosed”.

Differential Cascade Transitions. We extracted whether rates of transitioning along the ART cascade, including: rate of *HIV diagnosis*; rate of *ART initiation*; and rate of *ART cessation*, differed by any of the following stratifications: *sex*; *age*; *activity*; and *key populations*. If the study did not mention possible differences in such rates, then we assumed that no differences were modelled.

A.2.4.3 Behaviour Change

HIV Counselling. Whether any sexual behaviour change associated with HIV testing and counselling was applied to individuals in the diagnosed and/or on-ART states (binary), and what changed: *Condom Use*: increased; *Serosorting*: any; *Partners*: decreased rate of partnership formation; *Sex Acts per Partnership*: decreased frequency of sex per partnership; and/or *Generic*: representative decreased probability of transmission due to counselling.

A.2.5 ART Prevention Impact

The following data were extracted per scenario, rather than per-study.

A.2.5.1 Intervention

ART Initiation Criteria. What criteria were used for ART eligibility as part of the intervention: *Symptomatic* (*AIDS*); $CD4 < 200$; $CD4 < 350$; $CD4 < 500$; *All individuals*; *Other*.

Intervention Population. Among which population sub-group(s) was the scale-up of ART coverage/initiation applied. Only scenarios with ART intervention for all individuals were included in Dataset B.

Impact Population. Among which population sub-group(s) was the ART prevention impact measured. Only scenarios measuring ART prevention impacts in all individuals were included in Dataset B.

ART Coverage Target. The proportion of people living with HIV in the intervention population who are on ART by the end of ART scale-up.

ART Initiation Rate Target. The rate at which people living with HIV in the intervention population initiate ART by the end of ART scale-up.

Intervention t_0 and t_f . The years at which ART scale-up as part of the intervention started and stopped, respectively. If interventions were modelled as instantaneous, such as increasing ART initiation rate, then we considered $t_0 = t_f$. Impact time horizons were measured relative to t_0 .

A.2.5.2 Impact

For both measures of ART prevention impact, we extracted reported values from the text for any available time horizon, as well as figure data for any of the following time horizons, if available: 5, 10, 15, 20, 30,

and 40 years, with the help of a graphical measurement tool. If only absolute values were reported, we calculated the relative reductions manually. Where reported, we extracted confidence intervals for each outcome.

Relative Incidence Reduction. The relative reduction in overall annual HIV incidence (per 1000 person-years) in the intervention scenario as compared to the baseline scenario, both after an equal number of years since t_0 (time horizon). For example, if the baseline and intervention scenarios predicted overall HIV incidence of 1 and 0.7 per 1000 person-years 5 years after t_0 , then the relative incidence reduction for the 5-year time horizon would be 30%.

Proportion of Infections Averted. The relative reduction in cumulative new HIV infections in the intervention scenario as compared to the baseline scenario, both after an equal number of years since t_0 (time horizon). For example, if the baseline and intervention scenarios predicted 1000 and 700 new infections 5 years after t_0 , then the proportion of infections averted for the 5-year time horizon would be 30%.

A.3 Supplemental Results

Additional information on data sources, analysis, and results are available in a public repository:
github.com/mishra-lab/sr-heterogeneity-hiv-models

A.3.1 Map

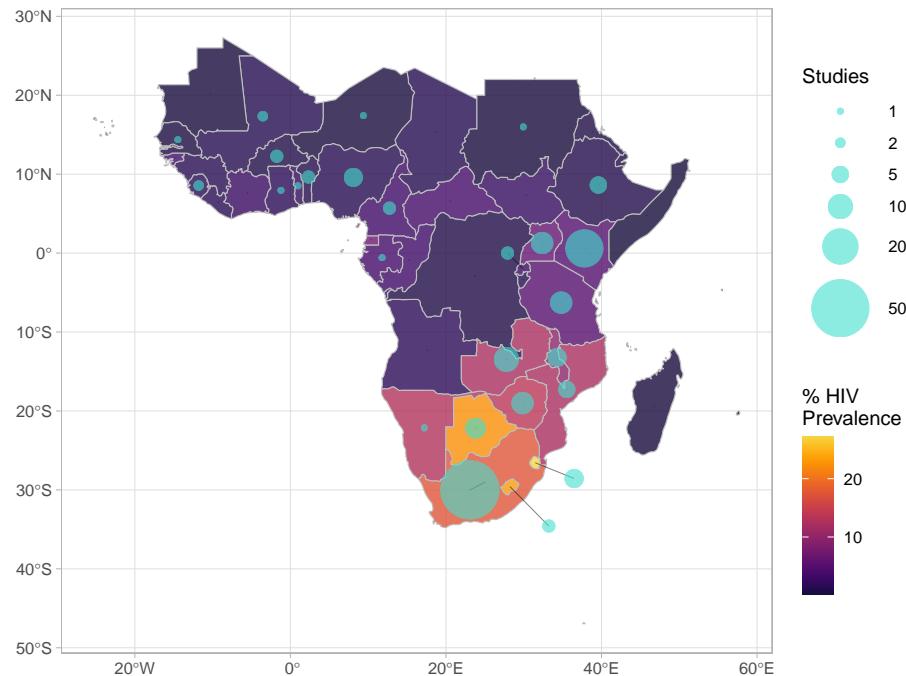


Figure A.1: Map showing number of studies (of 94 total) applying HIV transmission modelling in each country vs. the number of people living with HIV (PLHIV, millions)

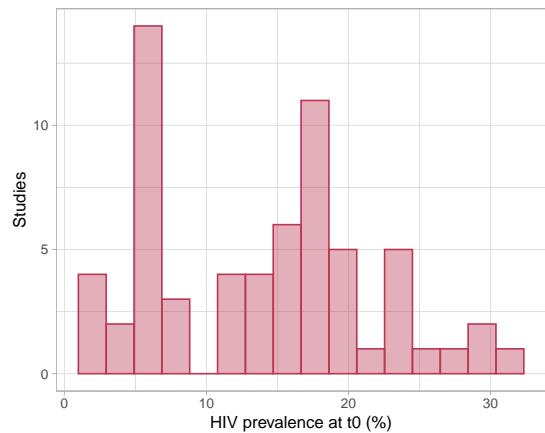
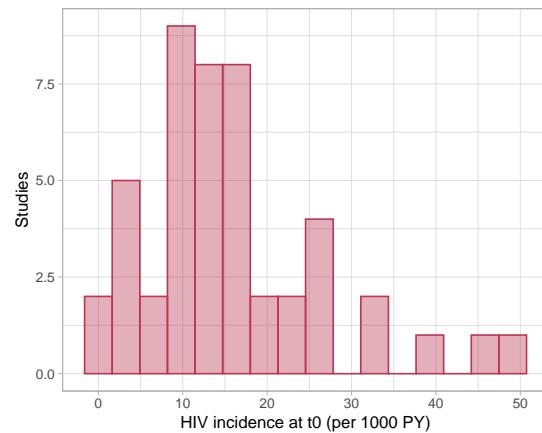
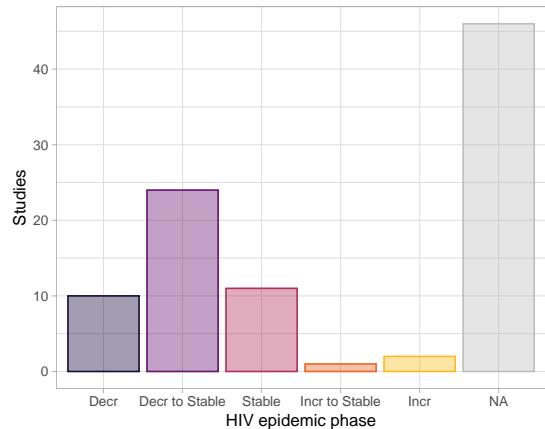
A.3.2 Risk Heterogeneity

A.3.2.1 Distributions

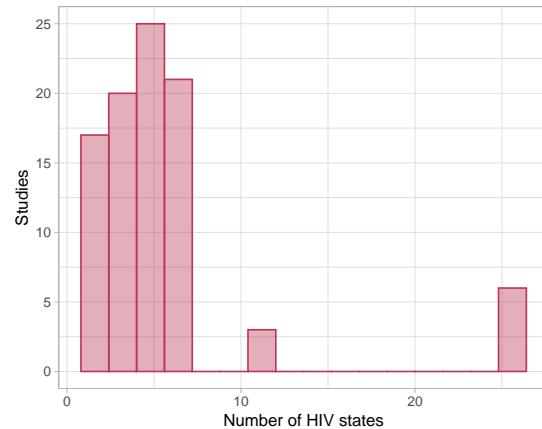
The following figures illustrate the distributions (number of studies) of various parameter values and modelling assumptions related to factors of heterogeneity and intervention contexts.

A.3 SUPPLEMENTAL RESULTS

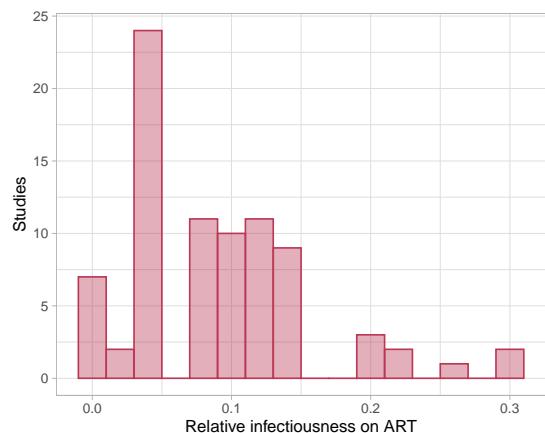
131

(a) HIV prevalence at t_0 (%)(b) HIV incidence at t_0 (per 1000 PY)

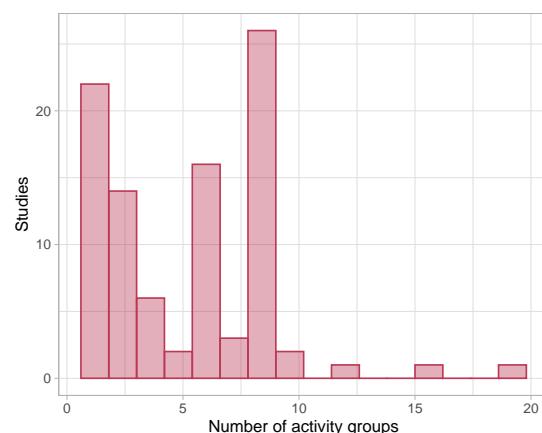
(c) HIV epidemic phase



(d) Number of HIV states



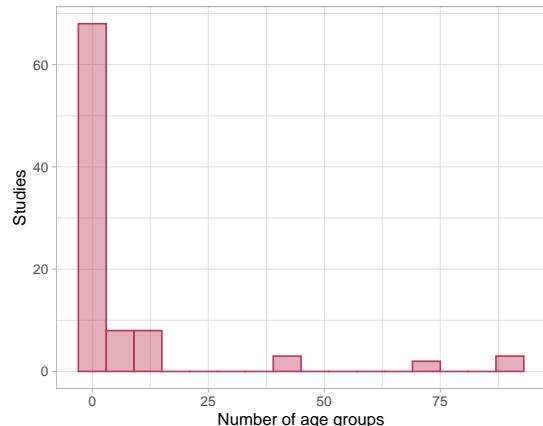
(e) Relative infectiousness on ART



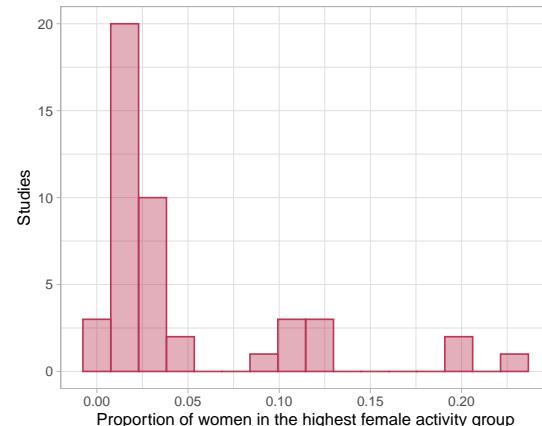
(f) Number of activity groups

A.3 SUPPLEMENTAL RESULTS

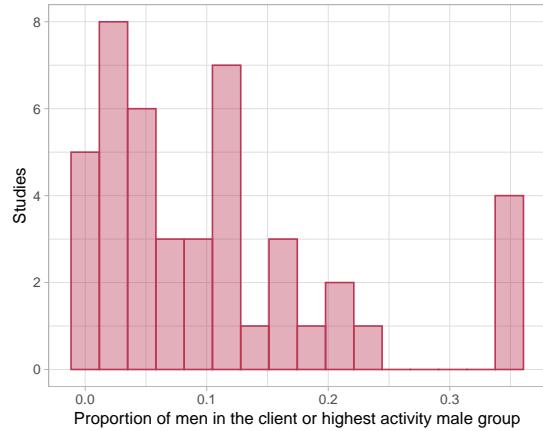
132



(g) Number of age groups



(h) Proportion of women in the highest female activity group

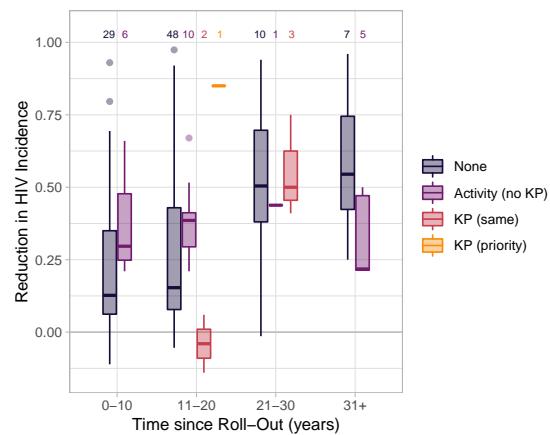


(i) Proportion of men in the client or highest activity male group

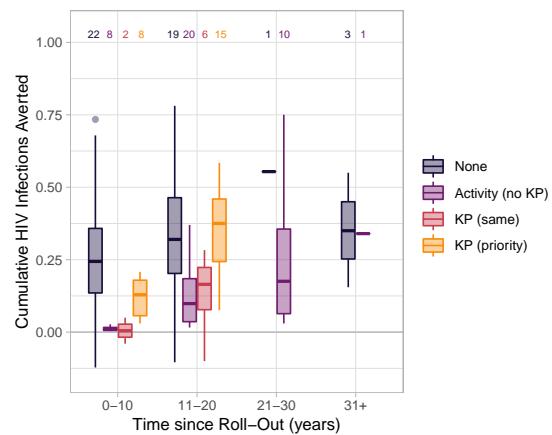
Figure A.2: Distributions of parameter values and modelling assumptions related to factors of heterogeneity and intervention contexts

A.3.3 ART Prevention Impact

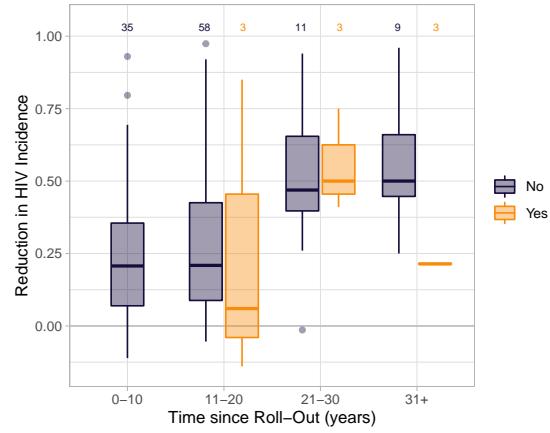
The following figures illustrate the projected ART prevention impact (Dataset B), stratified by various factors of heterogeneity and intervention contexts (colours). Left panels show the relative HIV incidence reduction (IR); right panels show the proportion of cumulative HIV infections averted (CIA); both as compared to a base-case scenario reflecting status quo. If any study included multiple scenarios of ART scale-up, then each scenario was included separately; if any scenario reported multiple time horizons, each time horizon was included separately. The number of studies (scenarios) reporting incidence reduction, cumulative infections averted, both, or either was: 23 (61), 24 (75), 7 (11), and 40 (125), respectively. If any factor could not be quantified due to missing data or varying values, it was omitted from that plot. In box plots, the numbers of unique scenario time-horizons contributing to each box are given above it.



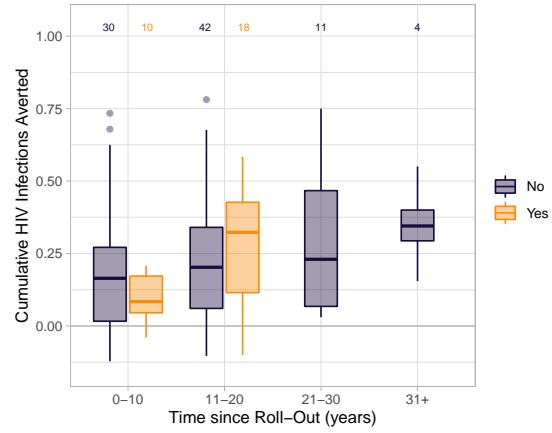
(a) Risk Stratification & ART cascade differences: IR



(b) Risk Stratification & ART cascade differences: CIA



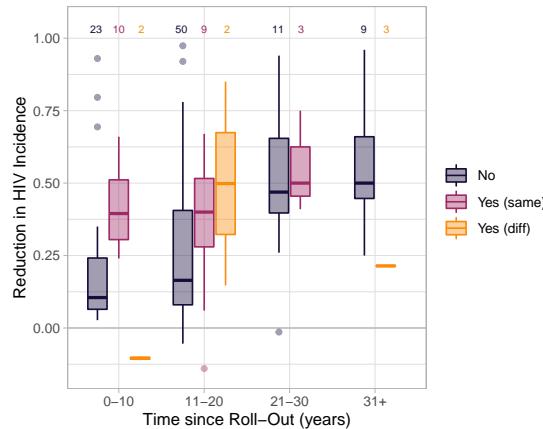
(c) Any activity group turnover: IR



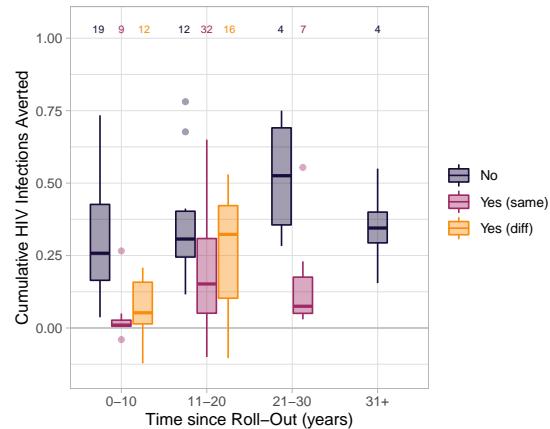
(d) Any activity group turnover: CIA

A.3 SUPPLEMENTAL RESULTS

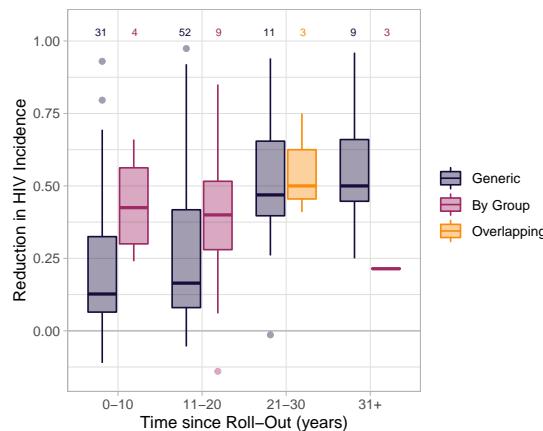
134



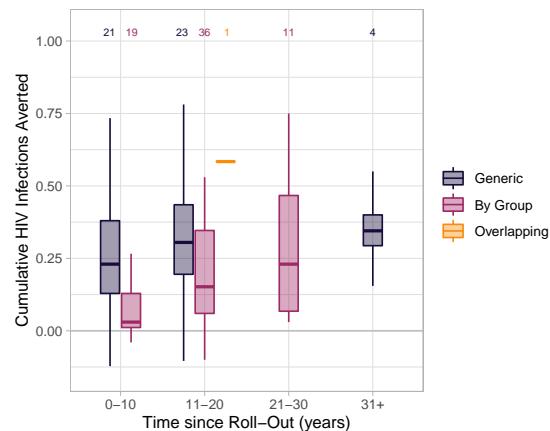
(e) Sex stratification & any ART cascade differences: IR



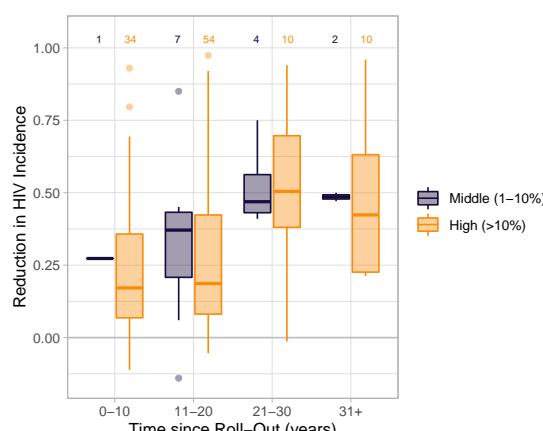
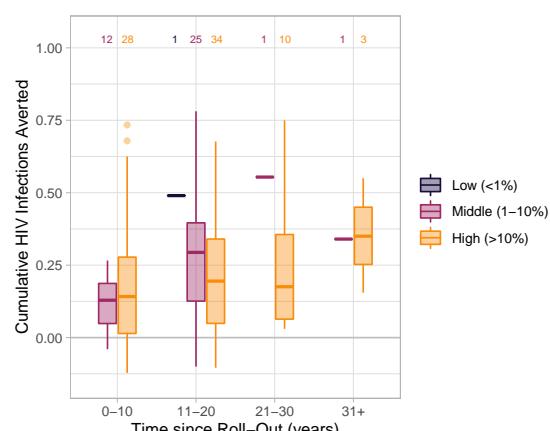
(f) Sex stratification & any ART cascade differences: CIA



(g) Type of partnership definition: IR

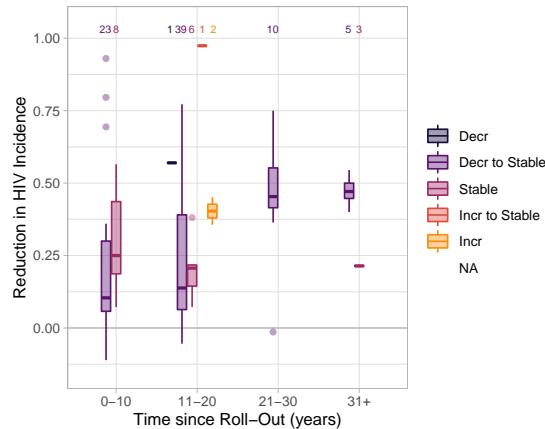


(h) Type of partnership definition: CIA

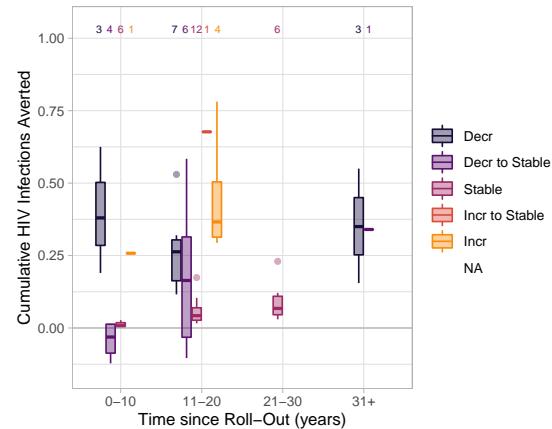
(i) HIV prevalence at t_0 (%): IR(j) HIV prevalence at t_0 (%): CIA

A.3 SUPPLEMENTAL RESULTS

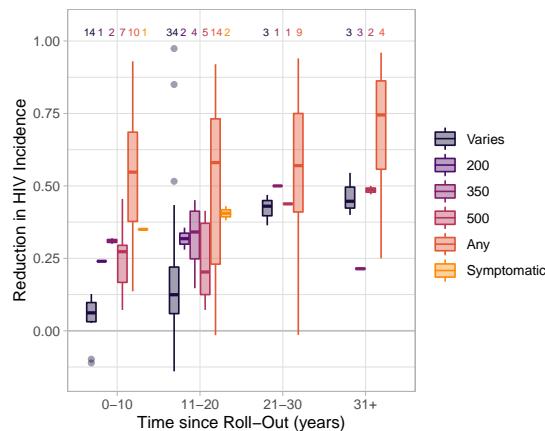
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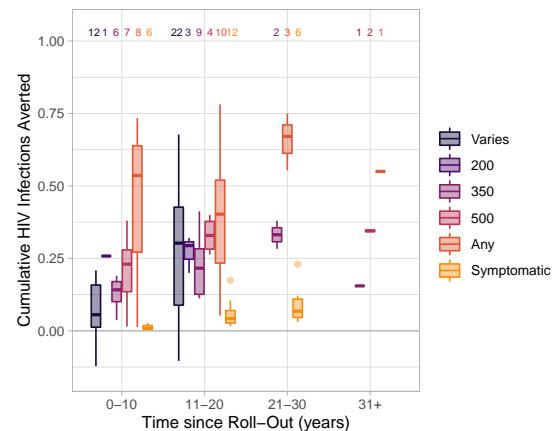
(k) HIV epidemic phase: IR



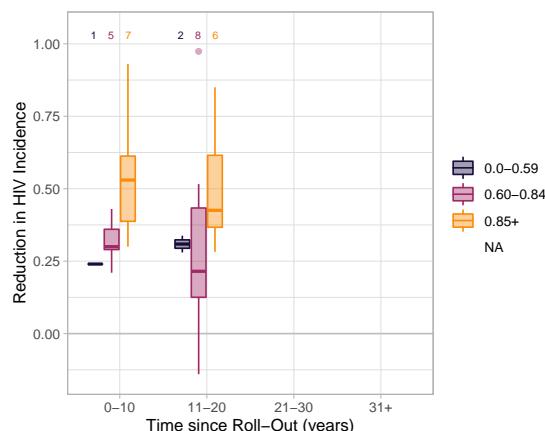
(l) HIV epidemic phase: CIA



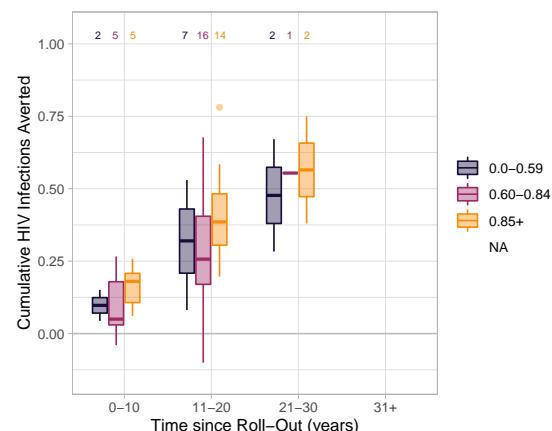
(m) CD4 initiation criteria: IR



(n) CD4 initiation criteria: CIA



(o) ART intervention coverage target: IR



(p) ART intervention coverage target: CIA

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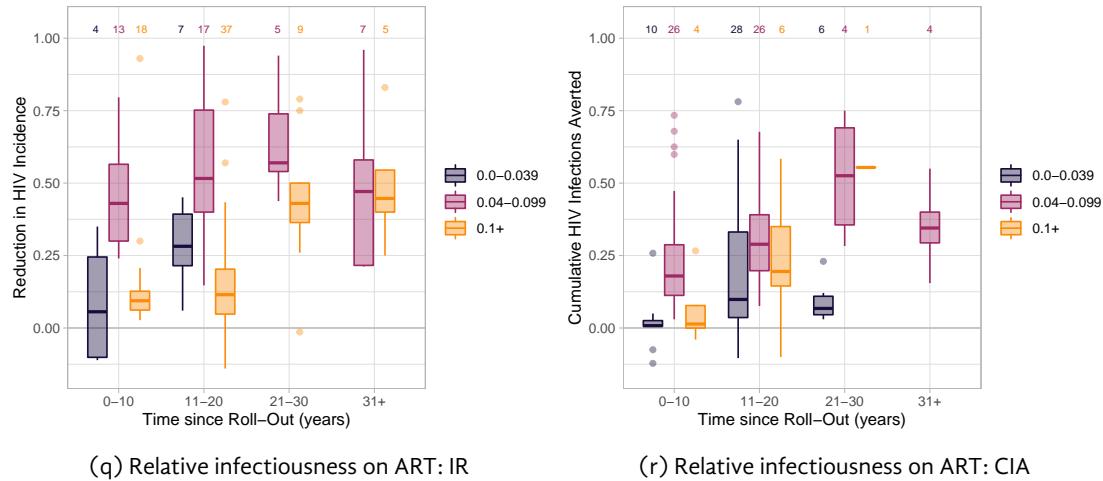


Figure A.3: Projected ART prevention impacts: incidence reduction (IR) and cumulative infections averted (CIA), stratified by factors of heterogeneity and intervention contexts

A.4 PRISMA-ScR Checklist

Page/section numbers refer to [174].

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Introduction
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N/A
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Methods 2.2 Appendix A.2
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Methods 2.2 Appendix A.1
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Methods 2.2 Appendix A.1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Methods 2.2 Appendix A.2
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Methods 2.3 Appendix B
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Meth 2.3 App B
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Meth 2.3 App B



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Results Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Results Appendix A.3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Results Appendix C
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Results App C
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Discussion
Limitations	20	Discuss the limitations of the scoping review process.	Discussion
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Discussion
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Funding

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.



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Appendix B

Supplement to Chapter 3

B.1 Supporting Mathematics

B.1.1 Exponential Duration Assumption in Compartmental Models

Let λ be the fixed exit rate from compartment A, which is assumed to be homogeneous. Then $\delta \sim \lambda e^{-\lambda \delta}$ is the exponentially distributed duration time in the group.

Mean & Median Duration. The mean duration is $\mu = 1/\lambda$ and the median is $m = \log(2)/\lambda \approx 0.69\mu$. Thus, if 50% of individuals progress from compartment A to B by time τ (median duration), the exit rate λ is given by $\log(2)/\tau$.

Collapsing Compartments in Series. Let compartments A and B be in series, with exit rates λ_A and λ_B respectively. Collapsing A and B into AB will sum the mean durations: $\delta_{AB} = 1/\lambda_A + 1/\lambda_B$; thus, the exit rate from AB will be $\lambda_{AB} = 1/(1/\lambda_A + 1/\lambda_B)$.

Collapsing Compartments in Parallel. Let compartments A and B be in parallel, with exit rates λ_A and λ_B respectively. Collapsing A and B into AB will sum the exit rates: $\lambda_{AB} = \lambda_A + \lambda_B$; thus, the mean duration in AB will be $\delta_{AB} = 1/(\lambda_A + \lambda_B)$.

B.1.2 Beta Approximation of the Binomial (BAB) Distribution

Numerous model parameters and calibration targets represent population proportions. Such proportions can be estimated as $\rho = n/N$, where N is the sample size and n is the number of individuals with the characteristic of interest. The uncertainty around n is then given by the binomial distribution:

$$p(n) = \binom{N}{n} \rho^n (1-\rho)^{N-n} \quad (\text{B.1})$$

However, Eq. (B.1) is only defined for discrete values of n . It is more convenient to have a continuous distribution for ρ , for sampling parameters and evaluating the likelihood of calibration targets, since compartmental models can have non-whole-number population sizes. For this purpose, I use a beta approximation of the binomial distribution (BAB):

$$p(\rho) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} \rho^{\alpha-1} (1-\rho)^{\beta-1} \quad (\text{B.2})$$

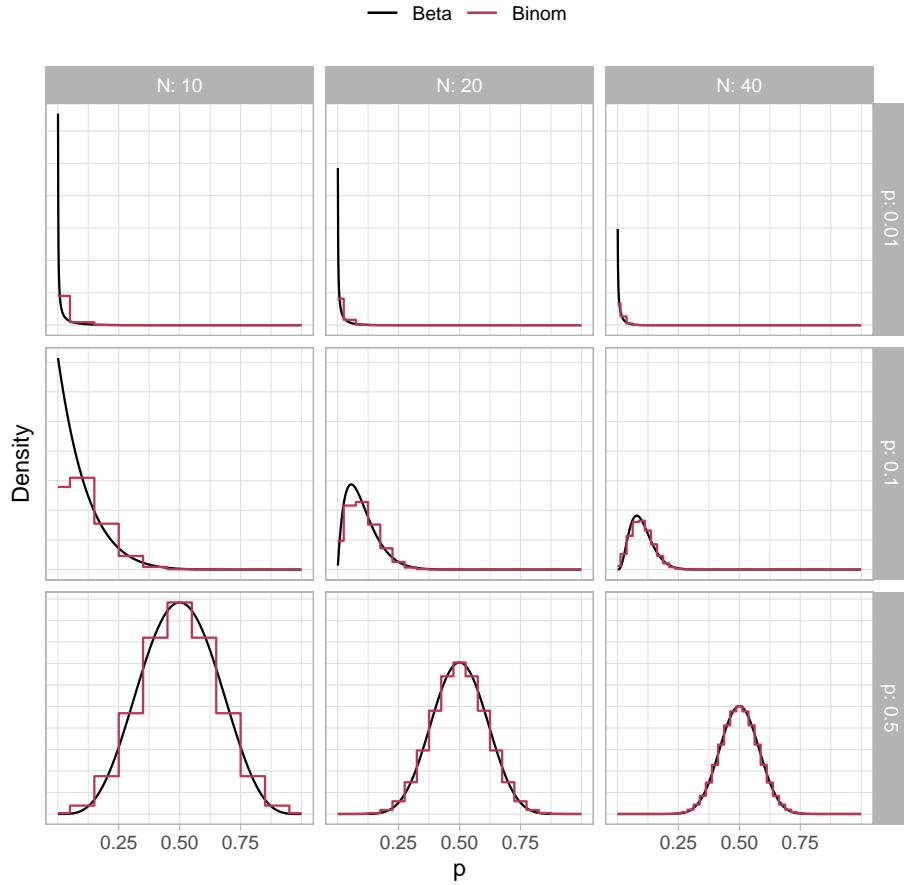


Figure B.1: Beta approximation of the binomial distribution (BAB)

with $\alpha = N\rho$ and $\beta = N(1-\rho)$. Unlike the approximation by a normal distribution, the beta distribution ensures that $\rho \in [0, 1]$. Figure B.1 illustrates the approximation for $N = \{10, 20, 40\}$ and $\rho = \{0.01, 0.1, 0.5\}$.

B.1.3 Joint Sampling with Relational Constraints

Figure B.2 illustrates the posterior (sampled) distributions for variables X_1, X_2, X_3 , having uniform priors but subject to $X_1 < X_2 < X_3$. Three approaches to enforcing $X_1 < X_2 < X_3$ were explored:

- **joint:** sample X_1, X_2, X_3 simultaneously; then discard any samples failing $X_1 < X_2 < X_3$.
- **forward:** sample X_1 ; then sample X_2 until $X_1 < X_2$; then sample X_3 until $X_2 < X_3$.
- **backward:** sample X_3 ; then sample X_2 until $X_2 < X_3$; then sample X_1 until $X_1 < X_2$.

All three methods result in a different posterior vs. the prior, but the forward and backward methods severely distort the distributions for X_3 and X_1 , respectively, while leaving the distributions for X_1 and X_3 unchanged. By contrast, the joint method influences the posterior distributions of each variable in a more “equitable” way, which is preferred.

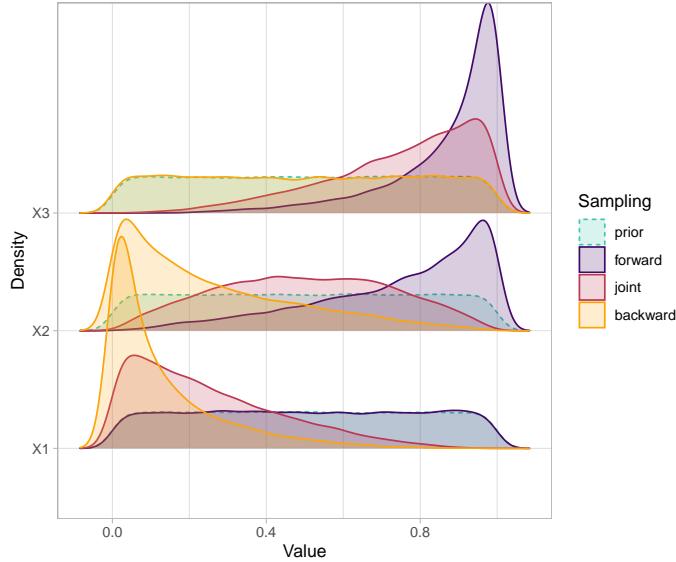


Figure B.2: Illustration of different sampling biases when enforcing $X_1 < X_2 < X_3$

B.1.4 Fitting Distributions

Uncertainty distributions for all parameters and calibration targets were estimated by fitting a parametric distribution to specified quantiles. Let $f(x | \theta)$ be the probability density function of random variable x (parameter or target) given distribution parameters θ . Then $F(x | \theta) = \int_0^x f(\tau) d\tau$ is the cumulative distribution function, and $Q(p | \theta) = F^{-1}(p | \theta)$ is the quantile function. Our objective is to estimate θ , given a set of quantiles (e.g., $q = \{q_{2.5}, q_{97.5}\}$ for the 95% CI). For each estimation, I minimized¹ the following error function:

$$J(\theta) = \sum_i |q_i - Q(p_i | \theta)|^\omega \quad (\text{B.3})$$

where ω can specify absolute differences ($\omega = 1$) or squared differences ($\omega = 2$) to improve convergence. Distribution fit was validated visually using a plot of the distribution quantiles $Q(p_i | \theta)$ vs. the target quantiles q_i , overlaid on the density distribution $f(x | \theta)$; e.g., Figure B.3.

B.2 Female Sex Worker Data

Raw data from two FSW surveys in Eswatini — 2011 [108] ($N = 325$) and 2014 [141] ($N = 781$) — were analyzed to support parameterization of FSW within the HIV transmission model, including substratification of lower vs. higher risk FSW.

B.2.1 FSW Risk Factor Variable Distributions

Figure B.4 illustrates the distributions of variable values across two FSW strata defined in § 3.2.7.3 (lower vs. higher risk).

¹ Using docs.scipy.org/doc/scipy/reference/optimize.minimize-lbfgsb.html

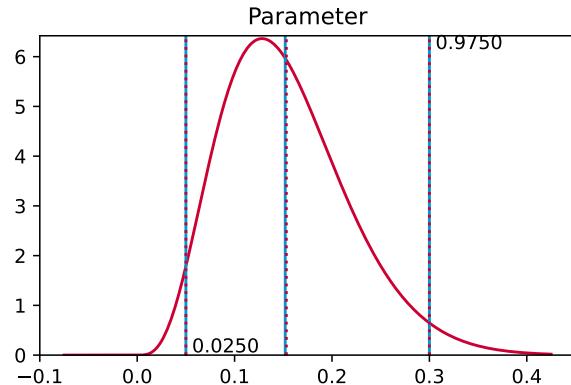


Figure B.3: Example distribution fitting validation plot

BAB distribution fit to $\{q_{2.5} = .05, q_{97.5} = .30\}$; blue solid lines: target quantiles q_i ; red dotted lines: distribution quantiles $Q(p_i | \theta)$; red solid line: density distribution $f(x | \theta)$.

B.2.2 Years Since First Sold Sex

Figure B.5 illustrates the distributions of reported years since first selling sex (unadjusted), stratified by whether respondents ever stopped selling sex. Figure B.6 illustrates the *cumulative* distribution of reported years since first selling sex after RDS adjustment, plus a fitted exponential distribution.

B.3 Wider Population: Adjusted Partner Numbers

Figure B.7 illustrates the results of § 3.2.8: the density distributions for adjusted proportions of women and men aged 15–49, stratified by union status and numbers of partners in the past 12 months.

B.3 WIDER POPULATION: ADJUSTED PARTNER NUMBERS

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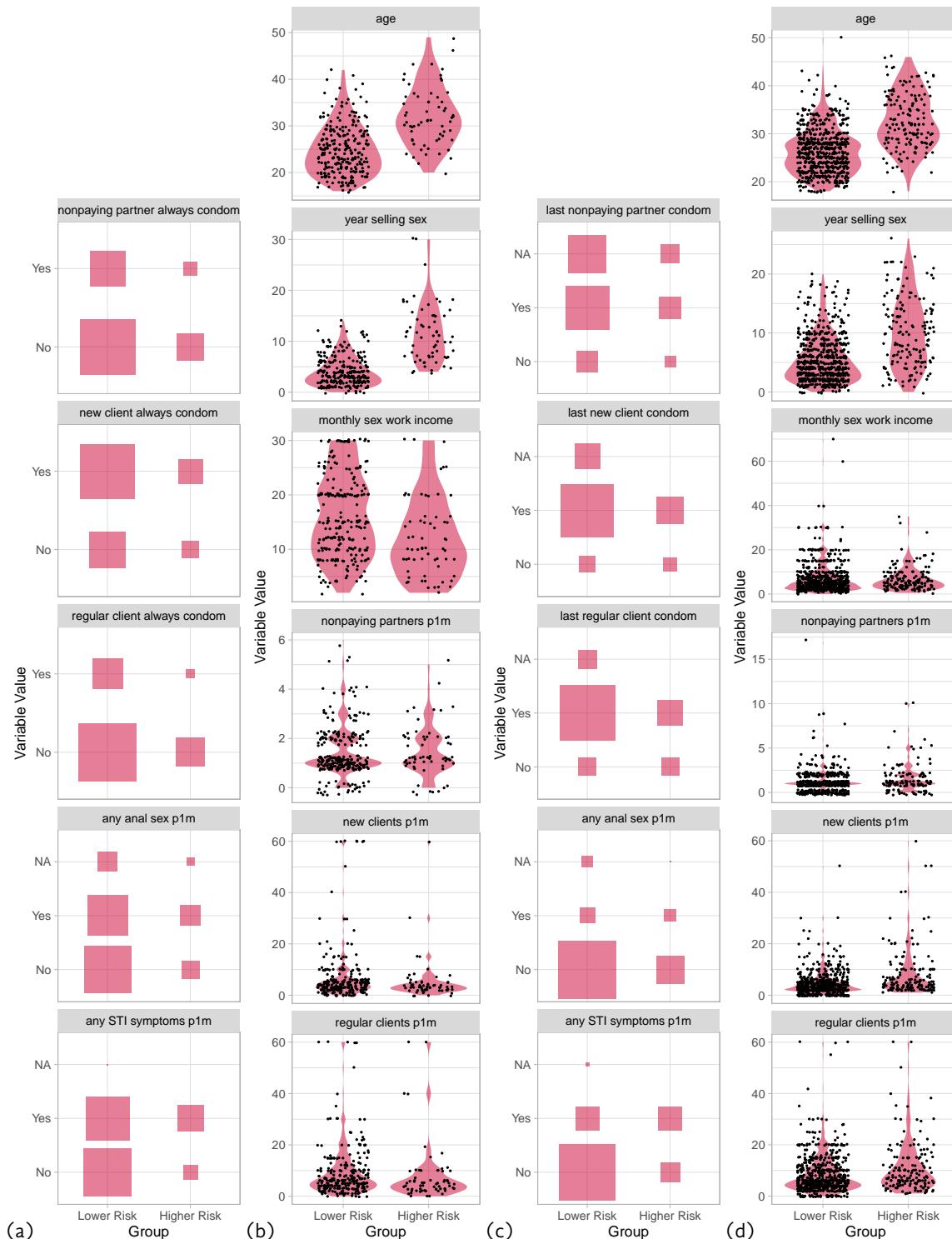


Figure B.4: Distributions of HIV risk factor variables among higher vs. lower risk FSW in Eswatini, as estimated by multivariable logistic regression model for HIV status

(a) 2011, serologic HIV status, factor variables; (b) 2011, serologic HIV status, continuous variables; (c) 2014, self-reported HIV status, factor variables; (d) 2014, self-reported HIV status, continuous variables; data sources: 2011 [108], 2014 [141].

B.3 WIDER POPULATION: ADJUSTED PARTNER NUMBERS

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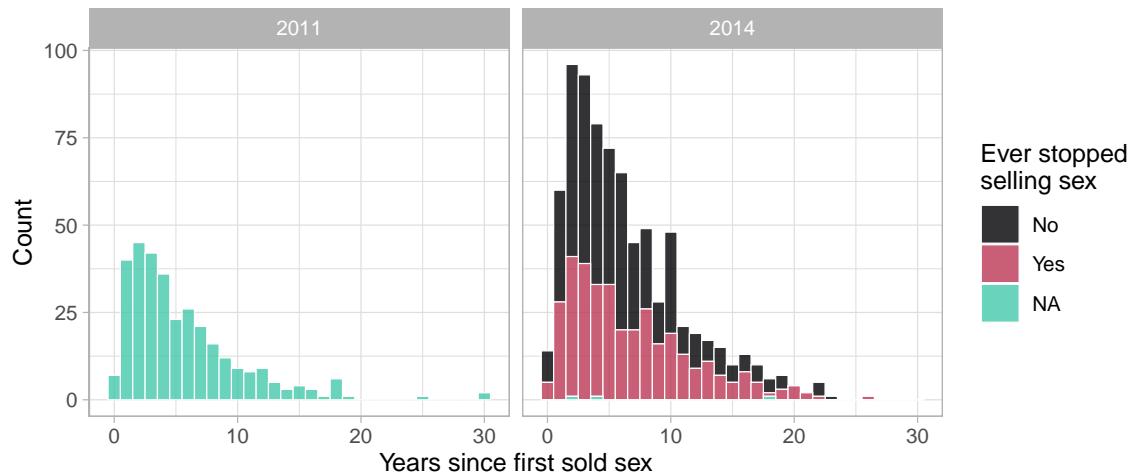


Figure B.5: Years since first sold sex among FSW in Eswatini (unadjusted)

Data sources: 2011 [108], 2014 [141].

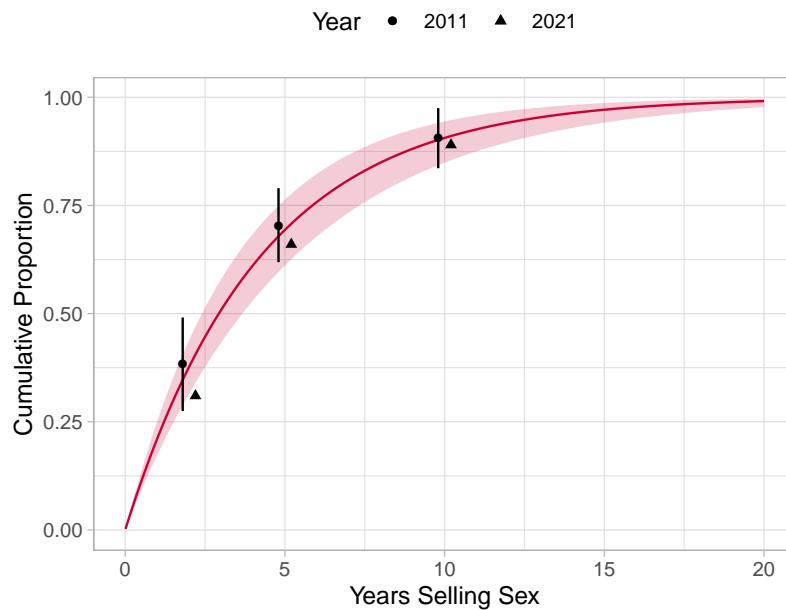


Figure B.6: Cumulative distribution of years selling sex among FSW in Eswatini (RDS-adjusted)

The line and shaded region illustrate the median and 95% CI of sampled exponential distributions, respectively; calibration data from [108] (2011) and [109] (2011).

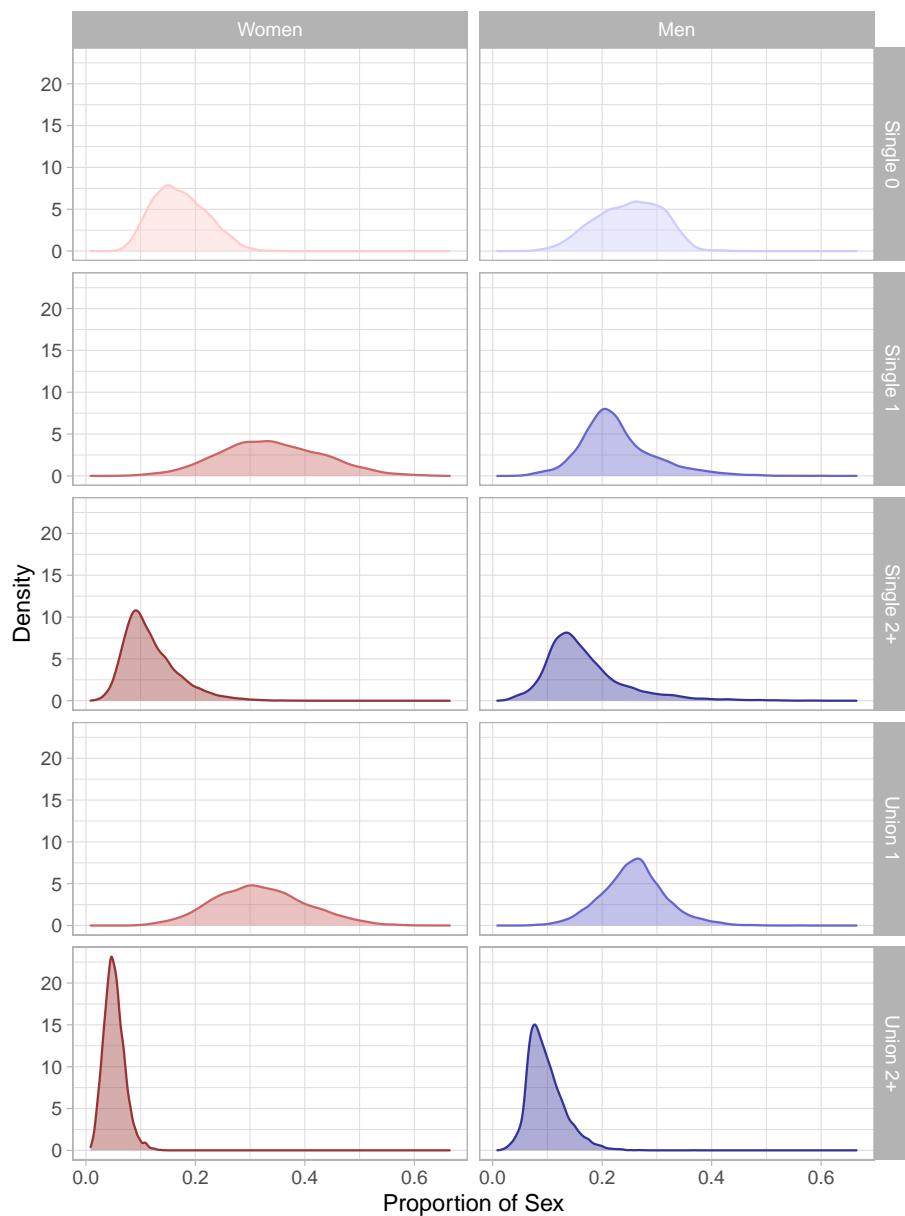


Figure B.7: Density distributions for adjusted proportions of women and men aged 15–49, stratified by union status and numbers of partners in the past 12 months

B.4 Model Calibration

Table B.1 gives the short names (used in code and some results figures), definitions, and distributions (prior and posterior mean and 95% CI) of the calibrated model parameters ($N = 73$). The exact sampling distributions, constraints, and application of each parameter to define the complete set of model inputs is available online:

github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/params.py

B.4.1 Relational Sampling Constraints

Several relational constraints were imposed on calibrated parameter values during sampling. Incorporating constraints within Latin hypercube sampling is challenging [516]. Thus, for each set of constraints below, the selected parameters were sampled randomly (not via Latin hypercube) and repeated until all constraints were satisfied; as noted in § B.1.3, this sampling strategy effectively changes the prior distribution to reflect both the original prior and the specified constraints.

- a. $K_{swo_fsw_l} * RC_{swo_fsw_h:l} * F_{swo} + K_{swr_fsw_l} * RC_{swr_fsw_h:l} * F_{swr} < 2*365$
where: $K_{swx_fsw_l} = C1m_{swx_fsw_l} * dur_{swx} / (dur_{swx} + 1/12)$
- b. Let “c_” denote PF_condom_:


```
c_msp_2006 < c_msp_2016
c_cas_2006 < c_cas_2016
c_swo_2002 < c_swo_2011 < c_swo_2014
c_swv_2002 < c_swv_2011 < c_swv_2014
c_msp_2006 < c_cas_2006
c_msp_2016 < c_cas_2016
c_swv_2002 < c_swo_2002
c_swv_2011 < c_swo_2011
c_swv_2014 < c_swo_2014
```
- c. $1 \leq (R\beta_{acute} * dur_{acute}) \leq 63$
- d. $P_{gud_fsw_l} > .07$
 $(P_{gud_fsw_l} * RP_{gud_fsw_h:l}) < 1$

B.4 MODEL CALIBRATION

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Table B.1: Definitions and distributions of calibrated parameters

Parameter	Definition	Prior		Posterior	
		Mean	(95% CI)	Mean	(95% CI)
to_hiv	year of HIV introduction to Eswatini	1982.5	(1980.1, 1984.9)	1982.3	(1980.1, 1984.9)
PX_w_fsw	proportion of women who are FSW	0.0288	(0.00703, 0.065)	0.0443	(0.0198, 0.0773)
PX_w_h	proportion of women who have 2+ partners in p12m	0.178	(0.0961, 0.278)	0.185	(0.106, 0.279)
PX_m_m	proportion of men who have 2+ partners in p12m	0.133	(0.1, 0.17)	0.133	(0.1, 0.17)
dur_fsw_1	duration in sex work among lower risk FSW	4.12	(2.96, 5.48)	3.97	(2.86, 5.13)
dur_fsw_h	duration in sex work among higher risk FSW	9.41	(6.3, 13.1)	9.31	(6.32, 13.0)
dur_cli	duration buying sex among clients	8.63	(4.0, 15.0)	8.32	(3.73, 14.4)
turn_xm_xl	turnover rate from medium to lowest activity (women and men)	0.216	(0.05, 0.5)	0.206	(0.058, 0.464)
Pturn_fsw_m:l	proportion of FSW who transition to medium activity	0.724	(0.503, 0.898)	0.721	(0.482, 0.89)
Pturn_cli_m:l	proportion of clients who transition to medium activity	0.602	(0.249, 0.9)	0.587	(0.252, 0.893)
growth_2050	rate of Eswatini population growth in 2050	0.011	(0.0072, 0.0148)	0.011	(0.00723, 0.0148)
C12m_msp_xl	number of main/spousal partners in p12m among lowest activity	0.37	(0.251, 0.498)	0.382	(0.265, 0.507)
C12m_cas_xl	number of casual partners in p12m among lowest activity	0.366	(0.201, 0.549)	0.377	(0.22, 0.552)
C12m_cas_wm	number of casual partners in p12m among medium activity women	1.58	(1.2, 2.0)	1.62	(1.24, 2.02)
RC_cas_cli:wm	relative casual partners among clients vs medium activity women	0.625	(0.269, 0.981)	0.702	(0.285, 0.99)
C1m_swo_fsw_1	number of occasional sex work partners in p1m among lower risk FSW	4.06	(2.5, 6.0)	4.08	(2.45, 6.0)
C1m_smr_fsw_1	number of regular sex work partners in p1m among lower risk FSW	6.93	(5.0, 9.17)	7.0	(5.04, 9.12)
RC_swo_fsw_h:1	relative occasional sex work partners among higher vs lower risk FSW	2.02	(1.59, 2.5)	2.03	(1.61, 2.51)
RC_swr_fsw_h:1	relative regular sex work partners among higher vs lower risk FSW	1.49	(1.3, 1.7)	1.5	(1.31, 1.71)
KF_swx_cli	rate of visiting FSW (sex acts) among clients overall	59.3	(35.0, 90.0)	59.7	(36.3, 87.1)
RKF_swx_cli:h:1	relative visits (sex acts) among higher vs lower risk clients	2.03	(1.6, 2.5)	2.04	(1.59, 2.55)
F_msp	rate of sex acts in main/spousal partnerships	77.3	(26.0, 156.0)	100.0	(44.5, 171.0)
RF_cas_msp	relative rate of sex acts in casual vs main/spousal partnerships	0.75	(0.512, 0.988)	0.792	(0.526, 0.99)
dur_msp	duration of main/spousal partnerships	16.5	(14.6, 18.4)	16.5	(14.6, 18.4)
dur_cas	duration of casual partnerships	0.743	(0.25, 1.5)	0.833	(0.353, 1.59)
dur_swr	duration of regular sex work partnerships	1.13	(0.5, 2.0)	1.11	(0.494, 2.08)
F_swr	rate of sex acts in regular sex work partnerships	24.0	(12.6, 35.4)	24.4	(12.9, 35.5)
PF_ai	proportion of sex acts which are anal in all partnerships	0.0573	(0.00603, 0.165)	0.0694	(0.00854, 0.186)
pref_msp_xl	log-odds of main/spousal partnership formation among lowest activity	2.19	(1.5, 3.0)	2.19	(1.43, 2.97)
pref_mcx_swx	log-odds of non-sex work partnership formation among FSW and clients	8.3	(2.0, 19.0)	8.04	(1.81, 18.5)
Rbeta_a_condom	relative per-act probability of HIV transmission with a condom	0.734	(0.571, 0.869)	0.74	(0.578, 0.865)
RPF_condom_a:v	relative condom use in anal vs vaginal sex	0.768	(0.594, 0.949)	0.768	(0.599, 0.954)
RPF_condom_1996	relative condom use in all partnerships in 1996 vs 2002 or 2006	0.5	(0.025, 0.975)	0.495	(0.0322, 0.976)

continued ...

B.4 MODEL CALIBRATION

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... continued

*	Parameter	Definition	Prior	(95% CI)	Prior	(95% CI)	Prior	(95% CI)
b	PF_condom_msp_2006	condom use in main/spousal partnerships in 2006	0.23	(0.153, 0.317)	0.23	(0.155, 0.316)		
b	PF_condom_msp_2016	condom use in main/spousal partnerships in 2016	0.416	(0.308, 0.529)	0.412	(0.309, 0.524)		
b	PF_condom_cas_2006	condom use in casual/partnerships in 2006	0.598	(0.501, 0.692)	0.591	(0.495, 0.676)		
b	PF_condom_cas_2016	condom use in casual/partnerships in 2016	0.694	(0.601, 0.78)	0.697	(0.609, 0.777)		
b	PF_condom_swo_2002	condom use in occasional sex work partnerships in 2002	0.432	(0.148, 0.744)	0.492	(0.249, 0.736)		
b	PF_condom_swo_2011	condom use in occasional sex work partnerships in 2011	0.777	(0.581, 0.923)	0.793	(0.66, 0.899)		
b	PF_condom_swo_2014	condom use in occasional sex work partnerships in 2014	0.787	(0.547, 0.95)	0.885	(0.782, 0.968)		
b	PF_condom_swr_2002	condom use in regular sex work partnerships in 2002	0.337	(0.118, 0.603)	0.294	(0.105, 0.501)		
b	PF_condom_swr_2011	condom use in regular sex work partnerships in 2011	0.754	(0.568, 0.9)	0.68	(0.526, 0.806)		
b	PF_condom_swr_2014	condom use in regular sex work partnerships in 2014	0.759	(0.481, 0.949)	0.786	(0.641, 0.909)		
b	PF_circum_2050	prevalence of circumcision by 2050	0.724	(0.503, 0.898)	0.726	(0.496, 0.897)		
c	beta_0	per-act probability of HIV transmission β for CD4 > 350 (REF)	0.00131	(0.000498, 0.00251)	0.00174	(0.000934, 0.00288)		
c	Rbeta_acute	relative β during acute infection	6.01	(1.11, 15.0)	9.12	(3.65, 18.1)		
c	Rbeta_350	relative β for 200 < CD4 < 350	1.59	(1.3, 1.9)	1.59	(1.32, 1.91)		
c	Rbeta_200	relative β for CD4 < 350	8.2	(4.5, 13.0)	8.29	(4.61, 12.9)		
c	Rbeta_v1_rec	relative β for receptive vaginal sex	1.5	(1.02, 1.98)	1.49	(1.02, 1.97)		
d	aRbeta_gud_sus	additional relative β for GUD among susceptible partner	2.05	(0.2, 6.0)	2.59	(0.35, 6.65)		
d	aRbeta_gud_inf	additional relative β for GUD among infectious partner	0.99	(0.2, 2.4)	1.16	(0.264, 2.6)		
c	dur_acute	duration of acute infection	0.172	(0.0174, 0.5)	0.3	(0.101, 0.662)		
d	P_gud_fsw_1	prevalence of GUD among lower risk FSW	0.232	(0.1, 0.399)	0.228	(0.111, 0.359)		
d	RP_gud_fsw_h:1	relative prevalence of GUD among higher vs lower risk FSW	3.0	(1.5, 5.0)	2.86	(1.52, 4.42)		
d	RP_gud_2050	relative prevalence of GUD overall in 2050 vs 2020	0.6	(0.22, 0.98)	0.607	(0.22, 0.984)		
c	iP_gud_h:1	interpolator for GUD among medium activity vs DHS and FSW	0.5	(0.025, 0.975)	0.465	(0.0205, 0.971)		
d	Rbeta_uv_ls	relative β on ART but before VLS	0.244	(0.0139, 0.656)	0.245	(0.0146, 0.664)		
d	Rdx_global	relative rate of diagnosis overall	0.75	(0.512, 0.988)	0.67	(0.507, 0.927)		
c	dx_w_2002	rate of diagnosis among women in 2002	0.094	(0.0452, 0.158)	0.094	(0.0447, 0.156)		
c	dx_w_2006	rate of diagnosis among women in 2006	0.248	(0.169, 0.337)	0.246	(0.17, 0.332)		
c	Rdx_m:w_2006	relative rate of diagnosis among men vs women in 2006	0.377	(0.207, 0.597)	0.382	(0.213, 0.603)		
c	dx_wq_2011	rate of diagnosis among non-FSW women in 2011	0.637	(0.466, 0.834)	0.611	(0.463, 0.791)		
c	Rdx_m:wq_2011	relative rate of diagnosis among men vs non-FSW women in 2011	0.529	(0.351, 0.742)	0.508	(0.343, 0.704)		
a	aRdx_fsw_wq_2011	additional relative diagnosis among FSW vs non-FSW women in 2011	0.521	(0.206, 0.98)	0.518	(0.213, 0.966)		
a	aRdx_wq_16:11	additional relative diagnosis among non-FSW women in 2016 vs 2011	0.204	(0.118, 0.313)	0.2	(0.12, 0.307)		
a	aRdx_fsw_wq_2016	additional relative diagnosis among FSW vs non-FSW women in 2016	0.619	(0.291, 1.07)	0.614	(0.289, 1.02)		
a	tx_2010	rate of ART initiation among diagnosed and eligible in 2010	1.5	(0.509, 3.02)	1.46	(0.547, 2.76)		

continued ...

B.4 MODEL CALIBRATION

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... continued

*	Parameter	Definition	Prior		Posterior	
			Mean	(95% CI)	Mean	(95% CI)
	t_{x_2012}	rate of ART initiation among diagnosed and eligible in 2012	8.75	(6.01, 12.0)	8.62	(5.94, 11.8)
	$R_{t_x_fsw:wq}$	relative rate of ART initiation among FSW vs non-FSW women	0.75	(0.512, 0.988)	0.75	(0.517, 0.985)
	i_{vx}	duration on ART before achieving VLs initially	0.62	(0.33, 1.0)	0.642	(0.368, 1.02)
	$Runv_{x_m:wq}$	relative rate of viral unsuppression among men vs non-FSW women	1.25	(1.01, 1.49)	1.25	(1.01, 1.48)
	$Runv_{x_fsw:wq}$	relative rate of viral unsuppression among FSW vs non-FSW women	1.25	(1.01, 1.49)	1.26	(1.01, 1.49)
	rev_{x_2010}	rate of viral re-suppression in 2010	0.729	(0.5, 1.0)	0.708	(0.495, 0.964)

* relational sampling constraints (see § B.4.1); FSW: female sex worker; p12m: past 12 months; β : per-act probability of HIV transmission; GUD: any genital ulcer disease in p12m; ART: antiretroviral therapy; VLs: viral load suppression; additional relative (aR): relative value beyond one, e.g., $R = 1.5 \rightarrow aR = 0.5$; prevalence interpolator (IP): e.g., $IP_x = 0.4, IP_0 = 0.2, P_0 = 0.2, P_1 = 0.4, IP_x = 0.5 \rightarrow P_x = 0.3$; all rates in per-year; all durations in years; all parameters reflect stratum averages.

B.4.2 Results

This section provides additional results to supplement § 3.4.2.

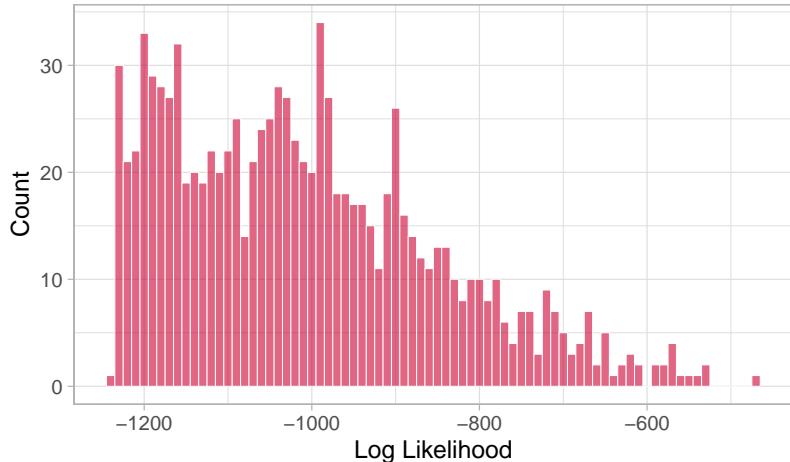


Figure B.8: Distribution of log-likelihoods among model fits

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets).

Figures B.9 and B.10 illustrate the modelled ratios of HIV prevalence and incidence, respectively, between selected risk groups, and associated calibration targets. Figure B.12 similarly illustrates the total Eswatini population size aged 15–49, and Figure B.13 illustrates condom use within each partnership type.

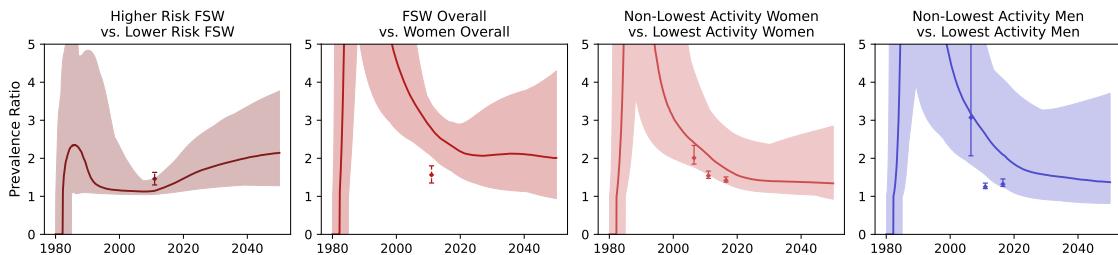


Figure B.9: Modelled HIV prevalence ratios between selected risk groups and associated calibration targets

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

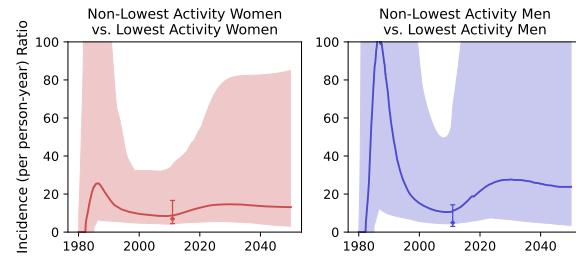


Figure B.10: Modelled HIV incidence ratios between selected risk groups and associated calibration targets

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.



Figure B.11: HIV prevalence data from antenatal care clinics in Eswatini

Figure B.12: Modelled Eswatini population aged 15–49 and associated calibration targets

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

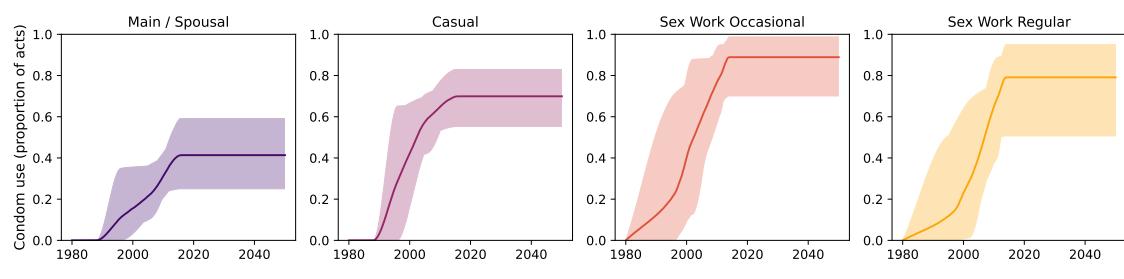


Figure B.13: Modelled condom use within different partnership types

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits.

Appendix C

Supplement to Chapter 4

C.1 Proof that $B_{WPH} \geq B_{BPH}$

In § 4.1.1, I claimed that the per-partnership probability of transmission B is larger for within- vs. between-partnership heterogeneity — $B_{WPH} \geq B_{BPH}$, from Eqs. (4.6) and (4.7), respectively — given the same set of transmission modifiers R_f, α_f . Here is a proof of that claim:

$$\begin{aligned} B_{WPH} &\geq B_{BPH} \\ 1 - \prod_f (1 - \beta_f)^{A\alpha_f} &\geq 1 - \sum_f \alpha_f (1 - \beta_f)^A \end{aligned} \tag{C.1}$$

Let $x_f = (1 - \beta_f)^A$; then

$$\prod_f x_f^{\alpha_f} \leq \sum_f \alpha_f x_f \tag{C.2}$$

Since $\sum_f \alpha_f = 1$ and $\alpha_f \in [0, 1]$ are effectively weights, Eq. (C.2) is the weighted arithmetic mean–geometric mean (AM-GM) inequality [378]. In fact, Aldaz [378] further shows that the gap between B_{WPH} and B_{BPH} increases with the α_f -weighted variance in $\beta_f^{\frac{1}{2}}$ (although the increase is not exact), which supports the results of § 4.3.1 mathematically.

Using Jensen's inequality [517] we can also show that the approach in [162] (and others) to aggregate heterogeneity by HIV infection stage first produces an intermediate per-partnership probability B' :¹

$$B_{WPH} \geq B' \geq B_{BPH}, \quad B' = 1 - (1 - \sum_f \alpha_f \beta_f)^A \tag{C.3}$$

C.2 Model Calibration under Different Approaches

This section illustrates the results of model calibration under the four force of infection approaches explored in § 4.3.3: Effective Partnerships Reduction (**EPA**), Instantaneous Rate-Duration (**IRD**), Instantaneous Rate-1-Year (**IRY**), and Instantaneous Proportion-1-Year (**IPY**). Figures C.1–C.4 illustrate the modelled HIV prevalence, prevalence ratios, incidence, and incidence ratios, plus associated calibration

¹ math.stackexchange.com/questions/4660409

targets, for each approach. Qualitative differences between approaches appear to be minimal, except for lower incidence among FSW in Figure C.3d, as expected (see § 4.3.3.2).

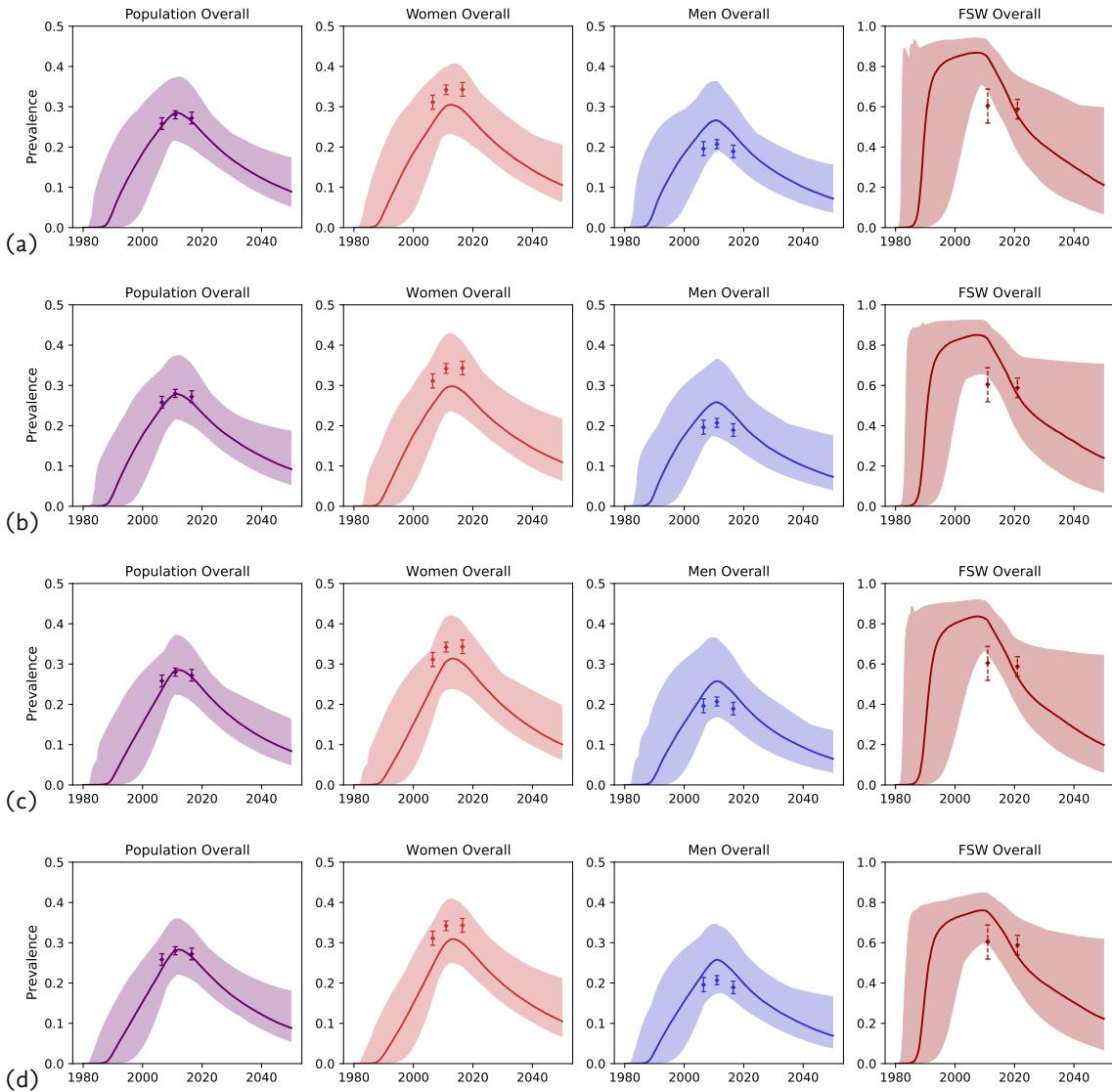


Figure C.1: Modelled HIV prevalence and associated calibration targets under different force of infection approaches

Approaches: (a): EPA; (b): IRD; (c): IRY; (d): IPY; Table 4.1 gives approach definitions; 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

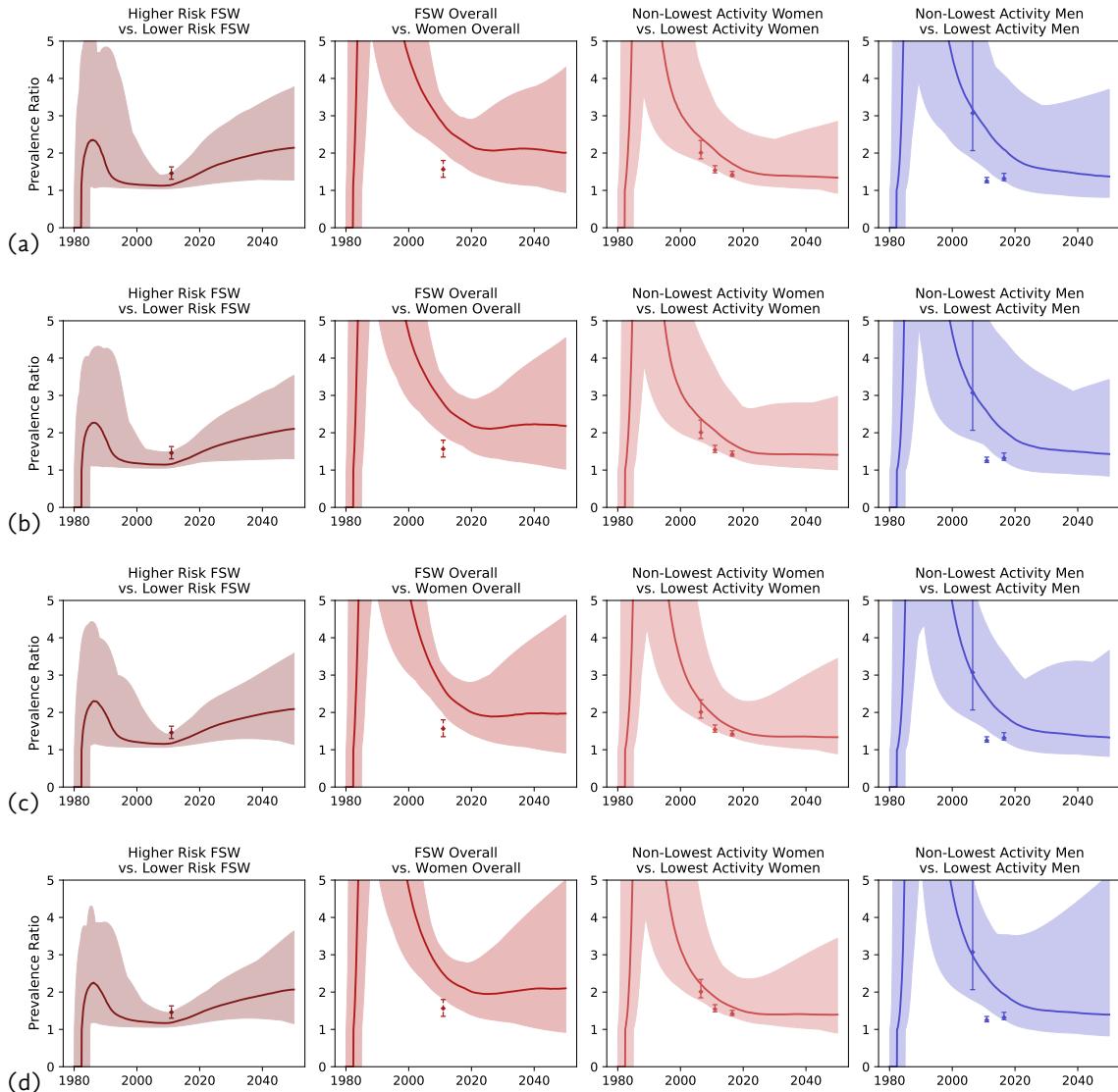


Figure C.2: Modelled HIV prevalence ratios between selected risk groups and associated calibration targets under different force of infection approaches

Approaches: (a): EPA; (b): IRD; (c): IRY; (d): IPY; Table 4.1 gives approach definitions; 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

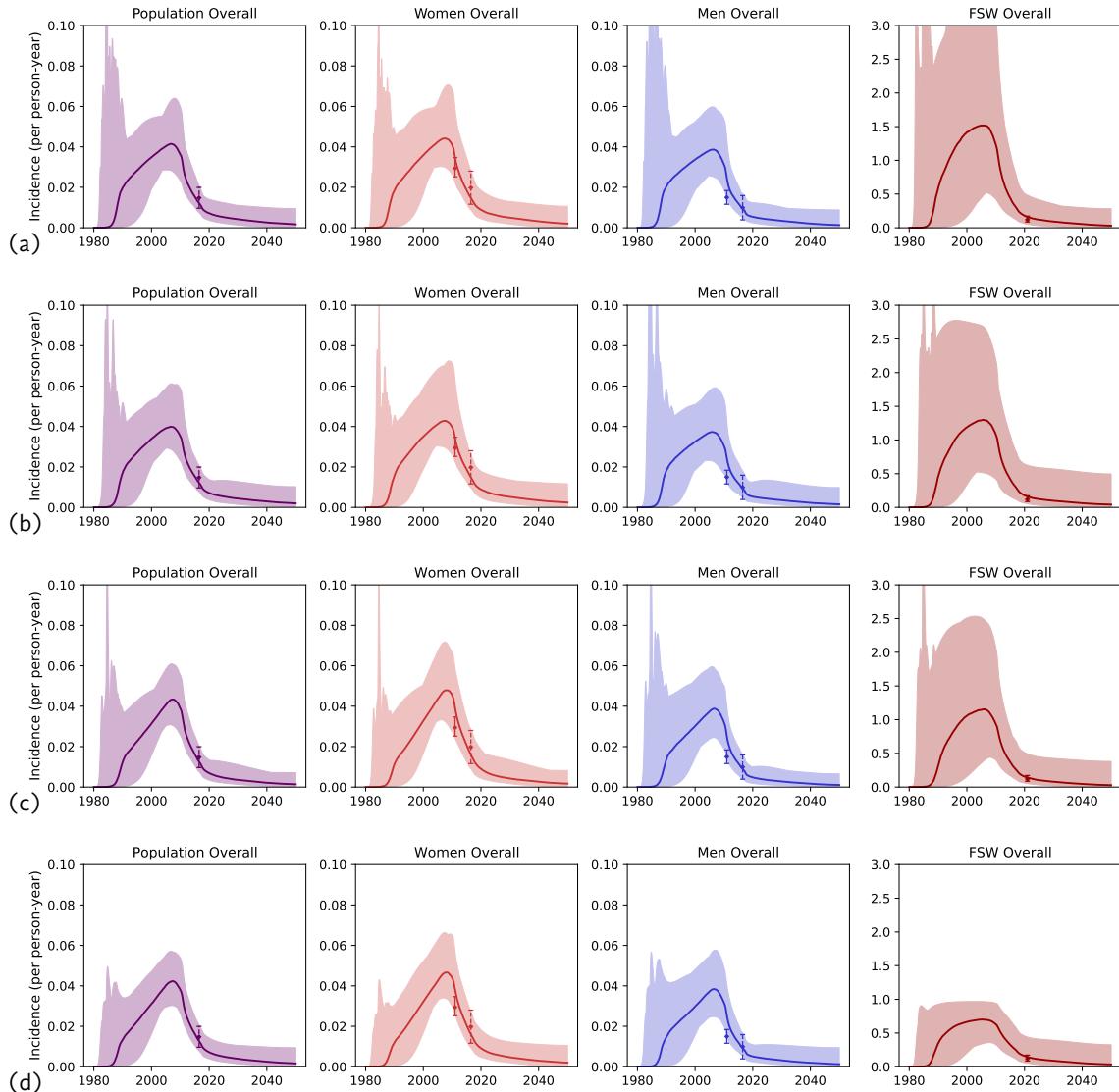


Figure C.3: Modelled HIV incidence and associated calibration targets under different force of infection approaches

Approaches: (a): EPA; (b): IRD; (c): IRY; (d): IPY; Table 4.1 gives approach definitions; 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

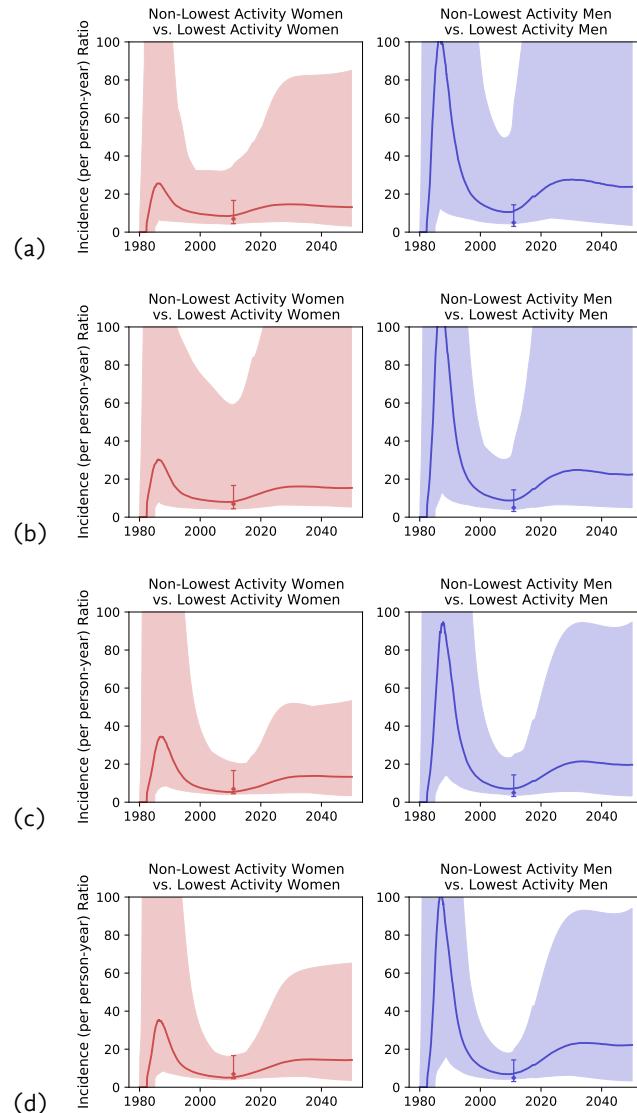


Figure C.4: Modelled HIV incidence ratios between selected risk groups and associated calibration targets under different force of infection approaches

Approaches: (a): EPA; (b): IRD; (c): IRY; (d): IPY; Table 4.1 gives approach definitions; 1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits; points and error bars: mean and 95% CI for each calibration target.

Appendix D

Supplement to Chapter 5

D.1 Objective 1

D.1.1 Scenario Cascades & HIV Incidence

Figure D.1 illustrates cascade attainment over time across the base case and “who is left behind” counterfactual scenarios (Table 5.1) for FSW, clients, everyone else, and the population overall. Transient declines in VLS among treated around 2010 correspond to expanding ART eligibility. Figure D.1 illustrates overall HIV incidence over time across scenarios.

D.1.2 Distributions of Additional Infections

As in § 3.4.3, Figure D.3 illustrates the distributions of additional infections over time vs. the base case across “who is left behind” counterfactual scenarios (Table 5.1), stratified by partnership type, transmitting group, and acquiring group.

D.2 Objective 2

Figure D.4 illustrates the distributions of cascade attainment by 2020 for FSW, clients, everyone else, and the population overall, in the 10,000 randomly generated counterfactual scenarios for the Objective 2 regression analysis.

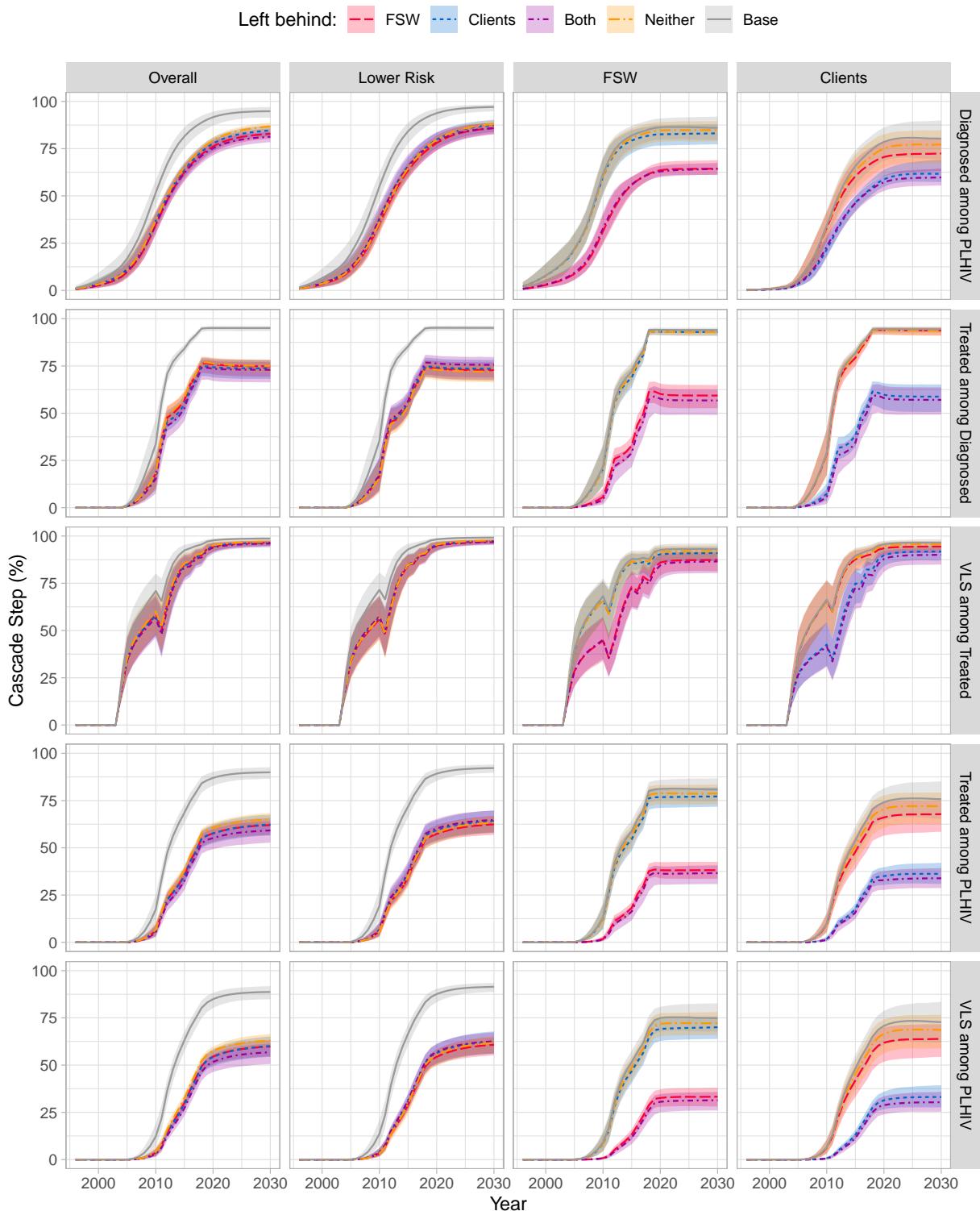


Figure D.1: Cascade attainment over time across scenarios

Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW; PLHIV: people living with HIV; VLS: viral load unsuppressed; Base case: 95-95-95 by 2020; "left behind" counterfactual scenarios: 80-80-90 overall by 2020, with reduced cascade (60-40-80) among FSW, clients of FSW, both, or neither; ribbon and curve: range and median of model fits.

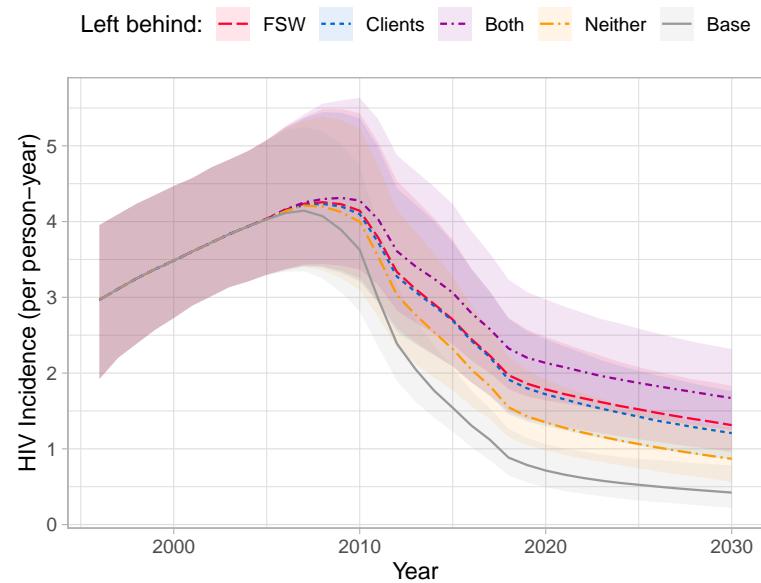


Figure D.2: Overall HIV incidence over time across scenarios

Base case: 95-95-95 by 2020; “left behind” counterfactual scenarios: 80-80-90 overall by 2020, with reduced cascade (60-40-80) among FSW, clients of FSW, both, or neither; ribbon and curve: range and median of model fits.

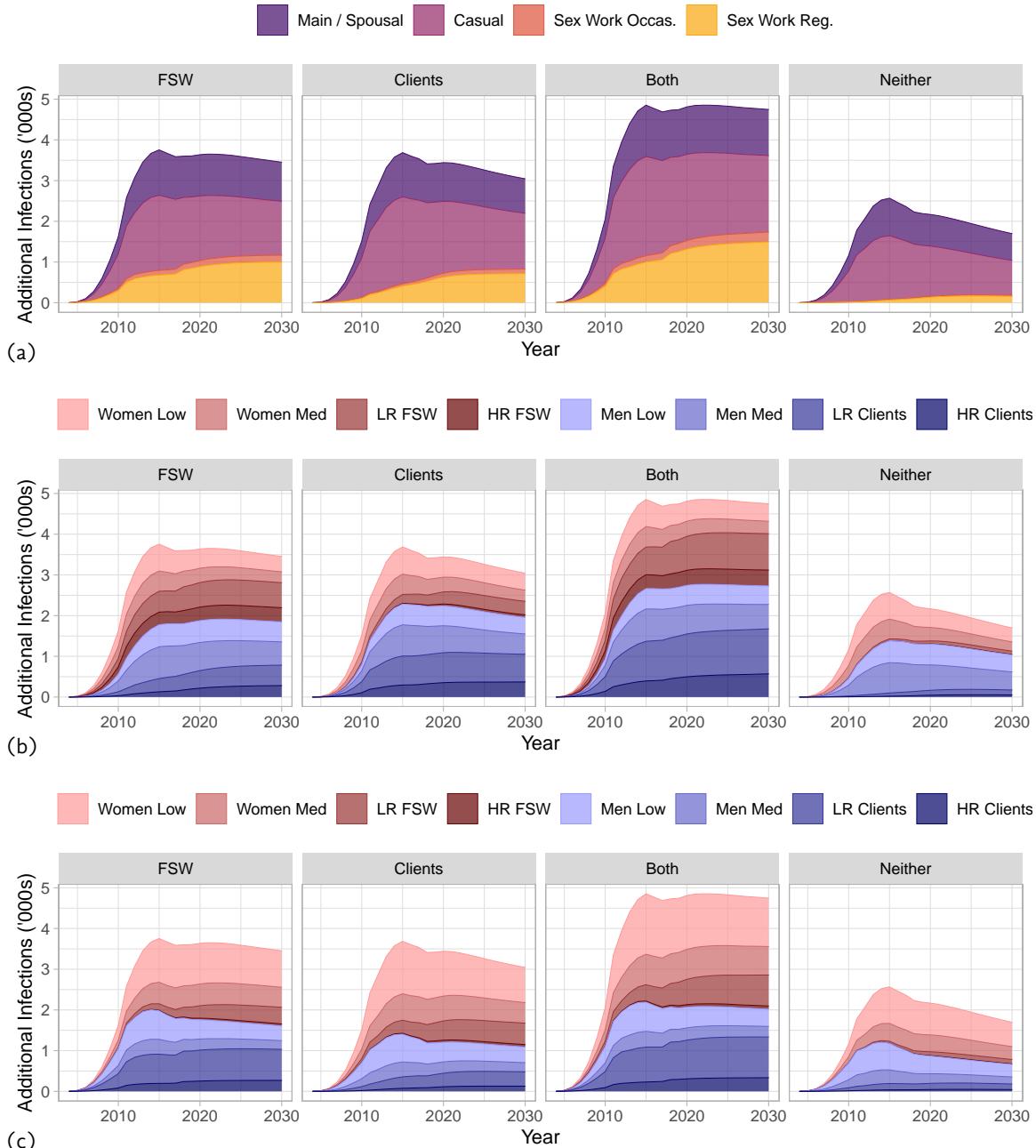


Figure D.3: Additional infections in each “who is left behind” counterfactual scenario vs. the base case, stratified by: (a) partnership type, (b) transmitting group, and (c) acquiring group

Base case: 95-95-95 by 2020; “left behind” counterfactual scenarios: 80-80-90 overall by 2020, with reduced cascade (60-40-80) among FSW, clients of FSW, both, or neither; median numbers of infections across all model fits shown.

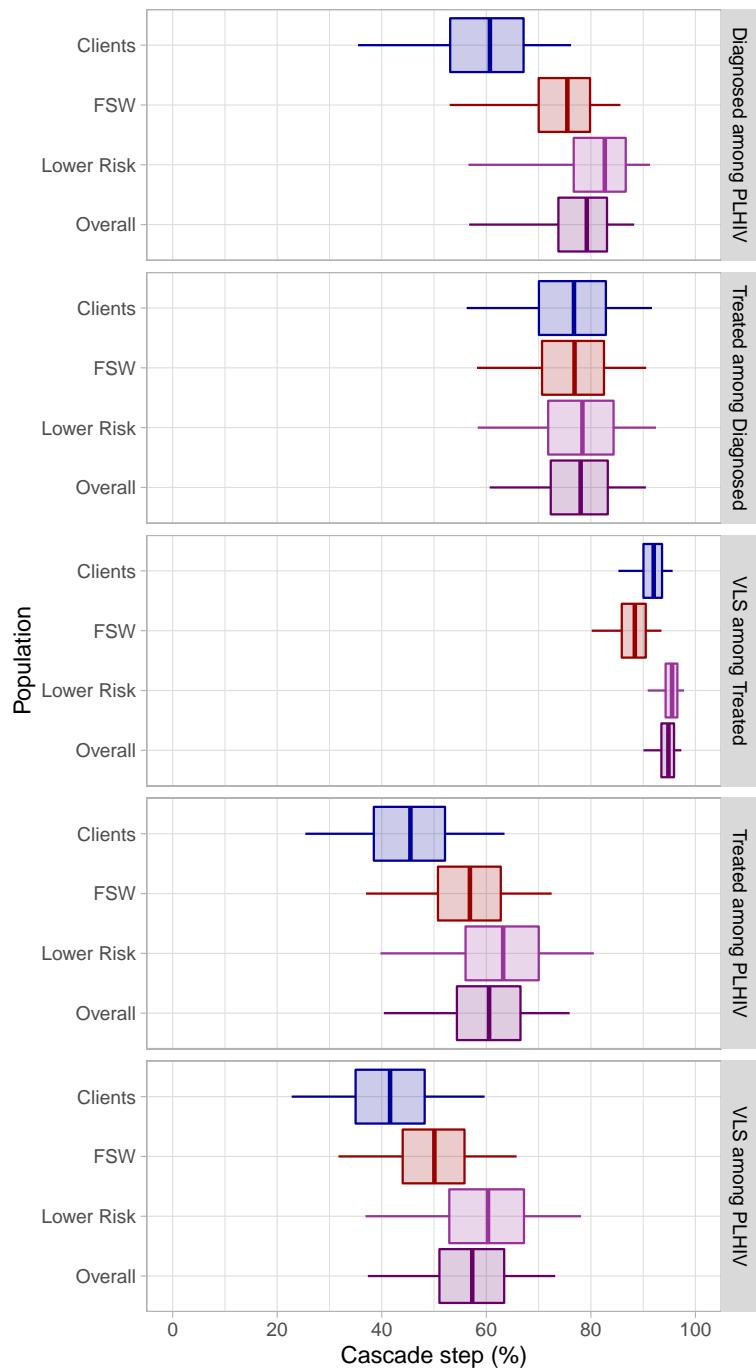


Figure D.4: Cascade attainment by 2020 across 10,000 randomly generated counterfactual scenarios

Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW; PLHIV: people living with HIV; VLS: viral load unsuppressed; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

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