

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



by

Jesse Knight

A thesis submitted in conformity with the requirements  
for the degree of Doctor of Philosophy

Institute of Medical Science  
University of Toronto

© Copyright 2023 by Jesse Knight

Reexamining Assumptions in  
Compartmental Models of Heterosexual HIV Transmission  
applied to Eswatini

Jesse Knight  
Doctor of Philosophy  
Institute of Medical Science  
University of Toronto  
2023

## **Abstract**

TODO

# Acknowledgements

TODO

*slow is smooth*

*smooth is fast*

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	HIV	1
1.1.1	Infection & Natural History	2
1.1.2	Epidemiology of HIV	2
1.1.3	Epidemic Response	4
1.2	Eswatini HIV Epidemic	5
1.2.1	Politics & Society	5
1.2.2	Eswatini HIV Epidemic & Response	6
1.3	Modelling HIV Transmission	8
1.3.1	Deterministic Compartmental Models	8
1.3.2	Applications of Transmission Modelling to Support HIV Response	9
1.3.3	Risk Heterogeneity	10
1.4	Research Questions	11
<b>2</b>	<b>Systematic Review of Compartmental HIV Transmission Model Structures</b>	<b>21</b>
2.1	Introduction	21
2.2	Methods	22
2.2.1	Conceptual Framework for Risk Heterogeneity	22
2.2.2	Search	22
2.2.3	Data Extraction	24
2.3	Results	25
2.3.1	Epidemic Context	25
2.3.2	Heterogeneity Factors	28
2.3.3	ART Prevention Impact	29
2.4	Discussion	31
<b>3</b>	<b>Model Structure, Parameterization, &amp; Calibration</b>	<b>38</b>
3.1	Model Structure	38
3.1.1	Initialization & Solving	39
3.2	Parameterization	40
3.2.1	Risk Heterogeneity Among FSW	41

3.2.2	Probability of HIV Transmission . . . . .	43
3.2.3	Prevalence of Transmission Modifiers . . . . .	47
3.2.4	HIV Progression & Mortality . . . . .	50
3.2.5	Antiretroviral Therapy . . . . .	51
3.2.6	Rates of HIV Diagnosis, ART Initiation, Viral Un-suppression & Re-suppression . . . . .	52
3.2.7	Sex Work: Population Sizes & Partner Numbers . . . . .	56
3.2.8	Non-Sex Work: Group Sizes & Partner Numbers . . . . .	58
3.2.9	Turnover . . . . .	63
3.2.10	Sex Frequency & Partnership Duration . . . . .	65
3.2.11	Mixing . . . . .	67
3.3	Calibration . . . . .	69
3.3.1	Approach . . . . .	69
3.3.2	Calibration Targets . . . . .	70
3.4	Results . . . . .	74
3.4.1	Posterior Parameter Distributions . . . . .	74
3.4.2	Calibration . . . . .	76
3.4.3	Who Infected Whom . . . . .	79
3.5	Discussion . . . . .	82
3.5.1	Methodological Contributions for Model Parameterization . . . . .	82
3.5.2	Limitations of the Model . . . . .	86
<b>4</b>	<b>Modelling HIV Transmission in Sexual Partnerships: Equations and Assumptions</b>	<b>101</b>
4.1	Prior Approaches . . . . .	102
4.1.1	Aggregating Sex Acts within a Partnership . . . . .	102
4.1.2	Heterogeneity in the Per-Act Probability of Transmission . . . . .	103
4.1.3	Aggregating Partnerships . . . . .	105
4.1.4	Revisiting Partnership Duration . . . . .	106
4.1.5	Limitations of Prior Approaches . . . . .	106
4.1.6	Alternate Modelling Frameworks . . . . .	107
4.2	Proposed Approach . . . . .	109
4.2.1	Illustrative Toy Scenario . . . . .	109
4.2.2	Conceptual Development . . . . .	110
4.2.3	Equations . . . . .	111
4.2.4	Transmission via Multiple Partnerships . . . . .	112
4.3	Experiments . . . . .	112
4.3.1	Within- vs. Between-Partnership Heterogeneity . . . . .	112
4.3.2	Partnership Durations . . . . .	113
4.3.3	Comparing Approaches in a Complete Model . . . . .	116
4.4	Discussion . . . . .	122

4.4.1	Heterogeneity in Per-Act Probability of Transmission	122
4.4.2	Beyond Instantaneous Partnerships	123
4.4.3	Transmission-Driven Emergence of Serosorting Patterns	126
4.4.4	Future Work	126
<b>5</b>	<b>Modelling Intersections of Differential Risk and ART Coverage</b>	<b>131</b>
5.1	Introduction	131
5.2	Methods	132
5.2.1	Model	132
5.2.2	Scenarios & Analyses	132
5.3	Results	133
5.4	Discussion	133
<b>6</b>	<b>Conclusion</b>	<b>139</b>
<b>A</b>	<b>Supporting Mathematics</b>	<b>140</b>
A.1	Distributions	140
A.1.1	Fitting Distributions	140
A.1.2	Beta Approximation of the Binomial (BAB) Distribution	140
A.1.3	Joint Sampling with Relational Constraints	141
A.2	Durations	141
A.2.1	Exponential Duration Assumption in Compartmental Models	141
A.2.2	Estimating Duration in Sex Work from Cross Sectional Data	142
A.2.3	Quantifying Partnerships	144
A.3	Miscellaneous	145
A.3.1	Proof that $B_{WPH} \geq B_{BPH}$	145
<b>B</b>	<b>Supplement to Chapter 2</b>	<b>147</b>
B.1	Search Strategy	147
B.1.1	Search Terms	147
B.1.2	Inclusion/Exclusion Criteria	149
B.1.3	Included Studies	150
B.2	Definitions & Extraction	151
B.2.1	Epidemic Context	151
B.2.2	Risk Heterogeneity	151
B.2.3	HIV Natural History	153
B.2.4	Antiretroviral Therapy	153
B.2.5	ART Prevention Impact	154
B.3	Supplemental Results	156
B.3.1	Map	156

- B.3.2 Risk Heterogeneity . . . . . 156
    - B.3.3 ART Prevention Impact . . . . . 159
  - B.4 PRISMA-ScR Checklist . . . . . 163
- C Supplement to Chapter 3 171
  - C.1 Female Sex Worker Data . . . . . 171
  - C.2 Non-Sex Work: Adjusted Partner Numbers . . . . . 173
  - C.3 Model Calibration . . . . . 174
    - C.3.1 Relational Sampling Constraints . . . . . 175
    - C.3.2 Results . . . . . 176
- D Supplement to Chapter 4 179
- E Supplement to Chapter 5 180
  - E.1 Supplementary Results . . . . . 180
    - E.1.1 Scenario Cascades . . . . . 180
    - E.1.2 Distributions of Additional Infections . . . . . 180



# List of Tables

1	Acronyms . . . . .	xiii
1.1	Estimated probability of HIV transmission per 10,000 exposures . . . . .	2
1.2	Main HIV data sources for Eswatini . . . . .	8
2.1	Factors of heterogeneity in HIV transmission and their possible mechanisms of influence on the prevention impact of ART interventions . . . . .	23
2.2	Summary of epidemic contexts within Sub-Saharan Africa where the prevention impacts of ART have been modelled . . . . .	27
2.3	Projected ART prevention impacts, stratified by factors of risk heterogeneity and contexts . . . . .	30
3.1	Overview of model dimensions and stratifications . . . . .	39
3.2	Risk factors explored for association with HIV+ status among FSW in Eswatini . . . . .	43
3.3	Ratios of HIV risk factor variables among higher vs. lower risk FSW in Eswatini . . . . .	44
3.4	Estimates of condom use in Eswatini . . . . .	48
3.5	Estimates of HIV prevalence in Eswatini . . . . .	71
3.6	Estimated HIV prevalence ratios in Eswatini . . . . .	72
3.7	Estimates of HIV incidence in Eswatini . . . . .	73
3.8	Estimated HIV incidence ratios in Eswatini . . . . .	74
3.9	Estimated HIV cascade of care in Eswatini . . . . .	75
4.1	Compared approaches to modelling HIV transmission via sexual partnerships . . . . .	116
5.1	Modelling scenarios defined by 2020 calibration targets . . . . .	132
B.1	Systematic review search terms and hits . . . . .	147
B.2	Systematic review criteria for inclusion and exclusion . . . . .	149
C.1	Definitions of calibrated parameters . . . . .	174

# List of Figures

1.1	Timeline of HIV response in Eswatini . . . . .	7
2.1	PRISMA flowchart of study identification . . . . .	26
2.2	Effect estimates for factors of heterogeneity on incidence reduction (% IR) and cumulative infections averted (% CHI) from linear multivariate regression with generalized estimating equations. . . . .	33
3.1	Model structure and transitions . . . . .	40
3.2	Illustration of time-to-event analysis framework for cross-sectional FSW survey data . . . . .	43
3.3	Predicted conditional effects (probability) of significant variables in multivariate logistic regression models from 2011 and 2014 surveys . . . . .	44
3.4	Reported proportions of women and men aged 15–49, stratified by union status and numbers of partners in the past 12 months . . . . .	59
3.5	Illustration of how women (and equivalently men) are reallocated between union/partners in p12m strata based on odds ratios $\phi$ . . . . .	61
3.6	Distributions of calibrated model parameters, stratified by top 1% (posterior) vs bottom 99% according to calibration likelihood . . . . .	77
3.7	Rank correlations among selected posterior model parameters . . . . .	78
3.8	Modelled HIV prevalence and incidence among selected risk groups and associated calibration targets . . . . .	79
3.9	Modelled ART cascade among selected risk groups and associated calibration targets . . . . .	80
3.10	Absolute numbers and proportions of modelled yearly HIV infections (a) transmitted from and (b) acquired among risk groups in Eswatini . . . . .	81
3.11	Ratio of modelled yearly infections transmitted from vs. acquired among risk groups in Eswatini . . . . .	82
3.12	Absolute numbers and proportions of modelled yearly HIV infections transmitted via different partnership types in Eswatini . . . . .	82
3.13	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 . . . . .	83
4.1	Per-partnership probability of transmission vs. number of acts . . . . .	103
4.2	Representations of health states and sexual partnerships under three different STI modelling frameworks . . . . .	108

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 . . . . .	109
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 . . . .	110
4.5	Average per-partnership probability of transmission $B$ given heterogeneity in the per-act probability of transmission $\beta$ within vs. between partnerships . . . . .	114
4.6	Parameter values ( $\alpha, A$ ) which maximize the difference between the average per-partnership probability of transmission given within- vs. between-partnership heterogeneity . . . . .	115
4.7	Effective probability of transmission per sex act over 1 year vs. total partnership duration . . . . .	115
4.8	HIV incidence among selected risk groups, estimated under different prior force of infection approaches (colours) vs. the new proposed approach using equal model parameters . . . . .	118
4.9	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) . . . . .	119
4.10	TPAF of transmission via different partnership types (horizontal facets), starting from different $t_0$ (vertical facets), estimated under different force of infection approaches (colours) . . . . .	120
4.11	TPAF of transmission from different risk groups (horizontal facets), starting from different $t_0$ (vertical facets), estimated under different force of infection approaches (colours) . . . . .	121
5.1	Relative additional infections under counterfactual scenarios vs. the base case . . . . .	134
A.1	Example distribution fitting validation plot . . . . .	141
A.2	Beta approximation of the binomial distribution (BAB) . . . . .	142
A.3	Illustration of different sampling biases when enforcing $X_1 < X_2 < X_3$ . . . . .	143
A.4	Illustrative steady-state population of 7 FSW, with varying true durations in sex work $\delta$ , vs. the observed durations in sex work $\delta_s$ via cross-sectional survey. . . . .	143
A.5	Illustration of conceptual framework for quantifying partnerships from the number reported during a given recall period . . . . .	145
B.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) . . . . .	156
B.2	Distributions of parameter values and modelling assumptions related to factors of heterogeneity and intervention contexts . . . . .	158
B.3	Projected ART prevention impacts: incidence reduction (IR) and cumulative infections averted (CIA), stratified by factors of heterogeneity and intervention contexts . . . . .	162
C.1	Years since first sold sex among FSW in Eswatini (unadjusted) . . . . .	171
C.2	Cumulative distribution of years selling sex among FSW in Eswatini (RDS-adjusted) . . . . .	172
C.3	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 . . . . .	173
C.4	Distribution of log-likelihoods among model fits . . . . .	176
C.5	Modelled HIV prevalence ratios between selected risk groups and associated calibration targets . . . . .	177

C.6 Modelled HIV incidence ratios between selected risk groups and associated calibration targets . . . . . 177

C.7 HIV prevalence data from antenatal care clinics in Eswatini . . . . . 177

C.8 Modelled Eswatini population aged 15–49 and associated calibration targets . . . . . 177

C.9 Modelled condom use within different partnership types . . . . . 177

E.1 Cascade attainment over time across scenarios . . . . . 181

E.2 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 . . . 182

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)
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
STI	sexually transmitted infection
VMMC	voluntary medical male circumcision
VLS	viral load suppression
WPH	within-partnership heterogeneity
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 epidemic response in numerous ways, such as projecting the impact of interventions [3], and generating fundamental insights about transmission dynamics [4]. These models mechanistically represent the populations, behaviours, probabilities, and interventions involved in transmission [5]. However, such models must make simplifying assumptions in order to remain tractable, and given limited quantity and quality of data [5, 6]. Previous work has shown that *which* assumptions are used can influence model outputs [4, 6–10]. Yet, the potential influence of many modelling assumptions remain unexplored. Therefore, this thesis aims to re-examine several key modelling assumptions and explore their potential influence on model outputs.

The remainder of this chapter introduces key concepts in HIV, including: infection, epidemiology, treatment, and prevention; plus key concepts in mathematical modelling of HIV transmission, including: types of models, applications, fundamental principles, and challenges in choosing assumptions. Special attention is given to the HIV epidemic in Eswatini and among female sex workers specifically, which are major foci in the thesis.

### 1.1 HIV

An estimated 38 million people are living with HIV globally, with 1.5 million new infections annually [11]. However, as discussed below, HIV disproportionately affects particular populations due to intersecting social, economic, and biological vulnerabilities [12, 13]. 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) [14]. However, application of these tools must remain responsive to the unique needs of different populations in order to rapidly and equitably end the epidemic [14].

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

Exposure	Risk <sup>a</sup>	(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 [16]; <sup>a</sup> per 10,000 exposures

### 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, 15]. 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 [15]. Table 1.1 (adapted from [16]) summarizes the average probability of transmission for different unprotected exposures, though transmission risk varies substantially with numerous factors [17].

Following infection, HIV spreads rapidly through the lymphoid system and becomes detectable in the blood within 10 days [15]. 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, 15, 18]. These trends are then reversed by an adaptive immune response, which temporarily suppresses infection, marking the transition from acute to chronic phase [1, 15]. Untreated asymptomatic chronic infection typically lasts multiple years, as HIV evades clearance and CD4 T cells are progressively depleted [15]. 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 [19] — and with re-increasing viral load [1, 15]. HIV infection also increases the risk of other diseases and mortality, with multiple hypothesized mechanisms [20].

### 1.1.2 Epidemiology of HIV

While global adult HIV prevalence is estimated at 0.7%, national estimates range from <0.1 to 28% [11]. Sub-Saharan Africa (SSA) bears the largest burden, with an estimated two-thirds of all current infections and over half of all new infections [11]. 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 [11, 21]. 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 [22–24].

### 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 [12, 13, 25–30]. 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 [31–36]. HIV disproportionately affects these populations due to intersections of behavioural risks, stigma, criminalization, violence, and poverty [12]. For example, women often enter sex work out of food/economic insecurity [28]. Then, criminalization of sex work leaves women vulnerable to sexual violence (including by police) and arrest for carrying condoms, or condom confiscation [28, 29]. 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 [37, 38].

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 even in higher prevalence SSA epidemics [27]. Higher numbers of sexual partners increases risk directly via more potential exposures, but also via co-transmission of other sexually transmitted infections (STIs) [28]. Some clients may also pay more for condomless and/or anal sex, or perpetrate sexual violence [28, 29]. Women, especially young women, also have increased biological susceptibility to HIV due to physical and immunological genital differences [39]. These vulnerabilities can be amplified through multiple structural factors noted above, as well as patriarchal attitudes [28, 29].

The contribution of transmission among key populations and via sex work is often suggested to be small in “generalized” epidemics [40, 41]. However, such analyses typically rely on biased household-based face-to-face survey data [42, 43], generic behavioural assumptions [41], and simplistic methodology which fails to account for onward transmission [44]. In fact, transmission models are among the best tools to capture the large indirect benefits of interventions prioritizing key population needs [44, 45]; such models have often found that these interventions are most cost effective [46–48].

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 [29, 49, 50]. 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 [12, 51]. 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 [43, 51, 52]. 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 [53–55]. 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) [56]. 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 [57].



### 1.1.3 Epidemic Response

HIV infection has been stigmatized since the earliest days of the epidemic; efforts to raise awareness and funding for HIV research and services are rooted in activism [58]. 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 [59], including: UNAIDS (Joint United Nations Programme on HIV and AIDS), PEPFAR (President's Emergency Plan for AIDS Relief), and the Global Fund (to Fight AIDS, Tuberculosis and Malaria). These funds support numerous prevention and treatment tools [14], which are ideally prioritized according epidemic drivers and cost effectiveness. However, understanding these drivers and estimating intervention impacts — where transmission modelling plays a key role — remains controversial [60–63].

#### 1.1.3.1 Prevention

The earliest efforts to prevent sexual transmission of HIV focused on condom promotion, behaviour change, voluntary counselling and testing (VTC), and treatment of other sexually transmitted infections (STIs) [64, 65]. The role of broader structural factors like economic and political stability, gender equality, and criminalization were also recognized early on [66]. Voluntary medical male circumcision (VMMC) is also protective [67], and has been recommended in some contexts since 2007 [68]. 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” [69]. 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 [60, 63, 70].

#### 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 [71]. This reservoir is then maintained against clearance mechanisms via viral replication and clonal expansion of latently infected cells [1, 71]. 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) [15, 20, 72].

Numerous antiretroviral agents are now available, which have multiple mechanisms of interrupting viral replication [1, 19]. 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 [19]. Since turnover of free virus in blood occurs rapidly (mean generation time estimated as 2.6 days) [73], ART initially reduces blood viral loads rapidly [1, 74]. Subsequent reductions are more gradual, and time to “undetectable” viral load (defined here as < 80 viral RNA copies per mL of blood)<sup>1</sup> is estimated as median 3.1 [IQR: 2.8, 5.5] months [75]. Recovery of CD4 T cells is even slower, and complete recovery to baseline levels is rare [1, 76].

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

**Treatment Eligibility & Benefits.** Early 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) [77], for whom ART is most beneficial [1, 78].<sup>2</sup> However, studies have since highlighted health benefits of earlier ART initiation [80–83], and WHO has progressively expanded recommended eligibility criteria, culminating in the 2016 “treat all” recommendation [19, 77, 84, 85]. Expanding eligibility has coincided with growing recognition of additional benefits of ART for preventing transmission, as demonstrated in several trials of serodiscordant couples [86–88]. This recognition, along with model-based predictions [3, 89], then motivated several large-scale studies of “treatment as prevention” designed to estimate the population-level incidence reduction achievable via ART scale-up [90–92]. Unfortunately, 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 [14, 63, 93, 94]. Improving ART coverage for individual-level and partnership-level benefits nevertheless remains a distinct goal [95].

**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 [96], the most basic cascade is defined as 3 steps: HIV diagnosis, ART initiation, and viral suppression [97]. These steps then form the basis of UNAIDS targets: 90-90-90 by 2020 [97] and 95-95-95 by 2030 [95], 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 [11], although differences across risk groups — and their potential implications for “treatment as prevention” — are increasingly highlighted [93, 98, 99].

## 1.2 Eswatini HIV Epidemic

Eswatini<sup>3</sup> 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 [100]. Since approximately 2004, Eswatini has had the highest HIV prevalence in the world (among ages 15–49), estimated to be 28% in 2021 [11, 100]. Even within this context, burden of HIV among FSW remains even higher, estimated around 60% in 2011 and 2021 [101, 102]. Yet, Eswatini was also recently among the first countries in SSA to achieve the UNAIDS 95-95-95 ART cascade goals [11, 95]. 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.

### 1.2.1 Politics & Society

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) [103]. Political

<sup>2</sup> 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 [79].

<sup>3</sup> Officially the *Kingdom of Eswatini*, and formerly known as *Swaziland* until 2018.

parties have been officially banned since 1973, and the monarchy retains powers to dissolve parliament, veto bills, and appoint the prime minister, cabinet, some House members and most Senators [104]. Socioeconomic inequality is high [105, 106] (e.g., Gini index consistently above 0.50 [100]) and lavish expenditures by the royal family have been criticized [103, 105]. Some authors have argued that cultural traditions and institutions have been appropriated to entrench and legitimize royal power [105, 107]. Although freedoms of expression remain severely restricted [103, 105], trade unions act as proxies for political parties, and calls for democratic reform have recently grown [103–105]. Pro-democracy protests have been met with violence [108], and the political trajectory of Eswatini is currently uncertain [104]. Patriarchal norms are strong and domestic violence is common in Eswatini [107, 109–112]. Husbands often earn and control most/all household income, and women prioritize “honour in marriage and performance of being a good wife” [112]. Moreover, 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 [112]. Such barriers can evidently cause substantial delays in accessing HIV treatment [112]. Food and/or economic insecurity is also a major driver of transactional sex and sex work [28].

Key populations are criminalized in Eswatini, including anybody buying or selling sex, engaging in same-sex sex acts, or possessing drugs [113]. 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 [12]. Despite the recognized importance of meeting these populations’ prevention needs [114], specific services were not prioritized for this purpose until approximately 2009 [115].

### 1.2.2 Eswatini HIV Epidemic & Response

The exact timing of HIV introduction to specific countries in SSA, including Eswatini, remains unclear [116]. The first cases of HIV and AIDS in Eswatini were diagnosed in 1986 and 1987, respectively [117].

TODO

Figure 1.1 gives a timeline of major events in the Eswatini epidemic response.

#### 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 [101, 118], for which individual-level data were obtained and analyzed directly.

**General Population.** The 2006–07 Demographic and Health Survey (DHS) [119] 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 Swaziland HIV Incidence Measurement Surveys (SHIMS) in 2010–11 [120] and 2016–17 [121] were conducted with the aim of estimating population-level incidence before and after national scale-up of

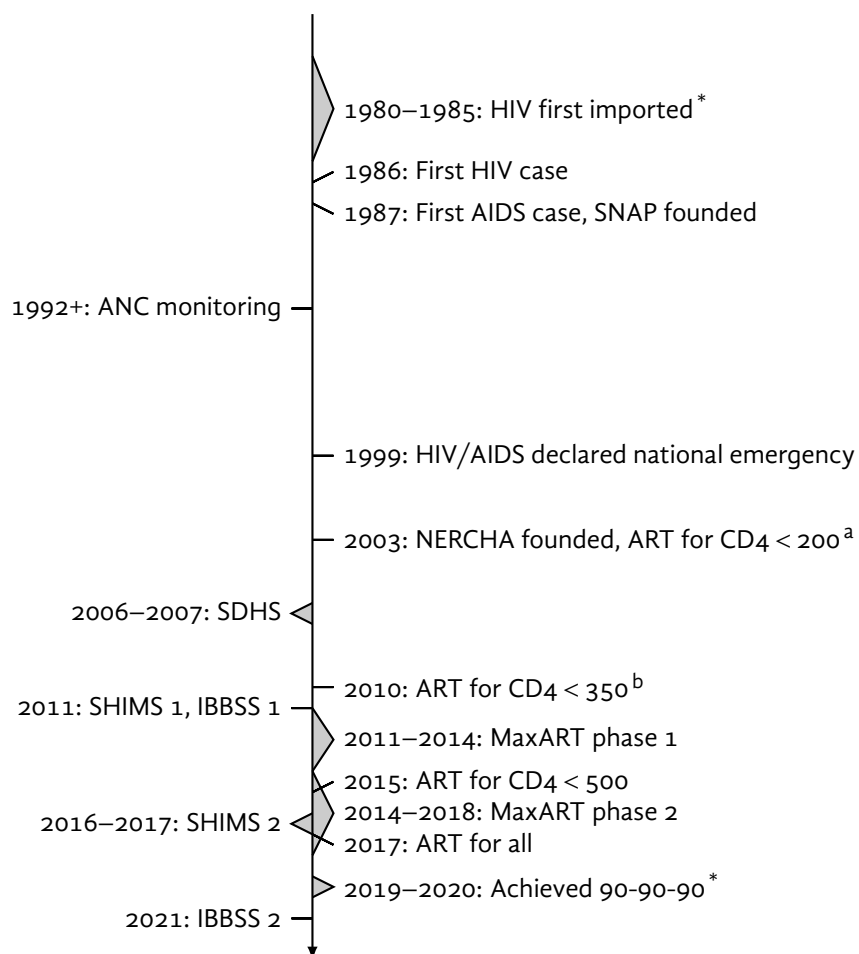


Figure 1.1: Timeline of HIV response in Eswatini

\* approximate dates; <sup>a</sup> plus CD4 < 350 and WHO stage III, or any CD4 and WHO stage IV; <sup>a</sup> 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 [15, Figure 3] for a timeline of global HIV response.

Table 1.2: Main HIV data sources for Eswatini

Ref	ID	Dates <sup>a</sup>	Population <sup>b</sup>	N <sup>c</sup>	HIV <sup>d</sup>
[119]	DHS'06	07/06–02/07	GP 15+	9,143	P
[120]	SHIMS1	12/10–06/11	GP 18–49	18,169	P, I
[121]	SHIMS2	08/16–03/17	GP 15+	9,146	P, I
[101]	KP'11	09/11–10/11	KP 15+	328	P
[118]	KP'14	09/14–01/15	KP 18+	781	—
[102]	KP'21	10/20–01/21	KP 18+	676	P, I

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

voluntary medical male circumcision. 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 [120], a large prospective 6-month cohort was used to estimate incidence and validate recency testing [122] as a cross-sectional measure of incidence, whereas in SHIMS2 [121], 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 & Men who Have Sex with Men.

TODO

## 1.3 Modelling HIV Transmission

Mathematical models of infectious disease transmission date back at least 100 years [123]. 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 [124]. Despite the limitations associated with these assumptions [8, 125], 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  $t$ ;  $\theta$  is a set of model parameters; and  $f_i$  defines the rate of change in  $y_i$  as a function of all other  $y$ ,  $\theta$ , 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  $\eta_k$ , then  $f_k$  would include a term  $-\eta_k y_k$  and  $f_{k+1}$  would include  $+\eta_k y_k$ .<sup>4</sup> 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 [123]. However, most modern DCMs must be solved computationally, for which many techniques and software packages exist (e.g., see footnote 9).

### 1.3.2 Applications of Transmission Modelling to Support HIV Response

Modelling of HIV transmission began shortly after discovery of the virus [126]. Early models focused on generating mechanistic insights into key determinants of epidemic dynamics [124, 127]. However, by now such models have been used in numerous applications to support epidemic response, including:

- generating mechanistic insights about epidemic dynamics [4, 10, 128]
- projecting HIV incidence, prevalence, mortality, etc. [129, 130]
- quantifying the contribution of particular contexts of transmission [131, 132]
- inferring parameter values through model fitting [8, 133]
- projecting the impact of interventions, and combinations thereof [3, 134, 135]
- uncertainty and sensitivity analysis of model outputs [7, 9, 136] or clinical trial results [137]
- and economic analyses [138–140]

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 [17, 133, 141, 142]. As model complexity and applications to specific policy questions have grown, so too has healthy scrutiny of modelling assumptions [44, 62, 130]. 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.

<sup>4</sup> A constant transition rate also implies an exponentially-distributed duration in the originating state; see § A.2.1 for further details.

### 1.3.3 Risk Heterogeneity

The central role of individuals with more sexual partners in STI/HIV transmission has long been recognized in so-called “core group theory” [143–145]. 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 [146], and can even be considered to comprise phenomena like superspreading events [147]. 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  $\mu$  and  $\sigma^2$  are the mean and variance of contact rates [126]; under like-with-like mixing by risk,  $R_0$  increases further [148].
- Endemic “equilibrium” prevalence is lower with vs. without risk heterogeneity [126];<sup>5</sup> 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 [126].
- Turnover of individuals in/out of risk states/groups, sometimes called “episodic risk”, mediates the influence of risk heterogeneity on epidemic dynamics [144]; where slow turnover can contribute to “sustaining populations” with high infection prevalence [145], 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 [44]; unfortunately, power asymmetries and stigma often undermine efforts to prioritize resources to marginalized higher risk groups [45, 149, 150].

#### 1.3.3.1 Where to Draw the Line

The importance of risk heterogeneity is evidently 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?*” [146]. The answers to such questions likely depend on both the modelled context and application. This uncertainty

<sup>5</sup> Many modelling analyses have explored infectious disease “equilibrium”; such analyses may offer theoretical insights, but are likely of limited value for applied modelling, due to numerous dynamic conditions and interventions which preclude epidemic stabilization.

in appropriate model specification is sometimes called “structural uncertainty” [9, 146]. Note that, 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., [151]).

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].<sup>6</sup> 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 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.<sup>7</sup> 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** during data analyses and model implementation.*

For example: survey data may give the numbers of sexual partners reported by respondents in the past 12 months, but these data may be interpreted in different ways to actually specify model parameters. 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.

Thus, the overarching research question of this thesis is:

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

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), causal inference (e.g., comparison of intervention scenarios), and qualitative interpretation of a collection of results.

<sup>6</sup> Notably, [7] and several other works [3] were effectively a direct response to an (in)famous study [89] that made bold conclusions based on a very simple model with little justification for model design or parameterization.

<sup>7</sup> What is a PhD research proposal if not overambitious?



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 Eswatini epidemic context, through the following specific aims, each reflecting a chapter in 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 and equations on model-estimated HIV incidence 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.

## References

- [1] Gary Maartens, Connie Celum, and Sharon R. Lewin. "HIV infection: Epidemiology, pathogenesis, treatment, and prevention". *The Lancet* 384.9939 (2014), pp. 258–271. [https://doi.org/10.1016/S0140-6736\(14\)60164-1](https://doi.org/10.1016/S0140-6736(14)60164-1).
- [2] GBD 2019 Diseases and Injuries Collaborators. "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019". *The Lancet* 396.10258 (2020), pp. 1204–1222. [https://doi.org/10.1016/S0140-6736\(20\)30925-9](https://doi.org/10.1016/S0140-6736(20)30925-9).
- [3] Jeffrey W. Eaton et al. "HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001245. <https://doi.org/10.1371/journal.pmed.1001245>.
- [4] G P Garnett and R M Anderson. "Factors controlling the spread of HIV in heterosexual communities in developing countries: Patterns of mixing between different age and sexual activity classes". *Philosophical Transactions of the Royal Society B: Biological Sciences* 342.1300 (1993), pp. 137–159. <http://www.ncbi.nlm.nih.gov/pubmed/7904355>.
- [5] Geoffrey P. Garnett et al. *Mathematical models in the evaluation of health programmes*. 2011.
- [6] Sharmistha Mishra et al. "Data and methods to characterize the role of sex work and to inform sex work programs in generalized HIV epidemics: evidence to challenge assumptions". *Annals of Epidemiology* 26.8 (2016), pp. 557–569. <https://doi.org/10.1016/j.annepidem.2016.06.004>.
- [7] Jan A.C. C. Hontelez et al. "Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study". *PLOS Medicine* 10.10 (2013). Ed. by Nathan Ford, e1001534. <http://doi.org/10.1371/journal.pmed.1001534>.
- [8] Leigh F. Johnson and Nathan Geffen. "A Comparison of two mathematical modeling frameworks for evaluating sexually transmitted infection epidemiology". *Sexually Transmitted Diseases* 43.3 (2016), pp. 139–146. <http://doi.org/10.1097/OLQ.0000000000000412>.
- [9] Cora L. Bernard and Margaret L. Brandeau. "Structural sensitivity in HIV modeling: A case study of vaccination". *Infectious Disease Modelling* 2.4 (2017), pp. 399–411. <https://doi.org/10.1016/j.idm.2017.08.002>.
- [10] Jesse Knight et al. "Contribution of high risk groups' unmet needs may be underestimated in epidemic models without risk turnover: A mechanistic modelling analysis". *Infectious Disease Modelling* 5 (2020), pp. 549–562. <https://doi.org/10.1016/j.idm.2020.07.004>.
- [11] UNAIDS. *AIDSinfo*. 2023. <http://aidsinfo.unaids.org>.
- [12] WHO. *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. 2016. <https://www.who.int/hiv/pub/guidelines/keypopulations-2016/>.
- [13] Harry Jin, Arjee Restar, and Chris Beyrer. "Overview of the epidemiological conditions of HIV among key populations in Africa". *Journal of the International AIDS Society* 24.S3 (2021), e25716. <https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25716> <https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25716> <https://onlinelibrary.wiley.com/doi/10.1002/jia2.25716>.
- [14] Robert W. Eisinger, Gregory K. Folkers, and Anthony S. Fauci. "Ending the Human Immunodeficiency Virus Pandemic: Optimizing the Prevention and Treatment Toolkits". *Clinical Infectious Diseases* 69.12 (2019), pp. 2212–2217. <https://doi.org/10.1093/cid/ciz998>.
- [15] Steven G. Deeks et al. "HIV infection". *Nature Reviews Disease Primers* 1.1 (2015), pp. 1–22. <https://doi.org/10.1038/nrdp.2015.35>.
- [16] Pragna Patel et al. "Estimating per-act HIV transmission risk: A systematic review". *AIDS* 28.10 (2014), pp. 1509–1519. <https://doi.org/10.1097/QAD.0000000000000298>.
- [17] Marie Claude Boily et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". *The Lancet Infectious Diseases* 9.2 (2009), pp. 118–129. [https://doi.org/10.1016/S1473-3099\(09\)70021-0](https://doi.org/10.1016/S1473-3099(09)70021-0).
- [18] Myron S. Cohen et al. "Acute HIV-1 Infection". *New England Journal of Medicine* 364.20 (2011), pp. 1943–1954. <https://doi.org/10.1056/NEJMr1011874>.
- [19] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland, 2016. <https://www.who.int/hiv/pub/arv/arv-2016>.

- [20] Andrew N. Phillips, James Neaton, and Jens D. Lundgren. "The role of HIV in serious diseases other than AIDS". *AIDS* 22.18 (2008), pp. 2409–2418. <https://doi.org/10.1097/QAD.0B013E3283174636>.
- [21] Peter H. Kilmarx. "Global epidemiology of HIV". *Current Opinion in HIV and AIDS* 4.4 (2009), pp. 240–246. <https://doi.org/10.1097/coh.0b013e32832c06db>.
- [22] Sharmistha Mishra et al. "HIV epidemic appraisals for assisting in the design of effective prevention programmes: Shifting the paradigm back to basics". *PLoS ONE* 7.3 (2012), e32324. <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0032324>.
- [23] Frank Tanser et al. "Concentrated HIV subepidemics in generalized epidemic settings". *Current Opinion in HIV and AIDS* 9.2 (2014), pp. 115–125. <https://doi.org/10.1097/COH.000000000000034>.
- [24] Marie Claude Boily et al. "What really is a concentrated HIV epidemic and what does it mean for West and Central Africa? Insights from mathematical modeling". *Journal of Acquired Immune Deficiency Syndromes* 68 (2015), S74–S82. <https://doi.org/10.1097/QAI.0000000000000437>.
- [25] Bradley M. Mathers et al. "Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review". *The Lancet* 372.9651 (2008), pp. 1733–1745. [https://doi.org/10.1016/S0140-6736\(08\)61311-2](https://doi.org/10.1016/S0140-6736(08)61311-2).
- [26] Chris Beyrer et al. "Global epidemiology of HIV infection in men who have sex with men". *The Lancet* 380.9839 (2012), pp. 367–377. [https://doi.org/10.1016/S0140-6736\(12\)60821-6](https://doi.org/10.1016/S0140-6736(12)60821-6).
- [27] Stefan Baral et al. "Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis". *The Lancet Infectious Diseases* 12.7 (2012), pp. 538–549. [https://doi.org/10.1016/S1473-3099\(12\)70066-](https://doi.org/10.1016/S1473-3099(12)70066-).
- [28] Fiona Scorgie et al. "Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review". *AIDS and Behavior* 16.4 (2012), pp. 920–933. <https://doi.org/10.1007/s10461-011-9985-z>.
- [29] Kate Shannon et al. "Global epidemiology of HIV among female sex workers: Influence of structural determinants". *The Lancet* 385.9962 (2015), pp. 55–71. [https://doi.org/10.1016/S0140-6736\(14\)60931-4](https://doi.org/10.1016/S0140-6736(14)60931-4).
- [30] Leonard S. Rubenstein et al. "HIV, prisoners, and human rights". *The Lancet* 388.10050 (2016), pp. 1202–1214. [https://doi.org/10.1016/S0140-6736\(16\)30663-8](https://doi.org/10.1016/S0140-6736(16)30663-8).
- [31] Catherine E. Oldenburg et al. *Global burden of HIV among men who engage in transactional sex: A systematic review and meta-analysis*. 2014. <https://doi.org/10.1371/journal.pone.0103549>.
- [32] Joyce Wamoyi et al. "Transactional sex and risk for HIV infection in sub-Saharan Africa: a systematic review and meta-analysis". *Journal of the International AIDS Society* 19.1 (2016), p. 20992. <https://doi.org/10.7448/IAS.19.1.20992>.
- [33] Carol S. Camlin and Edwin D. Charlebois. *Mobility and its Effects on HIV Acquisition and Treatment Engagement: Recent Theoretical and Empirical Advances*. 2019. <https://doi.org/10.1007/s11904-019-00457-2>.
- [34] Eve Cheuk et al. "Transitions: Novel Study Methods to Understand Early HIV Risk Among Adolescent Girls and Young Women in Mombasa, Kenya, and Dnipro, Ukraine". *Frontiers in Reproductive Health* 2 (2020), p. 10. <https://doi.org/10.3389/frph.2020.00007>.
- [35] Suzanne Day et al. *Adolescent participation in HIV research: consortium experience in low and middle-income countries and scoping review*. 2020. [https://doi.org/10.1016/S2352-3018\(20\)30269-1](https://doi.org/10.1016/S2352-3018(20)30269-1).
- [36] Aleya Khalifa et al. "Associations between Mobility, Food Insecurity, and Transactional Sex among Women in Cohabiting Partnerships: An Analysis from 6 African Countries 2016–2017". *Journal of Acquired Immune Deficiency Syndromes* 90.4 (2022), pp. 388–398. <https://doi.org/10.1097/QAI.0000000000002995>.
- [37] Kathryn E. Lancaster et al. "HIV care and treatment experiences among female sex workers living with HIV in sub-Saharan Africa: A systematic review". *African Journal of AIDS Research* 15.4 (2016), pp. 377–386. <https://doi.org/10.2989/16085906.2016.1255652>.
- [38] Alexandra Spyrelis and Latifat Ibisomi. "'It is just a lot to deal with': A qualitative study exploring the sexual and reproductive health needs of a sample of female sex workers in six locations in Southern Africa". *African Journal of Reproductive Health* 26.5 (2022), pp. 72–80. <https://doi.org/10.29063/ajrh2022/v26i5.8>.
- [39] Tae Joon Yi et al. "Genital immunology and HIV susceptibility in young women". *American Journal of Reproductive Immunology* 69.S1 (2013), pp. 74–79. <http://doi.wiley.com/10.1111/aji.12035>.

- [40] P. M. Leclerc and M. Garenne. "Commercial sex and HIV transmission in mature epidemics: A study of five African countries". *International Journal of STD and AIDS* 19.10 (2008), pp. 660–664. <http://journals.sagepub.com/doi/10.1258/ijsa.2008.008099>.
- [41] Zara Shubber et al. "The HIV modes of transmission model: A systematic review of its findings and adherence to guidelines". *Journal of the International AIDS Society* 17.1 (2014), p. 18928. <http://doi.wiley.com/10.7448/IAS.17.1.18928>.
- [42] Lisa F. Langhaug, Lorraine Sherr, and Frances M. Cowan. "How to improve the validity of sexual behaviour reporting: Systematic review of questionnaire delivery modes in developing countries: Systematic Review". *Tropical Medicine and International Health* 15.3 (2010), pp. 362–381. <https://doi.org/10.1111/j.1365-3156.2009.02464.x>.
- [43] Catherine M. Lowndes et al. "Polling booth surveys: A novel approach for reducing social desirability bias in HIV-related behavioural surveys in resource-poor settings". *AIDS and Behavior* 16.4 (2012), pp. 1054–1062. <https://doi.org/10.1007/s10461-011-0004-1>.
- [44] Sharmistha Mishra et al. "Validation of the modes of transmission model as a tool to prioritize HIV prevention targets: A comparative modelling analysis". *PLOS ONE* 9.7 (2014).
- [45] Lawrence C Long et al. "Getting resources to those who need them : the evidence we need to budget for underserved populations in sub-Saharan Africa". *J Int AIDS Soc* 24 (2021), pp. 67–72. <https://doi.org/10.1002/jia2.25707>.
- [46] Robyn M. Stuart et al. *How should HIV resources be allocated? Lessons learnt from applying optima HIV in 23 countries*. 2018. <https://doi.org/10.1002/jia2.25097>.
- [47] Mathieu Maheu-Giroux et al. "Cost-Effectiveness of Accelerated HIV Response Scenarios in Cote d'Ivoire". *Journal of Acquired Immune Deficiency Syndromes* 80.5 (2019), pp. 503–512. <https://doi.org/10.1097/QAI.0000000000001956>.
- [48] Leigh F. Johnson et al. "Optimal HIV testing strategies for South Africa: a model-based evaluation of population-level impact and cost-effectiveness". *Scientific Reports* 9.1 (2019), p. 12621. <https://www.nature.com/articles/s41598-019-49109-w>.
- [49] Chris Beyrer et al. *An action agenda for HIV and sex workers*. 2015. [https://doi.org/10.1016/S0140-6736\(14\)60933-8](https://doi.org/10.1016/S0140-6736(14)60933-8).
- [50] Chris Beyrer et al. "The global response to HIV in men who have sex with men". *The Lancet* 388.10040 (2016), pp. 198–206. [https://doi.org/10.1016/S0140-6736\(16\)30781-4](https://doi.org/10.1016/S0140-6736(16)30781-4).
- [51] UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. *Guidelines on Estimating the Size of Populations Most at Risk to HIV*. Geneva, Switzerland, 2010.
- [52] Abu S Abdul-Quader, Andrew L Baughman, and Wolfgang Hladik. *Estimating the size of key populations: Current status and future possibilities*. 2014. <http://doi.org/10.1097/COH.0000000000000041>.
- [53] Anna Grimsrud et al. "Reimagining HIV service delivery: the role of differentiated care from prevention to suppression". *Journal of the International AIDS Society* 19.1 (2016). <https://doi.org/10.7448/ias.19.1.21484>.
- [54] Peter Ehrenkranz, Anna Grimsrud, and Miriam Rabkin. *Differentiated service delivery: Navigating the path to scale*. 2019. <https://doi.org/10.1097/COH.0000000000000509>.
- [55] Amy Huber et al. "Differentiated service delivery models for HIV treatment in Malawi, South Africa, and Zambia: A landscape analysis". *Global Health Science and Practice* 9.2 (2021), pp. 296–307. <https://doi.org/10.9745/ghsp-d-20-00532>.
- [56] Carly A. Comins et al. "Opportunities and considerations for the design of decentralized delivery of antiretroviral therapy for female sex workers living with HIV in South Africa". *BMC Health Services Research* 2022 22:1 22.1 (2022), pp. 1–10. <https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-08506-0>.
- [57] Lydia Atuhaire et al. "Effect of community-based interventions targeting female sex workers along the HIV care cascade in sub-Saharan Africa: a systematic review and meta-analysis". *Systematic Reviews* 10.1 (2021), pp. 1–20. <https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-021-01688-4>.
- [58] Michael H. Merson et al. "The history and challenge of HIV prevention". *The Lancet* 372.9637 (2008), pp. 475–488. [https://doi.org/10.1016/S0140-6736\(08\)60884-3](https://doi.org/10.1016/S0140-6736(08)60884-3).
- [59] UNAIDS. *HIV Financial Database*. 2022. <https://hivfinancial.unaids.org/>.
- [60] James D. Shelton. "Two-component generalised HIV epidemics - Author's reply". *The Lancet* 376.9734 (2010), p. 22. [https://doi.org/10.1016/S0140-6736\(10\)61048-3](https://doi.org/10.1016/S0140-6736(10)61048-3).
- [61] Portia C. Mutevedzi and Marie Louise Newell. "The changing face of the HIV epidemic in sub-Saharan Africa". *Tropical Medicine and International Health* 19.9 (2014), pp. 1015–1028. <https://doi.org/10.1111/tmi.12344>.

- [62] Nathan Geffen and Alex Welte. "Modelling the human immunodeficiency virus (HIV) epidemic: A review of the substance and role of models in South Africa". *Southern African Journal of HIV Medicine* 19.1 (2018). <https://sajhivmed.org.za/index.php/hivmed/article/view/756/1088>.
- [63] Stefan Baral et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment". *The Lancet HIV* 6 (2019), e632–638. [http://doi.org/10.1016/S2352-3018\(19\)30226-7](http://doi.org/10.1016/S2352-3018(19)30226-7).
- [64] Rachel A. Royce et al. "Sexual transmission of HIV". *New England Journal of Medicine* 336.15 (Apr.10) (1997), pp. 1072–1078. <https://doi.org/10.1056/NEJM199704103361507>.
- [65] Elliot Marseille, Paul B. Hofmann, and James G. Kahn. "HIV prevention before HAART in sub-Saharan Africa". *The Lancet* 359.9320 (2002), pp. 1851–1856. [https://doi.org/10.1016/S0140-6736\(02\)08705-6](https://doi.org/10.1016/S0140-6736(02)08705-6).
- [66] Richard G Parker, Delia Easton, and C. H. Klein. "Structural barriers and facilitators in HIV prevention: A review of international research". *AIDS* 14.S11 (2000), pp. 22–32. <https://doi.org/10.1097/00002030-200006001-00004>.
- [67] Bertran Auvert et al. "Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial". *PLOS Medicine* 2.11 (2005). Ed. by Steven Deeks, pp. 1112–1122. <https://dx.plos.org/10.1371/journal.pmed.0020298>.
- [68] WHO. *Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations*. Geneva, Switzerland, 2020. <https://www.who.int/publications/item/978-92-4-000966-0>.
- [69] Mina Hosseinipour et al. "Can antiretroviral therapy be used to prevent sexual transmission of human immunodeficiency virus type 1?" *Clinical Infectious Diseases* 34.10 (2002), pp. 1391–1395. <https://doi.org/10.1086/340403>.
- [70] Myron S. Cohen et al. "HIV treatment as prevention: Debate and commentary-will early infection compromise treatment-as-prevention strategies?" *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001232. <https://doi.org/10.1371/journal.pmed.1001232>.
- [71] Thumbi Ndung'u, Joseph M. McCune, and Steven G Deeks. *Why and where an HIV cure is needed and how it might be achieved*. 2019. <https://doi.org/10.1038/s41586-019-1841-8>.
- [72] Tomas Cihlar and Marshall Fordyce. "Current status and prospects of HIV treatment". *Current Opinion in Virology* 18 (2016), pp. 50–56. <https://doi.org/10.1016/j.coviro.2016.03.004>.
- [73] Alan S. Perelson et al. "HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time". *Science* 271.5255 (1996), pp. 1582–1586. <https://doi.org/10.1126/science.271.5255.1582>.
- [74] Alan S. Perelson et al. "Decay characteristics of HIV-1-infected compartments during combination therapy". *Nature* 387.6629 (1997), pp. 188–191. <https://doi.org/10.1038/387188a0>.
- [75] Andrew Mujugira et al. "HIV transmission risk persists during the first 6 months of antiretroviral therapy". *Journal of Acquired Immune Deficiency Syndromes* 72.5 (2016), pp. 579–584. <https://doi.org/10.1097/QAI.0000000000001019>.
- [76] Manuel Battegay et al. "Immunological recovery and antiretroviral therapy in HIV-1 infection". *The Lancet Infectious Diseases* 6.5 (2006), pp. 280–287. [https://doi.org/10.1016/S1473-3099\(06\)70463-7](https://doi.org/10.1016/S1473-3099(06)70463-7).
- [77] WHO. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach*. Geneva, Switzerland, 2013.
- [78] Delphine Gabillard et al. "Mortality, AIDS-morbidity, and loss to follow-up by current CD4 cell count among HIV-1-infected adults receiving antiretroviral therapy in Africa and Asia: Data from the ANRS 12222 collaboration". *Journal of Acquired Immune Deficiency Syndromes* 62.5 (2013), pp. 555–561. <https://doi.org/10.1097/QAI.0b013e3182821821>.
- [79] MSF. *Untangling the Web of Antiretroviral Price Reductions*. Geneva, Switzerland, 2016. <https://msfaccess.org/utw>.
- [80] Myron S. Cohen et al. "Prevention of HIV-1 infection with early antiretroviral therapy". *New England Journal of Medicine* 365.6 (2011), pp. 493–505. <https://doi.org/10.1056/NEJMoa1105243>.
- [81] Beatriz Grinsztejn et al. "Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial". *The Lancet Infectious Diseases* 14.4 (2014), pp. 281–290. [https://doi.org/10.1016/S1473-3099\(13\)70692-3](https://doi.org/10.1016/S1473-3099(13)70692-3).
- [82] Jens D Lundgren et al. "Initiation of antiretroviral therapy in early asymptomatic HIV infection." *New England Journal of Medicine* 373.9 (2015), pp. 795–807. <https://doi.org/10.1056/NEJMoa1506816>.

- [83] TEMPRANO ANRS 12136 Study Group. "A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa". *New England Journal of Medicine* 373.9 (2015), pp. 808–822. <https://doi.org/10.1056/nejmoa1507198>.
- [84] WHO. *Chronic HIV Care with ARV Therapy and Prevention*. Geneva, Switzerland, 2007.
- [85] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland, 2013.
- [86] Andrew Anglemeyer et al. "Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples". *Cochrane Database of Systematic Reviews* 4 (2013). <https://doi.org/10.1002/14651858.CD009153.pub3>.
- [87] Myron S. Cohen et al. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission". *New England Journal of Medicine* 375.9 (2016), pp. 830–839. <https://doi.org/10.1056/nejmoa1600693>.
- [88] Alison J Rodger et al. "Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study". *The Lancet* 0.0 (2019). <https://linkinghub.elsevier.com/retrieve/pii/S0140673619304180>.
- [89] Reuben M Granich et al. "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model". *The Lancet* 373.9657 (2009), pp. 48–57. [https://doi.org/10.1016/S0140-6736\(08\)61697-9](https://doi.org/10.1016/S0140-6736(08)61697-9).
- [90] Diane V. Havlir et al. "HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa". *New England Journal of Medicine* 381.3 (2019), pp. 219–229. <https://doi.org/10.1056/nejmoa1809866>.
- [91] Richard J. Hayes et al. "Effect of universal testing and treatment on HIV incidence - HPTN 071 (popart)". *New England Journal of Medicine* 381.3 (2019), pp. 207–218.
- [92] Collins C. Iwuji et al. "Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial". *The Lancet HIV* 5.3 (2018), e116–e125. [http://doi.org/10.1016/S2352-3018\(17\)30205-9](http://doi.org/10.1016/S2352-3018(17)30205-9).
- [93] Adam Akullian et al. "The missing 27%". *AIDS* 31.17 (2017), pp. 2427–2429. <http://doi.org/10.1097/QAD.0000000000001638>.
- [94] Diane Havlir et al. *What do the Universal Test and Treat trials tell us about the path to HIV epidemic control?* 2020. <https://doi.org/10.1002/jia2.25455>.
- [95] UNAIDS. *Fast-Track: Ending the AIDS epidemic by 2030*. Geneva, Switzerland, 2014.
- [96] Elisa Mountain et al. "The HIV care cascade and antiretroviral therapy in female sex workers: Implications for HIV prevention". *Expert Review of Anti-Infective Therapy* 12.10 (2014), pp. 1203–1219. <http://doi.org/10.1586/14787210.2014.948422>.
- [97] UNAIDS. *90-90-90 An ambitious treatment target to help end the AIDS epidemic*. 2014. [http://www.unaids.org/sites/default/files/media\\_asset/90-90-90\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf).
- [98] Avi Joseph Hakim et al. "Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response". *Journal of the International AIDS Society* 21 (2018), e25119. <http://doi.org/10.1002/jia2.25119>.
- [99] Dylan Green et al. *Evidence of sociodemographic heterogeneity across the HIV treatment cascade and progress towards 90-90-90 in sub-Saharan Africa – a systematic review and meta-analysis*. 2020. <https://doi.org/10.1002/jia2.25470>.
- [100] The World Bank. *DataBank: World Development Indicators*. 2022. <https://databank.worldbank.org/> (visited on 08/23/2018).
- [101] Stefan Baral et al. "Reconceptualizing the HIV epidemiology and prevention needs of female sex workers (FSW) in Swaziland". *PLOS ONE* 9.12 (2014), e115465. <http://doi.org/10.1371/journal.pone.0115465>.
- [102] Eswatini Ministry of Health. *2020–2021 Integrated Biological-Behavioral Surveillance Survey among Female Sex Workers and Men Who Have sex with Men in Eswatini*. Mbabane, Eswatini, 2022.
- [103] Maxwell Vusumuzi Mthembu. "Pro-democracy protests in the Kingdom of Eswatini 2018–2019". *Popular Protest, Political Opportunities, and Change in Africa*. Ed. by Edalina Rodrigues Sanches. Routledge, 2022. Chap. 12, pp. 200–217. <https://doi.org/10.4324/9781003177371-12>.
- [104] Nothando Maphalala. *Kingdom of Eswatini: Conflict Insights*. Addis Ababa, Ethiopia: Institute for Peace and Security Studies, 2021. <https://www.africaportal.org/publications/kingdom-eswatini-conflict-insights/>.
- [105] Teresa Debly. "Culture and resistance in Swaziland". *Journal of Contemporary African Studies* 32.3 (2014), pp. 284–301. <https://doi.org/10.1080/02589001.2014.956496>.
- [106] Moeketsi Kali. "A comparative analysis of the causes of the protests in Southern Africa". *SN Social Sciences* 3.2 (2023), pp. 1–22. <https://doi.org/10.1007/s43545-023-00613-x>.



- [107] Casey Golomski. "Interrogating traditionalism: gender and Swazi Culture in HIV/AIDS policy". *Journal of Contemporary African Studies* (2019). <https://www.tandfonline.com/doi/abs/10.1080/02589001.2019.1701184>.
- [108] Human Rights Watch. *Eswatini: Activist, Rights Lawyer Brutally Killed*. Johannesburg, South Africa, 2023. <https://www.hrw.org/news/2023/01/25/eswatini-activist-rights-lawyer-brutally-killed>.
- [109] Alan Whiteside et al. *What is driving the HIV/AIDS epidemic in Swaziland, and what more can we do about it?* NERCHA, 2003.
- [110] Aaron G. Buseh, Laurie K. Glass, and Beverly J. McElmurry. "Cultural and gender issues related to HIV/AIDS prevention in rural Swaziland: A focus group analysis". *Health Care for Women International* 23.2 (2002), pp. 173–184. <https://doi.org/10.1080/073993302753429040>.
- [111] Hamilton Sipho Simelane. "'Sharing my bed with the enemy': Wives and violent husbands in post-colonial Swaziland". *Journal of Contemporary African Studies* 29.4 (2011), pp. 493–512. <https://doi.org/10.1080/02589001.2011.601045>.
- [112] Thandeka T.T. Dlamini-Simelane and Eileen Moyer. "'Lost to follow up': Rethinking delayed and interrupted HIV treatment among married Swazi women". *Health Policy and Planning* 32.2 (2017), pp. 248–256. <https://doi.org/10.1093/heapol/czw117>.
- [113] UNAIDS and WHO. *Laws and Policies Analytics*. Geneva, Switzerland, 2022. <https://lawsandpolicies.unaids.org>.
- [114] Swaziland Ministry of Health. *Swaziland Behavioral Surveillance Survey*. Mbabane, Swaziland, 2002.
- [115] National Emergency Response Council on HIV and AIDS. *National Multi-sectorial Strategic Framework for HIV and AIDS 2009-2014*. Mbabane, Swaziland, 2009.
- [116] John Iliffe. *The African AIDS Epidemic: A History*. Cape Town, South Africa: Ohio University Press, 2005. <https://isbnsearch.org/isbn/9780821442739>.
- [117] Alan Whiteside and Amy Whalley. *Reviewing Emergencies for Swaziland: Shifting the Paradigm in a New Era*. Mbabane, Swaziland: NERCHA, 2007.
- [118] PEPFAR. *Characterizing the HIV Prevention and Treatment Needs among Key Populations, including Men who Have Sex with Men and Female Sex Workers in Swaziland: From Evidence to Action*. Mbabane, Swaziland, 2015.
- [119] Central Statistical Office Swaziland. *Swaziland Demographic and Health Survey 2006-07*. Mbabane, Swaziland, 2008. <https://dhsprogram.com/>.
- [120] Swaziland Ministry of Health. *Swaziland HIV Incidence Measurement Survey: First Findings Report*. Mbabane, Swaziland, 2012. <http://shims.icap.columbia.edu/>.
- [121] Eswatini Ministry of Health. *Swaziland HIV Incidence Measurement Survey 2 (SHIMS2) 2016-2017*. Mbabane, Eswatini, 2019.
- [122] Yen T. Duong et al. "Detection of recent HIV-1 infection using a new limiting-antigen avidity assay: Potential for HIV-1 incidence estimates and avidity maturation studies". *PLOS ONE* 7.3 (2012), e33328. <https://doi.org/10.1371/journal.pone.0033328>.
- [123] Herbert W Hethcote. "The Mathematics of Infectious". *SIAM Review* 42.4 (2000), pp. 599–653. <https://www.jstor.org/stable/2653135>.
- [124] Valerie Isham. "Mathematical Modelling of the Transmission Dynamics of HIV Infection and AIDS: A Review". *Journal of the Royal Statistical Society. Series A: Statistics in Society* 151.1 (1988), p. 5. <https://doi.org/10.2307/2982179>.
- [125] Fredrik Liljeros, Christofer R. Edling, and Luis A.Nunes Amaral. "Sexual networks: implications for the transmission of sexually transmitted infections". *Microbes and Infection* 5.2 (2003), pp. 189–196. [https://doi.org/10.1016/S1286-4579\(02\)00058-8](https://doi.org/10.1016/S1286-4579(02)00058-8).
- [126] R. M. Anderson et al. "A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS". *Mathematical Medicine and Biology* 3.4 (1986), pp. 229–263. <https://doi.org/10.1093/imammb/3.4.229>.
- [127] G. P. Garnett and R. M. Anderson. "Sexually transmitted diseases and sexual behavior: Insights from mathematical models". *Journal of Infectious Diseases* 174.S2 (1996), S150–S161. [https://doi.org/10.1093/infdis/174.Supplement\\_2.S150](https://doi.org/10.1093/infdis/174.Supplement_2.S150).
- [128] Jeffrey W. Eaton and Timothy B. Hallett. "Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence". *Proceedings of the National Academy of Sciences* 111.45 (2014), pp. 16202–16207. <https://doi.org/10.1073/pnas.1323007111>.

- [129] L. Bao et al. "Modelling national HIV/AIDS epidemics: revised approach in the UNAIDS Estimation and Projection Package 2011." *Sexually transmitted infections* 88.S2 (2012), pp. i3–i10. <https://doi.org/10.1136/sextrans-2012-050637>.
- [130] Jeffrey W. Eaton et al. "Assessment of epidemic projections using recent HIV survey data in South Africa: A validation analysis of ten mathematical models of HIV epidemiology in the antiretroviral therapy era". *The Lancet Global Health* 3.10 (2015), e598–e608.
- [131] Christinah Mukandavire et al. "Estimating the contribution of key populations towards the spread of HIV in Dakar, Senegal". *Journal of the International AIDS Society* 21 (2018), e25126. <https://doi.org/10.1002/jia2.25126>.
- [132] Romain Silhol et al. "Quantifying the Evolving Contribution of HIV Interventions and Key Populations to the HIV Epidemic in Yaoundé, Cameroon". *Journal of Acquired Immune Deficiency Syndromes* 86.4 (2021), pp. 396–405. <https://doi.org/10.1097/QAI.0000000000002580>.
- [133] Steve E. Bellan et al. "Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts". *PLOS Medicine* 12.3 (2015). Ed. by Marie-Louise Newell, e1001801. <https://doi.org/10.1371/journal.pmed.1001801>.
- [134] Sharmistha Mishra et al. "Exploring the population-level impact of antiretroviral treatment: The influence of baseline intervention context". *AIDS* 28.S1 (2014). [https://journals.lww.com/aidsonline/Fulltext/2014/01001/Exploring\\_the\\_population\\_level\\_impact\\_of.7.aspx](https://journals.lww.com/aidsonline/Fulltext/2014/01001/Exploring_the_population_level_impact_of.7.aspx).
- [135] Mathieu Maheu-Giroux et al. "Population-level impact of an accelerated HIV response plan to reach the UNAIDS 90-90-90 target in Côte d'Ivoire: Insights from mathematical modeling". *PLOS Medicine* 14.6 (2017). Ed. by Nicola Low, e1002321. <https://doi.org/10.1371/journal.pmed.1002321>.
- [136] Leigh F. Johnson et al. "Prospects for HIV control in South Africa: a model-based analysis". *Global Health Action* 9.1 (2016). <https://doi.org/10.3402/gha.v9.30314>.
- [137] Anne Cori et al. "HPTN 071 (PopART): A cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: Mathematical model". *PLOS ONE* 9.1 (2014), e84511. <https://doi.org/10.1371/journal.pone.0084511>.
- [138] Sarah Jane Anderson et al. "Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study". *The Lancet* 384.9939 (2014), pp. 249–256. [https://doi.org/10.1016/S0140-6736\(14\)61053-9](https://doi.org/10.1016/S0140-6736(14)61053-9).
- [139] Cliff C. Kerr et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376. <https://doi.org/10.1097/QAI.0000000000000605>.
- [140] Andrew N. Phillips et al. "Cost-effectiveness of easy-access, risk-informed oral pre-exposure prophylaxis in HIV epidemics in sub-Saharan Africa: a modelling study". *The Lancet HIV* 9.5 (2022), e353–e362. [https://doi.org/10.1016/S2352-3018\(22\)00029-7](https://doi.org/10.1016/S2352-3018(22)00029-7).
- [141] Branwen Nia Owen et al. "What Proportion of Female Sex Workers Practise anal Intercourse and How Frequently? A Systematic Review and Meta-analysis". *AIDS and Behavior* 24.3 (2020), pp. 697–713. <https://doi.org/10.1007/s10461-019-02477-w>.
- [142] Katia Giguère et al. "Trends in knowledge of HIV status and efficiency of HIV testing services in sub-Saharan Africa, 2000–20: a modelling study using survey and HIV testing programme data". *The Lancet HIV* 8.5 (2021), e284–e293. [http://doi.org/10.1016/S2352-3018\(20\)30315-5](http://doi.org/10.1016/S2352-3018(20)30315-5).
- [143] James A Yorke, Herbert W Hethcote, and Annett Nold. "Dynamics and control of the transmission of gonorrhea". *Sexually Transmitted Diseases* 5.2 (1978), pp. 51–56. <http://doi.org/10.1097/00007435-197804000-00003>.
- [144] Hein Stigum, W. Falck, and P. Magnus. "The core group revisited: The effect of partner mixing and migration on the spread of gonorrhea, chlamydia, and HIV". *Mathematical Biosciences* 120.1 (1994), pp. 1–23. [https://doi.org/10.1016/0025-5564\(94\)90036-1](https://doi.org/10.1016/0025-5564(94)90036-1).
- [145] Charlotte Watts et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". *Sexually Transmitted Infections* 86.S3 (2010), pp. iii85–iii92. <https://doi.org/10.1136/sti.2010.044602>.
- [146] Sze chuan Suen, Jeremy D. Goldhaber-Fiebert, and Margaret L. Brandeau. "Risk stratification in compartmental epidemic models: Where to draw the line?" *Journal of Theoretical Biology* 428 (2017), pp. 1–17. <https://doi.org/10.1016/j.jtbi.2017.06.004>.



- [147] J. O. Lloyd-Smith et al. "Superspreading and the effect of individual variation on disease emergence". *Nature* 438.7066 (2005), pp. 355–359. <https://doi.org/10.1038/nature04153>.
- [148] John A. Jacquez et al. "Modeling and analyzing HIV transmission: the effect of contact patterns". *Mathematical Biosciences* 92.2 (1988), pp. 119–199. [https://doi.org/10.1016/0025-5564\(88\)90031-4](https://doi.org/10.1016/0025-5564(88)90031-4).
- [149] Tim Brown and Wiwat Peerapatanapokin. "Evolving HIV epidemics: The urgent need to refocus on populations with risk". *Current Opinion in HIV and AIDS* 14.5 (2019), pp. 337–353. <https://doi.org/10.1097/COH.0000000000000571>.
- [150] Sharmistha Mishra et al. "Estimating the epidemic consequences of HIV prevention gaps among key populations". *Journal of the International AIDS Society* 24.S3 (2021), e25739. <https://doi.org/10.1002/jia2.25739>.
- [151] Jiawei Zhang, Yuhong Yang, and Jie Ding. "Information criteria for model selection". *Wiley Interdisciplinary Reviews: Computational Statistics* (2023), e1607. <https://doi.org/10.1002/wics.1607>.

## Chapter 2

# Systematic Review of Compartmental HIV Transmission Model Structures

Much of this chapter is copied verbatim from [1].

### 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 [2]. In SSA and elsewhere, HIV treatment via antiretroviral therapy (ART) remains a key element of combination HIV prevention [3].

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 [4, 5] and partner-level prevention benefits [6, 7]. Expansion cumulated with the current recommendation of immediate ART following HIV diagnosis, or “universal test-and-treat” [3]. Parallel to ART expansion, interest has grown in estimating the population-level prevention benefits of ART, via both model-based studies [8–11] and recent large-scale community-based trials [12–14]. Mixed results from these trials [12–14] have renewed interest in understanding potential determinants of population-level ART prevention benefits [15, 16].

Risk heterogeneity is a well-established determinant of HIV epidemic emergence and persistence [17, 18]. 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 [19, 20]. 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 [21, 22]. 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 [23–25]. Indeed, data suggest that ART scale-up in practice has not reached subgroups equally [26].

Given the critical role of transmission modelling in estimating the prevention impacts of ART [9, 10], 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 B.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 [27]
- **Behaviour Change Effects:** differential transmission risk due to behavioural changes related to engagement in the ART cascade [28, 29]
- **Network Effects:** differential transmission risk within sub-populations that increases the challenge of epidemic control through core group dynamics [18, 30, 31]
- **Cascade Effects:** differential transmission risk within sub-populations who experience barriers to ART care and achieving viral suppression, such as youth and key populations [21, 26, 32, 33]

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 B.1). Search results were de-duplicated and screened by title and abstract in Covidence [44], followed by full-text screening using the criteria below. One reviewer (JK) conducted the search, screening, and data extraction.

#### 2.2.2.1 Inclusion/Exclusion Criteria

Table B.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

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

Factor	MP <sup>a</sup>	Definition	Possible mechanism(s) of influence on ART prevention impact
Acute Infection	$\beta_i$	Increased infectiousness immediately following infection [34, 35]	<b>Biological:</b> transmissions during acute infection are unlikely to be prevented by ART
Late-Stage Infection	$\beta_i$	Increased infectiousness during late-stage infection [34, 35]	<b>Biological:</b> transmissions during late-stage are more likely to be prevented by ART
Drug Resistance	$\beta_i$	Transmitted factor that requires regimen switch to achieve viral suppression [36]	<b>Biological:</b> 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 [37, 38]	<b>Behaviour Change:</b> 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 [29]	<b>Behaviour Change:</b> 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 [39]	<b>Network:</b> higher transmission risk among higher activity
Age Groups	$Q; \alpha$	Any stratification by age	<b>Network &amp; Cascade:</b> higher transmission risk and barriers to viral suppression among youth [26, 40]
Key Populations	$Q; \alpha$	Any epidemiologically defined higher risk groups [41]	<b>Network &amp; Cascade:</b> higher transmission risk and barriers to viral suppression among key populations [21]
Group Turnover	$\theta$	Individuals move between activity groups and/or key populations reflecting sexual lifecourse [30]	<b>Network &amp; Cascade:</b> counteract effect of stratification due to shorter periods in higher risk [42]; viral suppression may be achieved only after periods of higher risk
Assortative Mixing	$\Phi$	Any degree of assortative mixing (like-with-like) by age, activity, and/or key populations	<b>Network:</b> assortative sexual networks compound effect of stratification [39]
Partnership Types	$A; \alpha$	Different partnership types are simulated, with different numbers of sex acts and/or condom usage [43]	<b>Network:</b> longer duration and lower condom use among main versus casual/sex work partnerships counteracts effect of stratification
ART Cascade Gaps	$\delta; \tau$	Slower ART cascade transitions among higher activity groups or key populations [21, 26]	<b>Cascade:</b> ART prevention benefits may be allocated differentially among risk groups

<sup>a</sup> MP: Model Parameters —  $\beta_i, \beta_s$ : transmission probability per act (infectiousness, susceptibility);  $A$ : number of sex acts of each type per partnership;  $\alpha$ : proportion of sex acts unprotected by a condom;  $Q$ : partnership formation rate;  $\Phi$ : mixing matrix (probability of partnership formation);  $\mu$ : mortality rate;  $v$ : entry rate;  $\theta$ : internal turnover between activity groups;  $\delta$ : diagnosis rate;  $\tau$ : ART initiation rate (and retention-related factors).

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 (versus combination intervention); 2) examined ART intervention for the whole population (versus 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 B.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 >50× the partners per year of the lowest sexually active female activity group [43, 45]. Clients were defined as any male activity group described as clients of FSW, and being >3× 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) versus 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 multivariate regression, with generalized estimating equations [46] 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 [47]. We also plotted impacts versus 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 B.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 B.2a). No studies reported overall HIV prevalence of  $< 1\%$  at time of intervention, although for 30 studies, HIV prevalence was not reported or varied across

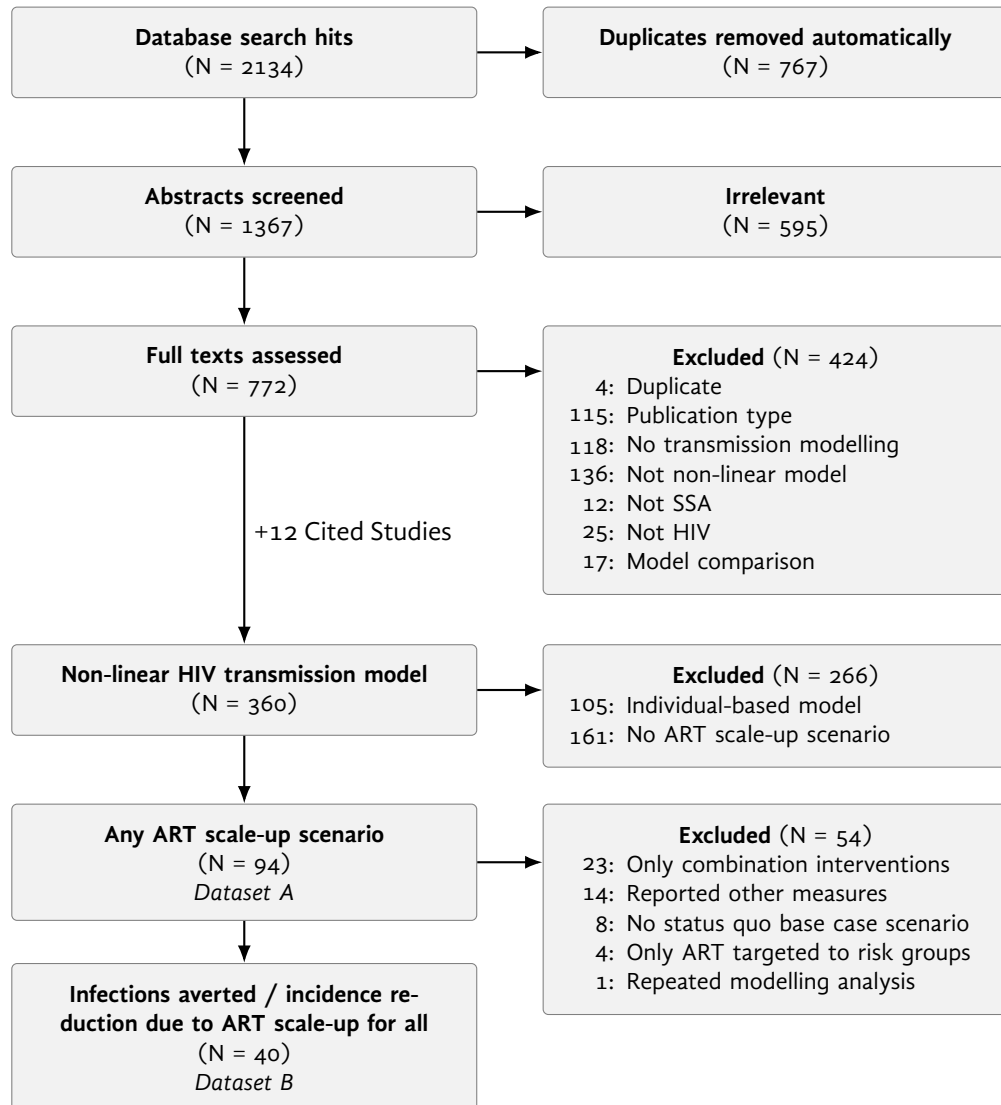


Figure 2.1: PRISMA flowchart of study identification

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 <sup>a</sup>	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 <sup>b</sup>	39
	Clients <sup>c</sup>	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; <sup>a</sup> does not sum to 94 as some studies modelled multiple countries; <sup>b</sup> groups described as FSW, not considering the epidemiological definitions given in Appendix B.2.2.1; <sup>c</sup> likewise for clients, and excluding studies where clients were modelled as a proportion of another risk group.

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 B.2a); and incidence (per 1000 person-years) was 14 [1, (9, 20), 50] (Figure B.2b). Most reported incidence trends were decreasing or stable (45 of 48 reporting, Figure B.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 > 50× partners per year versus 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 > 3× 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 > 3× 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 B.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 B.2e), representing an average “on-treatment” state in 78 studies, versus 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-naïve; 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 versus 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-naïve; 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 versus 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 B.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 B.2h and B.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 B.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 multivariate analysis. Figure B.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.

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

Factor	Level	Incidence Reduction (%)			Cumulative Infections Averted (%)		
		N <sup>a</sup>	Median (IQR)	Effect (95% CI) <sup>b</sup>	N <sup>a</sup>	Median (IQR)	Effect (95% CI) <sup>b</sup>
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 <sup>c</sup>	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 (%) <sup>c</sup>	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)

<sup>a</sup> N: number of unique scenarios and time horizons; sums across factor levels may be less than 126 and 115 due to missing variables.

<sup>b</sup> Effect estimates from linear multivariate regression with generalized estimating equations [46]; effects are illustrated in Figure C.20.

<sup>c</sup> 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 multivariate 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 [48–50], as well as in the wider population [51]. 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 [52]; however, the model in [52] 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 versus without turnover, and the reproduction number may actually increase [42]. 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 [42]. 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 [30].

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 [26, 33, 53, 54]. 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 [24, 55]. Moreover, barriers to ART may intersect with transmission risk, particularly among key populations, due to issues of stigma, discrimination, and criminalization [15, 56]. 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

[57]. 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 [58–60]. 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 [61, 62]. 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 [21, 32, 53]. Similarly, we found that the number of modelled clients per female sex worker, and the relative rate of partnership formation among female sex workers versus other women did not always reflect available data syntheses for sex work [30, 43]. 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 [43]. 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 [41], 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 [63, 64]. 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 [65, 66]. Third, we did not extract whether models were calibrated, and if so, which parameters were fixed versus fitted. If certain parameters were fitted, it could explain some counterintuitive effect estimates. For example, models with versus 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. For example, models with versus 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 [19, 31] 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 in risks related to key populations, to reflect intersections of transmission risk and barriers to HIV services that may undermine the prevention benefits of ART.

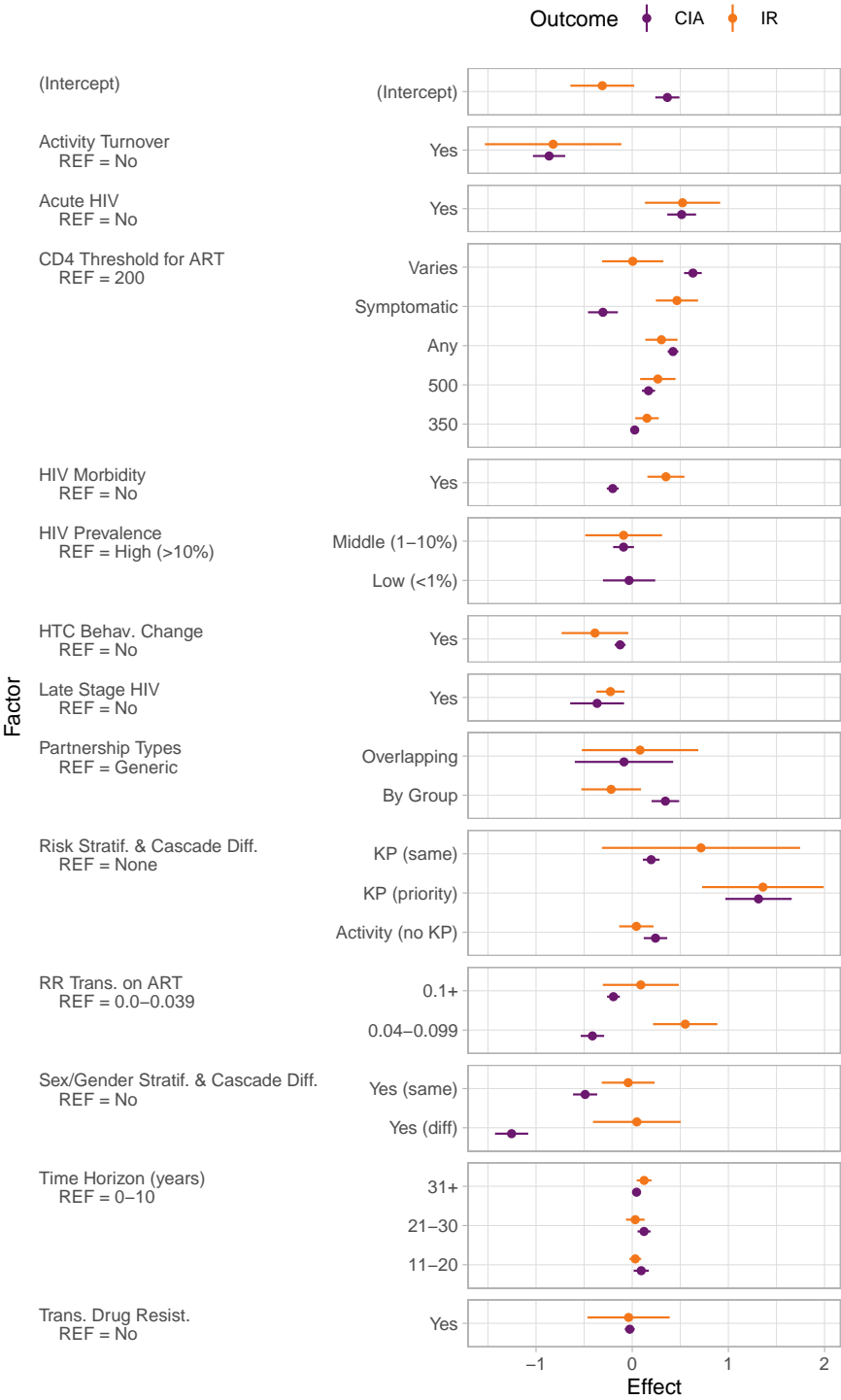


Figure 2.2: Effect estimates for factors of heterogeneity on incidence reduction (%, IR) and cumulative infections averted (%, CIA) from linear multivariate regression with generalized estimating equations.

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 B.2.

## References

- [1] Jesse Knight, Rupert Kaul, and Sharmistha Mishra. "Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review". *Epidemics* 40 (2022), p. 100608. <https://doi.org/10.1016/j.epidem.2022.100608>.
- [2] UNAIDS. *AIDSinfo*. 2023. <http://aidsinfo.unaids.org>.
- [3] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland, 2016. <https://www.who.int/hiv/pub/arv/arv-2016>.
- [4] Jens D Lundgren et al. "Initiation of antiretroviral therapy in early asymptomatic HIV infection." *New England Journal of Medicine* 373.9 (2015), pp. 795–807. <https://doi.org/10.1056/NEJMoa1506816>.
- [5] TEMPRANO ANRS 12136 Study Group. "A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa". *New England Journal of Medicine* 373.9 (2015), pp. 808–822. <https://doi.org/10.1056/nejmoa1507198>.
- [6] Andrew Anglemyer et al. "Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples". *Cochrane Database of Systematic Reviews* 4 (2013). <https://doi.org/10.1002/14651858.CD009153.pub3>.
- [7] Myron S. Cohen et al. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission". *New England Journal of Medicine* 375.9 (2016), pp. 830–839. <https://doi.org/10.1056/nejmoa1600693>.
- [8] Reuben M Granich et al. "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model". *The Lancet* 373.9657 (2009), pp. 48–57. [https://doi.org/10.1016/S0140-6736\(08\)61697-9](https://doi.org/10.1016/S0140-6736(08)61697-9).
- [9] Jeffrey W. Eaton et al. "HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001245. <https://doi.org/10.1371/journal.pmed.1001245>.
- [10] Wim Delva et al. "HIV treatment as prevention: Principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001239. <https://doi.org/10.1371/journal.pmed.1001239>.
- [11] Anne Cori et al. "HPTN 071 (PopART): A cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: Mathematical model". *PLOS ONE* 9.1 (2014), e84511. <https://doi.org/10.1371/journal.pone.0084511>.
- [12] Diane V. Havlir et al. "HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa". *New England Journal of Medicine* 381.3 (2019), pp. 219–229. <https://doi.org/10.1056/nejmoa1809866>.
- [13] Richard J. Hayes et al. "Effect of universal testing and treatment on HIV incidence - HPTN 071 (popart)". *New England Journal of Medicine* 381.3 (2019), pp. 207–218.
- [14] Collins C. Iwuji et al. "Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial". *The Lancet HIV* 5.3 (2018), e116–e125. [http://doi.org/10.1016/S2352-3018\(17\)30205-9](http://doi.org/10.1016/S2352-3018(17)30205-9).
- [15] Stefan Baral et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment". *The Lancet HIV* 6 (2019), e632–638. [http://doi.org/10.1016/S2352-3018\(19\)30226-7](http://doi.org/10.1016/S2352-3018(19)30226-7).
- [16] Diane Havlir et al. *What do the Universal Test and Treat trials tell us about the path to HIV epidemic control?* 2020. <https://doi.org/10.1002/jia2.25455>.
- [17] R. M. Anderson et al. "A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS". *Mathematical Medicine and Biology* 3.4 (1986), pp. 229–263. <https://doi.org/10.1093/imammb/3.4.229>.
- [18] Marie Claude Boily and Benoît Mâsse. "Mathematical models of disease transmission: A precious tool for the study of sexually transmitted diseases". *Canadian Journal of Public Health* 88.4 (1997), pp. 255–265. <https://doi.org/10.1007/bf03404793>.
- [19] Jan A.C. C. Hontelez et al. "Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study". *PLOS Medicine* 10.10 (2013). Ed. by Nathan Ford, e1001534. <http://doi.org/10.1371/journal.pmed.1001534>.



- [20] Ganna Rozhnova et al. Impact of Heterogeneity in Sexual Behavior on Effectiveness in Reducing HIV Transmission with Test-and-Treat Strategy". *PLOS Computational Biology* 12.8 (2016), e1005012. <https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005012>.
- [21] Avi Joseph Hakim et al. "Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response". *Journal of the International AIDS Society* 21 (2018), e25119. <http://doi.org/10.1002/jia2.25119>.
- [22] Daniel Nyato et al. "Facilitators and barriers to linkage to HIV care and treatment among female sex workers in a community-based HIV prevention intervention in Tanzania: A qualitative study". *PLOS ONE* 14.11 (2019). Ed. by Sphiwe Madiba, e0219032. <https://dx.plos.org/10.1371/journal.pone.0219032>.
- [23] Rachel Arnesen, Anthony P. Moll, and Sheela V. Shenoi. "Predictors of loss to follow-up among patients on ART at a rural hospital in KwaZulu-Natal, South Africa". *PLOS ONE* 12.5 (2017), e0177168. <https://doi.org/10.1371/journal.pone.0177168>.
- [24] Chido D. Chikwari, Stefanie Dringus, and Rashida A. Ferrand. "Barriers to, and emerging strategies for, HIV testing among adolescents in sub-Saharan Africa". *Current Opinion in HIV and AIDS* 13.3 (2018), pp. 257–264.
- [25] Caitlin Quinn et al. "Who are the missing men? Characterising men who never tested for HIV from population-based surveys in six sub-Saharan African countries". *Journal of the International AIDS Society* 22.10 (2019), e25398. <https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25398><https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25398><https://onlinelibrary.wiley.com/doi/10.1002/jia2.25398>.
- [26] Dylan Green et al. *Evidence of sociodemographic heterogeneity across the HIV treatment cascade and progress towards 90-90-90 in sub-Saharan Africa – a systematic review and meta-analysis*. 2020. <https://doi.org/10.1002/jia2.25470>.
- [27] Christopher D. Pilcher et al. "Brief but efficient: Acute HIV infection and the sexual transmission of HIV". *Journal of Infectious Diseases* 189.10 (2004), pp. 1785–1792. <https://doi.org/10.1086/386333>.
- [28] Sanjeev Ramachandran et al. *How do HIV-negative individuals in sub-Saharan Africa change their sexual risk behaviour upon learning their serostatus? A systematic review*. 2016. <http://doi.org/10.1136/sextrans-2015-052354>.
- [29] Ruchi Tiwari et al. *Sexual behaviour change following HIV testing services: a systematic review and meta-analysis*. 2020. <https://doi.org/10.1002/jia2.25635>.
- [30] Charlotte Watts et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". *Sexually Transmitted Infections* 86.S3 (2010), pp. iii85–iii92. <https://doi.org/10.1136/sti.2010.044602>.
- [31] Peter J Dodd, Geoff P Garnett, and Timothy B Hallett. "Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings". *AIDS* 24.5 (2010), pp. 729–735. <http://doi.org/10.1097/QAD.0b013e32833433fe>.
- [32] Elisa Mountain et al. "Antiretroviral therapy uptake, attrition, adherence and outcomes among hiv-infected female sex workers: A systematic review and meta-analysis". *PLOS ONE* 9.9 (2014). Ed. by Nicolas Sluis-Cremer, e105645. <https://doi.org/10.1371/journal.pone.0105645>.
- [33] Kathryn E. Lancaster et al. "HIV care and treatment experiences among female sex workers living with HIV in sub-Saharan Africa: A systematic review". *African Journal of AIDS Research* 15.4 (2016), pp. 377–386. <https://doi.org/10.2989/16085906.2016.1255652>.
- [34] T. Déirdre Hollingsworth, Roy M. Anderson, and Christophe Fraser. "HIV-1 transmission, by stage of infection". *Journal of Infectious Diseases* 198.5 (2008), pp. 687–693. <https://doi.org/10.1086/590501>.
- [35] Marie Claude Boily et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". *The Lancet Infectious Diseases* 9.2 (2009), pp. 118–129. [https://doi.org/10.1016/S1473-3099\(09\)70021-0](https://doi.org/10.1016/S1473-3099(09)70021-0).
- [36] René de Waal et al. "HIV drug resistance in sub-Saharan Africa: public health questions and the potential role of real-world data and mathematical modelling." *Journal of virus eradication* 4.S2 (2018), pp. 55–58. <http://www.ncbi.nlm.nih.gov/pubmed/30515315><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6248850><http://www.ncbi.nlm.nih.gov/pubmed/30515315><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6248850>.
- [37] Landon Myer et al. "Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: A cohort study". *PLOS Medicine* 7.2 (2010). Ed. by Lynne Mofenson, e1000229. <https://dx.plos.org/10.1371/journal.pmed.1000229>.
- [38] Nuala McGrath, Linda Richter, and Marie Louise Newell. "Sexual risk after HIV diagnosis: A comparison of pre-ART individuals with CD4 > 500 cells/μl and ART-eligible individuals in a HIV treatment and care programme in rural KwaZulu-Natal, South Africa". *Journal of the International AIDS Society* 16.1 (2013), p. 18048. <http://doi.wiley.com/10.7448/IAS.16.1.18048>.



- [39] Roy M Anderson and Robert M May. *Infectious diseases of humans: dynamics and control*. Oxford University Press, 1991.
- [40] Isolde Birdthistle et al. “Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis”. *The Lancet Global Health* 7.11 (2019), e1521–e1540.
- [41] WHO. *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. 2016. <https://www.who.int/hiv/pub/guidelines/keypopulations-2016/>.
- [42] Jesse Knight et al. “Contribution of high risk groups’ unmet needs may be underestimated in epidemic models without risk turnover: A mechanistic modelling analysis”. *Infectious Disease Modelling* 5 (2020), pp. 549–562. <https://doi.org/10.1016/j.idm.2020.07.004>.
- [43] Fiona Scorgie et al. “Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review”. *AIDS and Behavior* 16.4 (2012), pp. 920–933. <https://doi.org/10.1007/s10461-011-9985-z>.
- [44] Veritas Health Innovation. *Covidence systematic review software*. Melbourne, Australia, 2020. [www.covidence.org](http://www.covidence.org).
- [45] Judith Vandepitte et al. “Estimates of the number of female sex workers in different regions of the world”. *Sexually Transmitted Infections* 82.S3 (2006). <https://doi.org/10.1136/sti.2006.020081>.
- [46] Ulrich Halekoh, Søren Højsgaard, and Jun Yan. “The R package geepack for generalized estimating equations”. *Journal of Statistical Software* 15.2 (2006), pp. 1–11. <https://doi.org/10.18637/jss.v015.i02>.
- [47] Frank E. Harrell. *Regression Modelling Strategies*. New York: Springer, 2001. <https://doi.org/10.1007/978-1-4757-3462-1>.
- [48] Erika Fazito et al. “Analysis of duration of risk behaviour for key populations: a literature review.” *Sexually transmitted infections* 88.S2 (2012), pp. i24–i32. <https://doi.org/10.1136/sextrans-2012-050647>.
- [49] Ethan O. Romero-Severson et al. “Heterogeneity in Number and Type of Sexual Contacts in a Gay Urban Cohort”. *Statistical Communications in Infectious Diseases* 4.1 (2012). <https://doi.org/10.1515/1948-4690.1042>.
- [50] Elizabeth Roberts et al. “Low program access despite high burden of sexual, structural, and reproductive health vulnerabilities among young women who sell sex in Mombasa, Kenya”. *BMC Public Health* 20.1 (2020). <https://doi.org/10.1186/s12889-020-08872-6>.
- [51] Brian Houle et al. “Sexual behavior and HIV risk across the life course in rural South Africa: Trends and comparisons”. *AIDS Care* 30.11 (2018), pp. 1435–1443. <https://doi.org/10.1080/09540121.2018.1468008>.
- [52] Christopher J. Henry and James S. Koopman. “Strong influence of behavioral dynamics on the ability of testing and treating HIV to stop transmission”. *Scientific Reports* 5.1 (2015), p. 9467. <http://www.doi.org/10.1038/srep09467>.
- [53] James Stannah et al. “HIV testing and engagement with the HIV treatment cascade among men who have sex with men in Africa: a systematic review and meta-analysis”. *The Lancet HIV* 6.11 (2019), e769–e787. [https://doi.org/10.1016/S2352-3018\(19\)30239-5](https://doi.org/10.1016/S2352-3018(19)30239-5).
- [54] Huiting Ma et al. “Venue-Based HIV Testing at Sex Work Hotspots to Reach Adolescent Girls and Young Women Living with HIV: A Cross-sectional Study in Mombasa, Kenya”. *Journal of Acquired Immune Deficiency Syndromes* 84.5 (2020), pp. 470–479. <https://doi.org/10.1097/QAI.0000000000002363>.
- [55] Peter Ehrenkranz, Anna Grimsrud, and Miriam Rabkin. *Differentiated service delivery: Navigating the path to scale*. 2019. <https://doi.org/10.1097/COH.0000000000000509>.
- [56] Katrina F. Ortblad et al. *The arc of HIV epidemics in sub-Saharan Africa: New challenges with concentrating epidemics in the era of 90-90-90*. 2019. <https://doi.org/10.1097/COH.0000000000000569>.
- [57] Kelsey K Case, Gabriela B Gomez, and Timothy B Hallett. “The impact, cost and cost-effectiveness of oral pre-exposure prophylaxis in sub-Saharan Africa: a scoping review of modelling contributions and way forward”. *Journal of the International AIDS Society* 22.9 (2019). <https://doi.org/10.1002/jia2.25390>.
- [58] Chris Beyrer et al. “Global epidemiology of HIV infection in men who have sex with men”. *The Lancet* 380.9839 (2012), pp. 367–377. [https://doi.org/10.1016/S0140-6736\(12\)60821-6](https://doi.org/10.1016/S0140-6736(12)60821-6).
- [59] Stefan Baral et al. “Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis”. *The Lancet Infectious Diseases* 12.7 (2012), pp. 538–549. [https://doi.org/10.1016/S1473-3099\(12\)70066-](https://doi.org/10.1016/S1473-3099(12)70066-).

- [60] Sharmistha Mishra et al. "Data and methods to characterize the role of sex work and to inform sex work programs in generalized HIV epidemics: evidence to challenge assumptions". *Annals of Epidemiology* 26.8 (2016), pp. 557–569. <https://doi.org/10.1016/j.annepidem.2016.06.004>.
- [61] Linda-Gail Bekker et al. "Combination HIV prevention for female sex workers: What is the evidence?" *The Lancet* 385.9962 (2015), pp. 72–87. [https://doi.org/10.1016/S0140-6736\(14\)60974-0](https://doi.org/10.1016/S0140-6736(14)60974-0).
- [62] Jack Stone et al. "Estimating the contribution of key populations towards HIV transmission in South Africa". *Journal of the International AIDS Society* 24.1 (2021), e25650. <https://doi.org/10.1002/jia2.25650>.
- [63] Frank Tanser et al. "HIV treatment cascade in migrants and mobile populations". *Current Opinion in HIV and AIDS* 10.6 (2015), pp. 430–438. <http://doi.org/10.1097/COH.000000000000192>.
- [64] Rachael C. Dellar, Sarah Dlamini, and Quarraisha Abdool Karim. "Adolescent girls and young women: Key populations for HIV epidemic control". *Journal of the International AIDS Society* 18.2 (2015), pp. 64–70. <https://doi.org/10.7448/IAS.18.2.19408>.
- [65] Jay G. Silverman. *Adolescent female sex workers: Invisibility, violence and HIV*. 2011. <https://doi.org/10.1136/adc.2009.178715>.
- [66] Rebecca F. Baggaley et al. "Heterosexual Anal Intercourse: A Neglected Risk Factor for HIV?" *American Journal of Reproductive Immunology* 69.S1 (2013), pp. 95–105. <https://doi.org/10.1111/aji.12064>.

## Chapter 3

# Model Structure, Parameterization, & Calibration

Drawing on the insights from Chapter 2, this chapter details the development of a compartmental model of heterosexual HIV transmission in Eswatini. 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 [1] 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.<sup>1</sup>

### 3.1 Model Structure

The model aims to capture heterosexual HIV transmission among the Swati population aged 15–49. The model stratifies the modelled population along four dimensions: two sexes ( $s$ ), four activity groups ( $i$ ), six HIV states ( $h$ ), and five cascade states ( $c$ ), summarized in Table 3.1 and Figure 3.1. In total,  $2 \times 4 \times (1 + 5 \times 5) = 208$  states are modelled. Two additional “dimensions” help organize: four partnership types ( $p$ ), and two types of sex acts ( $a$ ).

Sexual activity groups were defined to reflect persistent differences in HIV incidence and prevalence [2–5] — reflecting acquisition and/or onward transmission risk — as well as common stratifications in the available data, and epidemiologically relevant sub-populations. 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 § 3.2.1 for more details), and the highest two activity groups among men ( $i = 3, 4$ ) likewise comprise lower and higher risk clients of FSW.

---

<sup>1</sup> [github.com/mishra-lab/hiv-fsw-art](https://github.com/mishra-lab/hiv-fsw-art)

Table 3.1: Overview of model dimensions and stratifications

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

See footnote 4 regarding indices in the code.

Four types of sexual partnerships are modelled, with different levels of condom use and expected durations: 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 [6], historical ART eligibility [7–10], and, with CD4 as a proxy for viral load, infectiousness [11]. The modelled ART cascade (Figure 3.1c) includes the major 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 the rates of ART initiation and viral suppression.

### 3.1.1 Initialization & Solving

The first cases of HIV and AIDS in Eswatini were diagnosed in 1986 and 1987, respectively [12], although HIV may have been present several years earlier [13]. 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

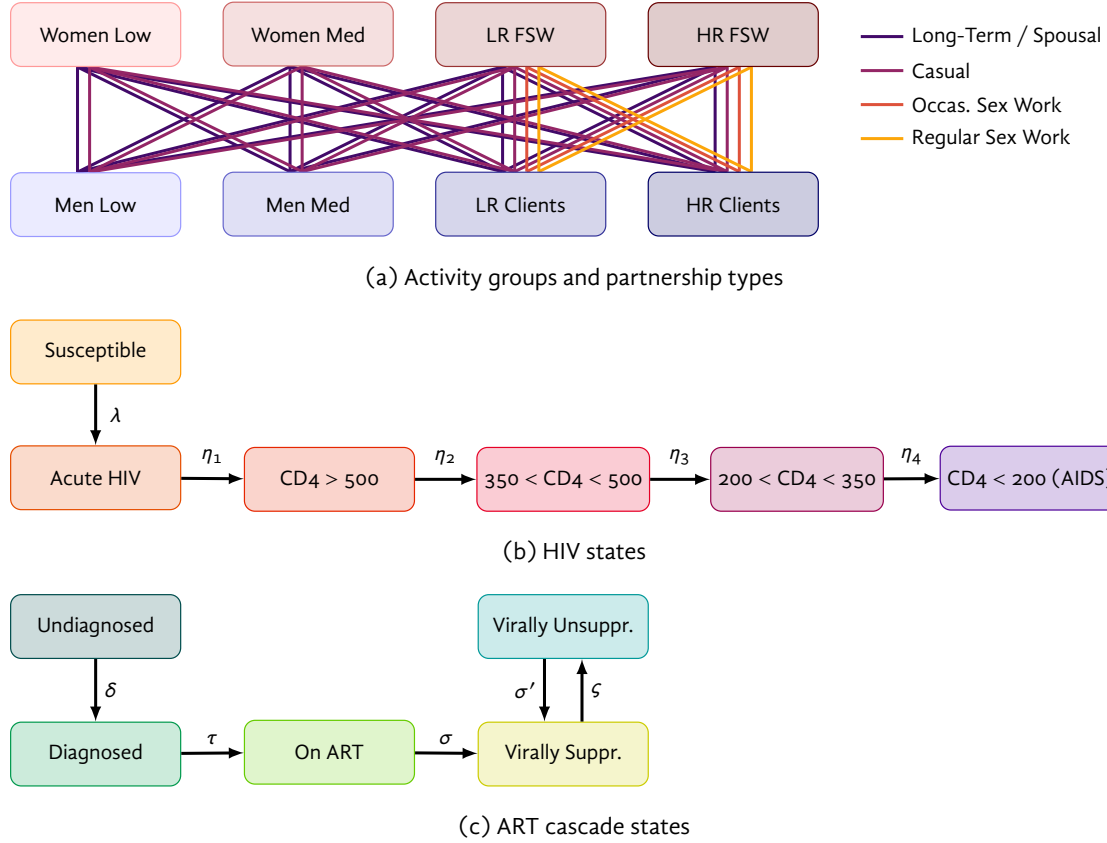


Figure 3.1: Model structure and transitions

Low: lowest activity; Med: medium activity; LR/HR: lower/higher risk; FSW: female sex workers; Clients: of FSW; CD4: CD4+ T-cell count per mm<sup>3</sup>; Not shown: turnover amongst activity groups in (a).

introduction is modelled as exogenous infection of 0.01% ( $\sim 24$ ) individuals in the model,<sup>2</sup> 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 ( $c = 1$ ).<sup>3</sup> The population size of EmaSwati aged 15–49 in 1980 was defined as 243,000 from [14].

## 3.2 Parameterization

Model parameterization involves specification of model parameter values, such as proportions, probabilities, rates, and ratios, including stratified values to reflect heterogeneity, and sampling distributions to reflect uncertainty. Proportions and probabilities were generally modelled using a beta approximation of the binomial distribution (BAB, see § A.1.2), while rates and ratios were generally modelled using a gamma, skewnormal, or inverse gaussian distribution.

<sup>2</sup> 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 [13]. However, I assume that such transmissions have low overall influence on epidemic dynamics.

<sup>3</sup> In compartmental models, the numbers of individuals in each state (compartment) need not be whole numbers.

**Notation.** If  $X$  is a parameter 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.<sup>4</sup> Finally, I re-use several dummy variables throughout the chapter:  $p$  for proportions,  $\lambda$  for rates,  $T$  for time periods, and  $f$  for constants.

### 3.2.1 Risk Heterogeneity Among FSW

HIV transmission models which include FSW rarely sub-stratify this population, such as to reflect differential HIV risk or distinct typologies of sex work [15, 16]; yet such heterogeneities likely influence transmission dynamics. Among the studies identified in Chapter 2, only three sub-stratified FSW by risk-related factors: Cremin et al. [17] defined three levels of risk via regression analysis, Low et al. [18] distinguished between occasional and full-time FSW, while Shannon et al. [19] sub-stratified FSW by work environment, violence exposure, and context-specific structural factors. Seven other studies, reflecting two unique models [20, 21], 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 lower versus higher 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 [16, 22–24]. However, serostatus reflects cumulative risk exposure, whereas sexual risk behaviour is dynamic [25, 26], as is use of prevention resources [27]. For example, while HIV prevalence often increases with age, HIV incidence among women can peak shortly after sexual debut [28]. 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 [29]. Cohort studies that measure incidence can help identify risk factors for HIV acquisition [30, 31], but large sample sizes are often required to accurately estimate overall incidence rate, let alone risk factors [32].

#### 3.2.1.1 FSW Survey Data

Three surveys, in 2011 [33] ( $N = 325$ ), 2014 [34] ( $N = 781$ ), and 2021 [35] ( $N = 676$ ) provide HIV and biobehavioural data on FSW in Eswatini. The 2011 survey employed respondent driven sampling (RDS, details in [36]), as did the 2021 survey. The 2014 survey employed venue-based snowball sampling, based on the Priorities for Local AIDS Control Efforts (PLACE) methodology, which aims to identify areas of higher incidence [37]. I analyzed the individual-level data from 2011 and 2014 (data from 2021 not yet

<sup>4</sup> 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.

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 versus higher risk FSW.

### 3.2.1.2 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%) [33]. 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 [37], and 2014 versus 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.

### 3.2.1.3 Risk Factors

Next, I explored the potential association of risk factors with HIV via the following three models:<sup>5</sup>

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 3.2, including univariate and multivariate association under each model. Variable selection for multivariate models was performed using backward selection as described by Lawless and Singhal [38], using a  $p \leq 0.1$  (per variable) threshold for stepwise variable retention. Estimated conditional effects of variables retained in the multivariate logistic regression models are illustrated in Figure 3.3.

<sup>5</sup> Logistic regression models were implemented using `lrm` from: [cran.r-project.org/package=rms](https://cran.r-project.org/package=rms).

Cox proportional hazards models were implemented using `coxalen` from: [cran.r-project.org/package=coxinterval](https://cran.r-project.org/package=coxinterval).

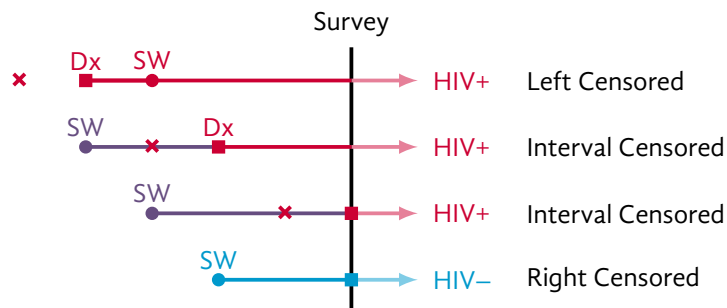


Figure 3.2: Illustration of time-to-event analysis framework for cross-sectional FSW survey data

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

Table 3.2: 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 <sup>a</sup>	1.11	<0.001*	—	—	1.14	<0.001*	1.15	<0.001*	1.09	<0.001*	1.09	<0.001*
Years selling sex <sup>a</sup>	1.13	<0.001*	1.13	<0.001*	1.12	<0.001*	—	—	1.08	<0.001*	—	—
Monthly sex work income <sup>b</sup>	0.98	0.155	—	—	0.98	0.097	0.97	0.084	0.98	0.019*	0.97	0.001*
Non-paying partners <sup>c</sup>	0.88	0.307	—	—	1.07	0.233	—	—	1.05	0.312	—	—
Monthly new clients <sup>c</sup>	1.01	0.412	—	—	1.05	<0.001*	1.07	<0.001*	1.04	<0.001*	1.04	<0.001*
Monthly regular clients <sup>c</sup>	1.01	0.351	—	—	1.03	0.002	—	—	1.02	<0.001*	1.02	0.034*
Non-paying condom use <sup>d</sup>	0.90	0.703	—	—	0.90	0.673	—	—	0.92	0.677	—	—
New client condom use <sup>d</sup>	0.60	0.100	—	—	0.48	0.006*	1.25	0.599	0.56	0.004*	—	—
Regular client condom use <sup>d</sup>	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*

<sup>a</sup> OR per year; <sup>b</sup> OR per Swati lilangeni per month; <sup>c</sup> OR per partner; <sup>d</sup> 2011: always vs. not always, 2014: at last sex. — indicates variable was not selected in the multivariate 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.

Following variable selection, each multivariate model was used to predict 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 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 [39] to support model parameterization; these ratios are summarized in Table 3.3.

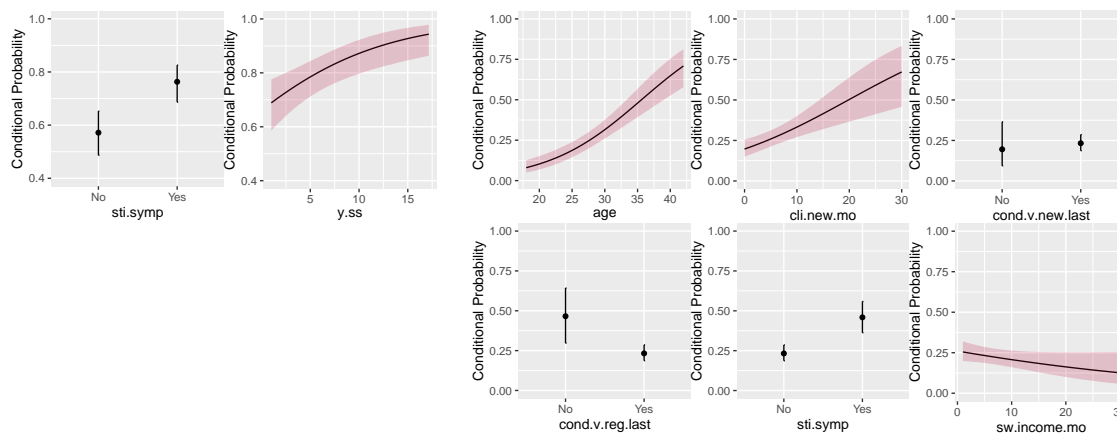
### 3.2.2 Probability of HIV Transmission

I parameterized the overall probability of transmission per sex act  $\beta$  as the product of a base rate  $\beta_0$ , 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



## 3.2 PARAMETERIZATION

44



(a) 2011 (serologic HIV status)

(b) 2014 (self-reported HIV status)

Figure 3.3: Predicted conditional effects (probability) of significant variables in multivariate logistic regression models from 2011 and 2014 surveys

sti.symp: any STI symptoms past year; y.ss: years selling sex; cli.new.mo: monthly new clients; sw.income.mo: monthly sex work income. Conditional probabilities shown for fixed covariates at arbitrary values.

Table 3.3: 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 <sup>a</sup>	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 <sup>bc</sup>	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 <sup>bc</sup>	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 <sup>bc</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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 multivariate model-predicted risk score; odds ratio from logistic regression (LR); hazards ratio from Cox proportional hazards (CPH). <sup>a</sup> Swati lilangeni per month; <sup>b</sup> 2011: always vs. not always, 2014: did use condom at last sex; <sup>c</sup> proportion of respondents; <sup>d</sup> 2011: serologic HIV status; 2014: self-reported HIV status; \* statistically significant,  $p < 0.05$ .

partners. Thus,  $\beta$  was defined as:

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

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. [11] 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 [11]. Such differences in transmission are most likely due to differences in viral load, which is associated with HIV stage [40, 41]. The probability of transmission during the middle asymptomatic period, was reported as mean (95% CI) 0.072 (0.053, 0.097)% per act, reflecting  $\beta_0$ . 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  $\beta_0$ . This probability was assumed to apply to vaginal intercourse, based on the studies considered.

For early infection ( $h = 2$ ), Boily et al. [11] 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 [42–44]. In a recent reanalysis of the Rakai cohort data, Bellan et al. [45] 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 [11], 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 [11, 41, 46] 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  $\beta_0$ .

### 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 [46, 47], and others reporting up to 2-times higher male-to-female ( $s' = 2, s = 1$ ) transmission vs. female-to-male ( $s' = 1, s = 2$ ) [11, 48]. 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. [49] synthesized the per-act transmission probability for anal intercourse, with most data from MSM studies. Analyses in [49] were not stratified by HIV stage, so I assumed the same relative rates derived in § 3.2.1 applied equally to vaginal and anal intercourse. Overall female-to-male (insertive) per-act transmission probabilities were similar for anal intercourse [50] (without ART): 0.14 (0.04, 0.29)% vs. vaginal intercourse [11] (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 [49] (without ART): 1.67 (0.44, 3.67)% vs. vaginal intercourse [11] (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 § 3.2.10 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 consistently been estimated as approximately 0.50, with 95% CI spanning (0.29, 0.96) [11, 47, 51]. Since circumcision status is unrelated to the research question, I fixed this effect at 50% relative risk. For anal intercourse, Wiysonge et al. [52] 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.<sup>6</sup> 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 [52, 53], 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 in heterosexual couples by Giannou et al. [54] 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 [55]. Thus, condom effectiveness was fixed at 74%. See § 3.2.3.2 for levels of condom use in Eswatini over time.

### 3.2.2.5 Genital Ulcer Disease

Genital ulcer disease (GUD) is another established risk factor for HIV transmission [56, 57]. Some, but not all GUD is associated with sexually transmitted infections (STIs), and some, but not all STIs can cause GUD [57]. GUD is thought to increase both HIV susceptibility and infectiousness through a variety of mechanisms [57–59], but HIV may also facilitate transmission of various STIs through immunosuppression [60]. The meta-analysis by Boily et al. [11] found that presence of STI alone was not associated with

<sup>6</sup> See § 3.2.1 for more discussion.

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 [61] 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 [2]. 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 [5]. Voluntary medical male circumcision (VMMC) increased circumcision coverage to 8.2% by 2007, following demand for mainly hygienic reasons [2]. In 2007, the government further increased scale-up of VMMC services as part of HIV prevention efforts [2], leading to 17.1% coverage in 2011 [62], 30.0% in 2017 [5], and 37% in 2021 [63]. Since VMMC continues to be a key element of Eswatini’s HIV response [63], 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 [62], so I assumed no differences. Similarly, while circumcision differed by union status in [5] (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 [64].

#### 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 [65] suggesting over-reporting of condom use, and [66] suggesting under-reporting of condom use. As such, I made no systemic adjustments to the available condom use data. Table 3.4 summarizes the available condom use data for Eswatini.

**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.<sup>7</sup>

<sup>7</sup> “Higher risk” partners were defined in [2] as: “Sexual intercourse with a partner who was neither a spouse nor lived with the respondent”, effectively matching the model definition of “casual” partnerships.

Table 3.4: 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)	[2]	a
		Men	last sex	23.1	(19.4, 26.9)	[2]	a
	2016	Women	last sex	52.7	(52.5, 52.9)	[5]	a
		Men	last sex	33.7	(30.8, 36.7)	[5]	a
Main or Casual	1988	Women	currently	0.6	(0.4, 1.3)	[67]	b
		Men	currently	7.3	(5.9, 12.1)	[67]	b
	2002	FSW	last sex	60	—	[68]	cd
			always	45.8	—	[68]	cd
	2006	Women	last sex	36.5	—	[2]	
		Men	last sex	47.2	—	[2]	
	2011	Women	always	30	—	[2]	
		Men	always	34	—	[2]	
		FSW	last sex	51.1	(41.8, 60.4)	[33]	de
			always	20.8	(14.7, 26.9)	[33]	de
	2014	FSW	last sex	80.6	(64.7, 89.6)	[34]	g
	2016	Women	last sex	58.3	—	[5]	
		Men	last sex	53.1	—	[5]	
Casual	2006	Women	last sex	53.5	—	[2]	
		Men	last sex	66.0	—	[2]	
	2016	Women	last sex	64.9	—	[5]	
		Men	last sex	73.7	—	[5]	
Sex Work Unspecified	2002	FSW	last sex	90	—	[68]	d
			always	74.4	—	[68]	d
	2020	FSW	always	50	—	[35]	
New Sex Work	2011	FSW	last sex	84.8	(57.9, 92.4)	[33]	ef
			always	56.7	(47.8, 65.6)	[33]	d
	2014	FSW	last sex	88.5	(54.9, 95.9)	[34]	g
Regular Sex Work	2011	FSW	last sex	82.9	(56.8, 90.0)	[33]	ef
			always	38.6	(29.5, 47.7)	[33]	e
	2014	FSW	last sex	85.6	(47.9, 95.0)	[34]	g

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

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

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 [2] and 2016 [5]. 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 back-calculation assuming 5% and 95%, yielding the confidence intervals shown in Table 3.4. 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 [69] 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 [68] 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. [70] estimate that among FSW globally, condom use in anal sex is approximately 79 (66, 94)% that of condom use in vaginal sex.<sup>8</sup> In Eswatini [33, 34], 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 [67]. 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 § A.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 [71].

### 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 [2, Table 13.14]; this prevalence was not stratified by numbers of partners, so I assumed it was equal across sexually active individuals in lowest and medium activity groups. However,

<sup>8</sup> I integrated the reported confidence intervals using the delta method after assuming binomial-distributed proportions.

approximately 19 and 32% of the lowest activity women and men were not sexually active during p12m (see § 3.2.8); thus I reduced GUD prevalence by 19 and 32%, respectively, among these groups.

The 2011 and 2014 FSW surveys did not ask respondents about GUD specifically, but about any STI symptoms in p12m.<sup>9</sup> In the wider population [2], approximately 60% of women self-reporting any STI symptoms specifically reported GUD in p12m; thus, self-reported STI symptoms among FSW may 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 § 3.2.1, 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. However, STI prevalence among Swati youth in 2017–18 remained high [72]. 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 [73], Senegal [74] and Zambia [64] 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 sampled higher risk client GUD prevalence uniformly between 7% and that of lower risk FSW, and sampled lower risk client GUD prevalence uniformly between 7% and that of higher risk clients.

### 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  $\eta_h$ , rates of additional HIV-attributable mortality by stage  $\mu_{\text{HIV},h}$ , and treatment via antiretroviral therapy (ART). Lodi et al. [75] estimate median times from seroconversion to CD4 < 500, < 350, and < 200 cells/mm<sup>3</sup>, while Mangal [6] directly estimate the rates of progression between CD4 states  $\eta_h$  in a simple compartmental model. Based on these data, I modelled mean durations ( $1/\eta_h$ ) of:<sup>10</sup> 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 [6, 76, 77]; based on these data, I estimated yearly HIV-attributable mortality rates  $\mu_{\text{HIV},h}$  as: 0 during acute phase

<sup>9</sup> 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”.

<sup>10</sup> Assuming exponential distributions for durations in each CD4 state (see § A.2.1 for more details).

( $h = 2$ ); 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).

### 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” [78]. Mujugira et al. [79] 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 [79]) 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 [80, 81]. 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”) [82]. 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 ( $c = 3$ ) [79]. Donnell et al. [41] estimate an adjusted incidence ratio of 0.08 (0.0, 0.57) for all individuals on ART. However, in [41] and [83], 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 [41] results in approximately 3.13 times higher estimated incidence ratio: 0.25 for this specific period.<sup>11</sup> 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 [84, 85]. Most CD4 recovery occurs within the first year of treatment [84]. Due to the limited number of modelled treatment states, I model this initial recovery to be associated with the pre-VLS ART state ( $c = 3$ ). Lawn et al. [85] and Gabillard et al. [86] estimate an increase of between 25–39 cells/mm<sup>3</sup> per month during the first 3 months of treatment. After initial increases, CD4 recovery is modest and plateaus. Battegay et al. [84] report approximate increases of 22.4 cells/mm<sup>3</sup> 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

<sup>11</sup> In [41], 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.



$h = 6 \rightarrow 5 \rightarrow 4 \rightarrow 3$  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 associated with increased risk of death by non-AIDS causes — i.e., unrelated to CD4 count — including cardiovascular disease and renal disease [87]. Lundgren et al. [88] estimated 61% reduction in non-AIDS life-threatening events due to ART. For the same CD4 strata, Gabillard et al. [86] 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  $\delta$ , ART initiation  $\tau$ , viral un-suppression  $\zeta$  (including treatment failure, discontinuation, or loss to follow-up), and viral re-suppression  $\sigma'$  (Figure 3.1c) were defined to reflect historical trends and ART eligibility for Eswatini. 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 [71].

#### 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 [89]. Indeed, EmaSwati living with HIV were more likely to have reported previously testing for HIV in 2006 [2, Table 14.9], 2011 [90, Table 5], and 2016 [5, 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  $\lambda$  can be calculated from the proportion tested  $\rho$  over period  $T$  via:

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

Moreover, [66] 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 [91] — 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 [92, 93]. Based on antenatal clinic data [94], 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 [95]. I assumed no initial differences between FSW and other women, due to the lack of specific key populations prevention programs [96]. 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 [2]<sup>12</sup> — 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 [95]. 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) [95, 97]. 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 [33, 90],<sup>13</sup> 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 [98] 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 [5], 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 [34] and 2020 [35] 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  $\tau$  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 [99–102]. Initial eligibility included one of [7]:

- CD4 < 200 cells/mm<sup>3</sup> and any WHO clinical stage
- CD4 < 350 cells/mm<sup>3</sup> and WHO clinical stage III
- any CD4 count and WHO clinical stage IV

<sup>12</sup> Unless otherwise noted, “tested for HIV” will imply “and received the results” throughout this section.

<sup>13</sup> The adjustment for missing ages 15–17 in [90] 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.

Eligibility was revised in 2010 [8] to:

- CD4 < 350 cells/mm<sup>3</sup> and any WHO clinical stage
- any CD4 count and WHO clinical stage III or IV

and again in 2015 [9] to:

- CD4 < 500 cells/mm<sup>3</sup> 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) [10, 103]. 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) [103]. Relative to the 114 total facilities offering ART nationally at this time [104], I assumed this trial had minimal direct impact on population-level ART initiation — notwithstanding valuable insights gained regarding effective implementation [103].

I implemented the CD4-only eligibility criteria directly in the model, which is structured to match these 200, 350, and 500 CD4 cells/mm<sup>3</sup> 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 [105, Table 4] and Saudi Arabia [106, 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 [95]. Early ART scale-up was modest, with 31 facilities offering ART by the end of 2009 [107]; however, this number increased rapidly to 110 facilities by the end of 2011 [95]. Phase 1 of MaxART (2011–2014) sought to further increase ART coverage among eligible PLHIV [98], including decentralization to lower level facilities, bringing the total number of facilities to 170 by 2015 [108]. 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 [103].

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 [109]; 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-naïve PLHIV in Eswatini, and 16% PLHIV with prior ART exposure [110]. 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 (e.g., Dolutegravir) can combat the population-level impacts of this resistance [111].

All available data suggests that retention in ART care — i.e., not discontinued or LTFU — has improved over time in Eswatini [5, 112, 113]. Assuming an exponentially-distributed retention time (consistent with inherent compartmental modelling assumptions), I averaged the available data [113, Table 6] to calculated 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 [5], 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 [114, 115]; 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 [114], which would be consistent with observed lower viral suppression among men vs. women on ART in Eswatini (Table 3.9) [114]. The same study estimated that LTFU did not significantly differ by the modelled CD4-strata [114]. No estimates of LTFU were available for FSW specifically in Eswatini, but among 354 FSW on ART in [35] (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 [109].

Considering all of the above data, I assumed: a yearly rate of viral un-suppression  $\zeta$  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  $\sigma'$  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 [8], but incorporated into standard of care by 2015 (yearly testing) [9]. Without viral load testing, treatment failure can still be indicated clinically [8]. After suspecting

treatment failure, at least three months of additional monitoring is typically required to rule-out issues of adherence [8–10], before another regimen is started. Moreover, second/third-line regimen options were limited in Eswatini until at least 2014 [104, 116]. Upon switching to an improved regimen, I assume that viral suppression occurs at the same rate as among ART-naïve 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 [117] 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  $\sigma'$  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 Sex Work: Population Sizes & Partner Numbers

#### 3.2.7.1 Population Sizes

Population sizes of all activity groups are modelled as proportions of the total population, which are assumed to remain roughly constant, although individuals can move between groups (see § 3.2.9.2), and disproportionate mortality due to HIV between groups may cause higher risk groups to shrink over time.

**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 [66, 118–121]. Therefore, FSW population size estimates require targeted surveys and unique methodologies [122, 123]. In both [34] and [35], 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) [122]. In 2011 [34], 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 [35], 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 § 3.2.1, the proportion of all FSW in the higher risk FSW group was fixed at 20%, and likewise the lower risk group at 80%.

**Clients of FSW.** Similar to FSW, household-based surveys are not considered reliable data sources for estimating the population size of clients of FSW [66]. 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 [69], similar to the “multiplier method” [124]. 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:

$$\sum_i P_{s_2 i_{34}} = \frac{\sum_{pi} P_{s_1 i} Q_{p_{34} s_1 i_{34}} F_{p_{34}}}{\sum_{pi} Q_{p_{34} s_2 i_{34}} F_{p_{34}}} \quad (3.3)$$

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 § 3.2.7.2, the client population size  $P_{s_2 i_{34}}$  estimated by this method was 13.1 (2.1, 38.5)% of men.

### 3.2.7.2 Sex Work Partnerships

**Female Sex Workers.** Table 3.3 summarizes the numbers of numbers of new and regular clients *per month* reported by Swati FSW, stratified by higher vs. lower risk per the analysis in § 3.2.1.3. In general, the numbers of partners “C” reported for a given recall period  $\gamma$  (e.g., 1 month) do not directly inform a partnership formation rate  $Q$  nor a number of concurrent partners  $K$  (see § A.2.3); rather, under certain assumptions,  $Q$  and  $K$  can be defined as:

$$Q = \frac{C}{\gamma + \delta} \quad (3.4)$$

$$K = \frac{C\delta}{\gamma + \delta} = Q\delta \quad (3.5)$$

The choice of force of infection model (see Chapter 4) will determine whether  $Q$  or  $K$  is used. Moreover, based on the survey questions,<sup>14</sup> it’s not clear whether these reported partner numbers  $C$  represent the numbers of unique men or unique client visits.

I assumed that all *new* clients were one-off visits; thus the reported partner numbers effectively represented 1/12th 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  $\delta_{p_3}$ , 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  $K_{p_3} = Q_{p_3}/12$  (per year).

For *regular* sex work partnerships, uncertainties remain regarding partnership duration  $\delta_{p_4}$  (see § 3.2.10.3), frequency of sex per month  $F_{p_4}/12$ , and survey responses  $C$  reflecting unique clients or total client visits per month. If  $C$  reflects the numbers of unique clients, then  $Q_{p_4s_1i_3}$  can be defined via Eq. (3.4) using  $C$  directly; whereas if  $C$  reflects the numbers of unique visits, then  $Q_{p_4s_1i_3}$  should be defined using  $C/(F_{p_4}/12)$ . 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:

$$C' = \rho C + (1 - \rho) C/(F_{p_4}/12) \quad (3.6)$$

Taking  $F_{p_4}/12 = 2$  as the prior mean from § 3.2.10.1, Eq. (3.6) simplifies to  $C' = \frac{5}{6} C$ . Then, sampling  $C_{p_4s_1i_3}$  from a gamma distribution with mean (95% CI) 8.4 (6.0, 11.0) from Table 3.3, and  $\delta_{p_4}$  as specified in § 3.2.10.3, I defined  $Q_{p_4s_1i_3}$  and  $K_{p_4s_1i_3}$  via Eq. (3.4) using  $C'_{p_4s_1i_3}$  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 3.3) as before.

**Clients.** For Sub-Saharan African clients of FSW, data 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 [125]. 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 [126]. Johnson and Dorrington [127] modelled yearly sex work visits among South African clients of FSW as gamma-distributed with age over

<sup>14</sup> The survey questions were: “In the last 30 days, how many (new/regular) clients have you had sex with?”, or similar.

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 ( $K_{p_{34}s_2i_{34}} F_{p_{34}}/12$ , 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 risk. Finally, since the distribution of sex acts between new vs. regular sex work partnerships must match that among FSW, the specific values of  $K_{p_{34}s_2i_{34}}$  were computed automatically. See § 3.2.8.4 for numbers of main/spousal and casual partnerships among FSW and clients.

### 3.2.8 Non-Sex Work: Group Sizes & Partner Numbers

#### 3.2.8.1 Reported Partner Numbers

The 2006-07 DHS [2], 2011 SHIMS [62], and 2016-17 SHIMS2 [5] 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.<sup>15</sup> However, 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 neither are those reporting 2+ partners in p12m. Moreover, such reports are likely substantially biased by social desirability bias due to the face-to-face interview format [66, 118, 120, 128].

Regarding the types of partnerships reported. Both the 2006 DHS [2, Tables 14.6.1 and 14.6.2] and 2016-17 SHIMS [5, Tables 15.4.A and 15.4.B] summarize the numbers of women and men by partners in p12m and by marital/union status, although 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).<sup>16</sup> The assumptions were:

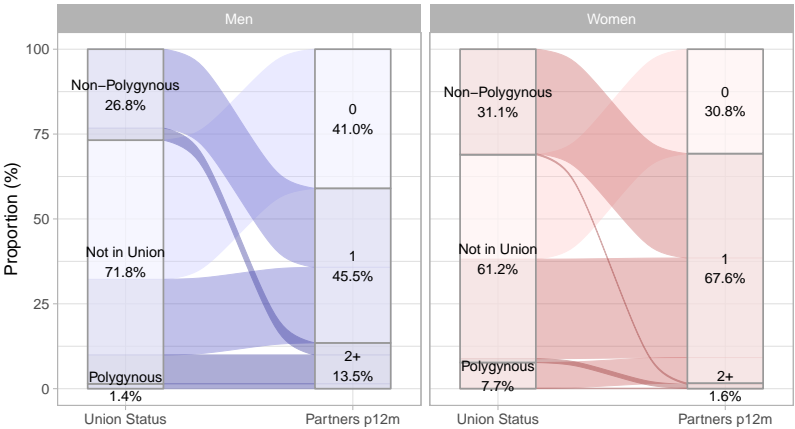
- $W_{2+}$  included all women in non-polygynous unions (married or cohabiting) reporting sex with a “casual” (non-marital, non-cohabiting) partner
- $M_{2+}$  included all men in polygynous unions, plus all men in non-polygynous unions reporting sex with a casual partner
- the remaining  $W_{2+}$  and  $M_{2+}$  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).

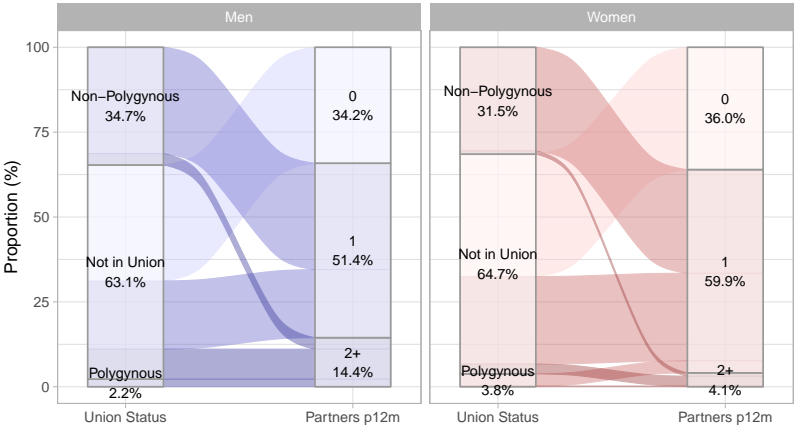
**Reporting Bias.** Next, I consider the issue of reporting bias.  $M_{2+}$  is consistently much greater than  $W_{2+}$ . This difference is common in surveys [129, 130], and could be explained by either: (a) a small number of women with many partners, such as FSW, who may also not be reached by the 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 [2, Table 14.7.1]

<sup>15</sup> From Tables 14.7.1 and 14.7.2 (ages 15-49) in [2], Table 3 (ages 18-49) in [62], Table 15.3.A (ages 15+) in [5], with manual adjustment for survey skip patterns in [2, 5].

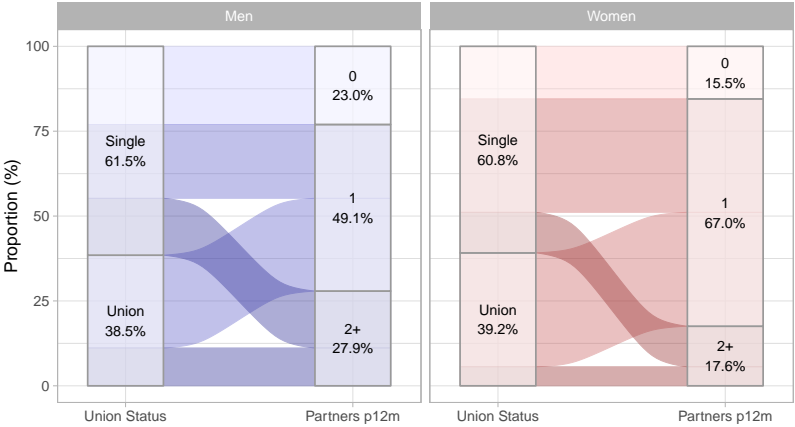
<sup>16</sup> Regarding notation in this section,  $W_{2+} = P_{s_1i_{234}}/P_{s_1}$ ,  $W_1 + W_0 = P_{s_1i_1}/P_{s_1}$ , and likewise for men ( $M$ ,  $s = 2$ ).



(a) 2006-07 [2]



(b) 2016 [5]



(c) Adjusted (mean)

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



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. [119] (Zimbabwe), Nnko et al. [131] (Tanzania) and Clark, Kabiru, and Zulu [132] (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 [133–136]. In fact, a review comparing computer-based tools vs. face-to-face interviews for surveying sexual behaviour [137] found that *both* women and men may under-report sexual partners, but women more so. A notable study in Benin [66] 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 surveys 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 women in p12m. Such findings were similar to those from Zimbabwe (1990s) [119].

### 3.2.8.2 Bias Adjustment: Approach

Reflecting these potential reporting biases and qualitative insights from [133–136], I modelled the “true” 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 “true” (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. [66]:<sup>17</sup>

$$\varphi_{W,s1:0} = \frac{W'_{s1}}{W'_0} \bigg/ \frac{W_{s1}}{W_0} \quad (3.7)$$

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. The corresponding transitions of women from reported to “true” 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  $\varphi$ , 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  $\varphi$  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 [2, 5]; thus  $\varphi_{u1:0}$ ,  $\varphi_{u1:s1}$ , and  $\varphi_{u2+:s2+}$  would be small but greater than 1 (horizontal transitions in Figure 3.5). Moreover, based on the median age of marriage, 23–29 [2], 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 [2]. Thus, I sampled each of  $\varphi_{u1:0}$ ,  $\varphi_{u1:s1}$ , and  $\varphi_{u2+:s2+}$  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.

<sup>17</sup> Odds ratios ensure no proportions become greater than one or negative.

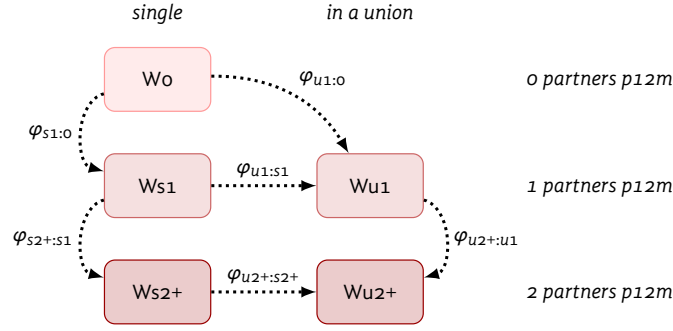


Figure 3.5: Illustration of how women (and equivalently men) are reallocated between union/partners in p12m strata based on odds ratios  $\varphi$

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 2+ partners in p12m; Ws2+: single and 2+ partners in p12m; Wu2+: in a union and 2+ partners in p12m.  $\varphi$ : odds of truly being in the second (arrowhead) vs first (tail) group.

**Partner Numbers.** Next, I defined  $\varphi_{s1:0}$ ,  $\varphi_{s2+:s1}$ , and  $\varphi_{u2+:u1}$  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 [2]. 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 [66], 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  $\varphi_{s2+:s1}$  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  $\varphi_{u2+:u1}$  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).

### 3.2.8.3 Bias Adjustment: Resulting Group Sizes & Partner Numbers

The mean resulting adjusted proportions  $W'$  and  $M'$  from solving the system with the assumed odds ratios  $\varphi$  are illustrated in Figure 3.4c, which can be compared to the reported proportions in a and b. Figure C.3 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
- $W'_{u1}/W'_{o1} = 38$  (21, 57)% women and  $M'_{u1}/M'_{o1} = 35$  (23, 50)% men with 0–1 partners in p12m were in a main/spousal partnership
- $W'_{s1}/W'_{o1} = 41$  (19, 65)% women and  $M'_{s1}/M'_{o1} = 31$  (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.

**Group Sizes.** From these results, 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 (see § 3.2.7.1). Thus, the populations size of medium activity women was defined as  $P_{s_1i_2} = W'_{2+} - P_{s_1i_{34}}$ . Sampling  $W'_{2+}$  from a BAB distribution with 95% CI (10, 27)%, the resulting 95% CI for medium activity women  $P_{s_1i_2}$  was (6, 25)% of women. The lowest activity women population size was then defined as  $1 - P_{s_1i_{234}}$ , 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  $P_{s_2i_2}$  could yield negative values. Instead, I sampled  $P_{s_2i_2}$  directly from a BAB distribution with 95% CI (10, 17)%, yielding 95% CI for  $P_{s_2i_{234}}$  of (15, 50)% of men, which is close to (15, 44)% from  $M_{2+}$ . The lowest activity men were then defined as  $1 - P_{s_2i_{234}}$ , representing (50, 85)% of men.

**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 ( $C_{p_1s_{12}i_1}$ ), as well as all women in the median activity group ( $C_{p_1s_{12}i_2}$ ). Then, Eqs. (3.4) and (3.5) were used to define  $Q$  and  $K$ , respectively. Since FSW and clients had fewer main/spousal partnerships (see § 3.2.8.4), I calculated the proportion of men in the medium activity group having main/spousal partnerships  $K_{p_1s_{2i_2}}$  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  $C_{p_2s_{12}i_1}$  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 p12m for the medium activity groups must be at least about 1.5 to ensure these women and men actually have 2+ partners in p12m. Thus, I sampled the number of casual partners reported by women in the medium activity group  $C_{p_2s_{12}i_2}$  from a gamma distribution with 95% CI (1.2, 2), and computed  $Q$  and  $K$  via Eqs. (3.4) and (3.5). As before, I calculated the numbers of casual partnerships among men in the medium activity group  $K_{p_2s_{2i_2}}$  to balance total casual partnerships.

#### 3.2.8.4 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 3.3), which may include both main/spousal partners and casual partners. Among FSW in South Africa [138] and Kenya [139], 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.,  $C_{p_1s_{12}i_3} = 0.5$ ); lower risk FSW reported  $C_{p_2s_{12}i_3} = 0.5$  casual partners; and higher risk FSW reported  $C_{p_2s_{12}i_4} = 1.0$  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 [74, 140]. Non-paying partners of FSW are also often clients of other FSW [139, 141]. Yet, clients of FSW also tend to be younger and more likely to be never/formerly married vs. non-client men [140, 142]. So, I assumed that clients reported half the numbers of main/spousal partnerships compared to lowest activity men:  $C_{p_1s_{2i_3}} = 0.5 C_{p_1s_{2i_1}}$ , and 25–

100% the numbers of casual partnerships compared to medium activity women (uniform prior). As before, I computed  $Q$  and  $K$  via Eqs. (3.4) and (3.5).

### 3.2.9 Turnover

#### 3.2.9.1 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 [2, 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 [WHO2006EswMort]. 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  $\nu$  to fit population size of ages 15–49 in Eswatini [14], and approximate population growth rates [143], given that I model HIV/AIDS-attributable mortality separately. Specifically, I assumed a population growth rate  $g = \nu - \mu$  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 [143]. Finally, I calculated the population entry rate as  $\nu = g + \mu$ . These parameter values were informally validated by comparison of model outputs with Swati population sizes for ages 15–49 from [14]. 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 § 3.2.9.2.

#### 3.2.9.2 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 [16]. Previous modelling has shown that activity group turnover (sometimes called “episodic risk”) can strongly influence parameter fitting and intervention impact [144, 145]. I model turnover from activity group  $si$  to  $si'$  as a constant rate  $\theta_{si'i}$ , which implies an assumption that (in the absence of HIV) duration in group  $si$  is exponentially distributed with mean  $D_{si}$  [146]:

$$D_{si} = \frac{1}{\mu + \sum_{i'} \theta_{si'i}} \quad (3.8)$$

where  $\mu$  is the overall exit rate from § 3.2.9.1. As shown previously [145], the relative sizes of each sex-activity group  $P_{si}$  can be maintained at fixed values by satisfying the following “mass-balance” equation:

$$\nu P_{si} = \nu E_{si} + \sum_{i'} \theta_{si'i} P_{si'} - \sum_i \theta_{sii} P_{si} \quad (3.9)$$

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

**Duration Selling Sex.** The FSW survey data for 2011 [33], 2014 [34], and 2021 [35] 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 were median [IQR]: 4 [2, 7] in 2011 and 5 [3, 9] in 2014, with histograms shown in Figure C.1. 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 [147]. I fit an exponential distribution to the cumulative adjusted proportions (Figure C.2), yielding an estimated distribution mean  $\lambda^{-1}$  of 4.2 (3.5, 5.3) years. However, the reported years selling sex in a cross sectional survey will underestimate the eventual duration in sex work among respondents by a factor  $f \leq 2$ , because respondents continue selling sex after the survey — i.e., the observed duration is right censored (see § A.2.2 for derivation and further discussion). 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 [34] (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 [148].

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 3.3). Thus, durations in sex work among higher risk ( $D_{HR}$ ) and lower risk ( $D_{LR}$ ) FSW can be resolved using:

$$\begin{aligned}\bar{D} &= 0.2 D_{HR} + 0.8 D_{LR} \\ R_D &= D_{HR}/D_{LR}\end{aligned}\tag{3.10}$$

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. [148] estimated mean durations of 4.6–5.5 years based on studies in Benin [140] and Kenya [125]. Hodgins et al. [149, 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 [129] 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  $\theta_{siv}$ . Since higher and lower risk FSW (and clients) are conceptualized as mutually exclusive groups, I modelled no turnover between these groups:  $\theta_{s_{i3}i_4} = \theta_{s_{i4}i_3} = 0$  (+2 constraints). Next, since FSW often enter sex work shortly after sexual debut [147, 150], and sexual activity is roughly constant or slightly declining with age [129], I assumed that  $E_{si} = f P_{si}$ ,<sup>18</sup> 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 [16, 151], I further assumed that (50, 90)% of women exiting sex work transition to the medium activity group (BAB prior) (+2 constraints). In the absence of relevant data, I made a similar assumption regarding clients, with (25, 90)% former clients transitioning to the medium activity group. These 10 < 12 total constraints then allow two degrees of freedom to resolve the values of  $\theta_{siv}$  and  $E_{si}$ . A non-negative solution to the system of constraints is solved as described in [145],<sup>19</sup> repeated at each timestep as  $v$  varies with time.

### 3.2.10 Sex Frequency & Partnership Duration

#### 3.2.10.1 Sex Frequency

The Eswatini general population data sources [2, 5, 62] 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) [152], 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 [153, Figure 3.15], which is roughly consistent with [152], 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” [154]. 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  $F_{p_2}/F_{p_1} \sim \text{Unif}(0.25, 1)$ . As described in § 3.2.7.2, 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.

<sup>18</sup> Subject to  $f \leq (v - \mu + D_{si}^{-1})v^{-1}$ , which can be derived from Eq. (10) in [145].

<sup>19</sup> Using [docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.nnls.html](https://docs.scipy.org/doc/scipy/reference/generated/scipy.optimize.nnls.html)

### 3.2.10.2 Anal Sex

Among Eswatini data sources, only [34] (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 [155], and face-to-face interview survey design may result in under-reporting [70]. 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 [156], vs 2.4–15.9% among FSW [70]. To reflect this greater uncertainty, the proportions of sex acts which are anal in main/spousal and casual partnerships are sampled from a gamma prior distribution with 95% CI (0.6, 16.5)%, and likewise for occasional and regular sex work partnerships with 95% CI (2.4, 15.9)%. Finally, I ensure a greater proportion of anal sex in sex work vs. main/spousal and casual partnerships per § A.1.3.

### 3.2.10.3 Partnership Duration

As explored in Chapter 4, the durations of sexual partnerships can be key determinants of epidemic dynamics and intervention impact.<sup>20</sup> 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 [157]. Similar to challenges in estimating sex work duration (§ A.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.<sup>21</sup> The difference between the exponential distribution mean and median should also be kept in mind (see § A.2.1).

**Main/Spousal Partnerships.** Detailed data on marriage in Eswatini was only captured in 2006 [2, 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 [158]; such data may not capture non-marital secondary unions. Thus, I assumed 5–20% of unions among EmaSwati aged 50–54 were secondary. Further assuming an exponential distribution for the proportion of enduring partnerships  $\rho$  vs. time  $T$  per Eq. (3.2), I defined  $\rho \in (0.56, 0.71)$ ,  $t = 52 - 26 = 26$  years, yielding an effective partnership termination rate of  $\lambda \in (1.32, 2.23)\%$  per year, and an effective partnership duration of  $\delta_{p_1} = \lambda^{-1} \in (45, 76)$  years.

Classically, partnership duration is used to define the total numbers of sex acts per modelled partnership (see § 4.1); with this approach, we should therefore use  $\delta_{p_1} = \rho (49 - 26) \in (14.5, 18.5)$  years, since the modelled population only includes ages 15–49. However, the proposed approach to modelling partnerships introduced in § 4.2 can make use of the effective termination rate. In fact, the proposed approach uses a

<sup>20</sup> Chapter 4 also discusses the related phenomenon of partnership concurrency, and how concurrency is represented in compartmental models.

<sup>21</sup> 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).



partnership *change* rate, which would be even slower than the partnership termination rate, as the change rate would 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 unions ended via spousal death (83% of unions among women and 56% among men by age 50–54) [2]. For simplicity, I assumed an effective main/spousal partnership change rate of 1–2% per year with the proposed approach (regardless of mortality), and effective duration of 14.5–18.5 years with the classic approach (both uniform priors).

**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 [159–161], Rural Tanzania [131], and four cities in Kenya, Zambia, Benin, and Cameroon [162]. Based on these data, I defined a gamma prior distribution for the mean duration of casual partnerships  $\delta_{p_2}$  with 95% CI (0.25, 1.5) years, roughly consistent with prior models [163].

**Sex Work Partnerships.** As noted in § 3.2.7.2, 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 [139, 164]. Based on [125], I defined a gamma prior distribution for the mean duration of regular sex work partnerships  $\delta_{p_4}$  with 95% CI (0.5, 2.0) years.

### 3.2.11 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  $M_{pi i'}$  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  $M_{pi i'}$  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).

#### 3.2.11.1 Classic $\epsilon$ 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 [165]. This approach is often attributed to [166], 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:

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

where:  $I$  represents complete like-with-like mixing (an identity matrix),  $\pi$  represents random mixing (random but proportional to the number of partnerships “offered”), and  $\epsilon$  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  $M_{pi i'} = M_{pi} \rho_{pi i'}$ . Three advantages of Eq. (3.11) are: (1) simplicity; (2)  $\epsilon$  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, although some modest extensions can be made, such as asymmetric age mixing among women and men (e.g., [167]).

### 3.2.11.2 Log-Linear Mixing

A more general approach to mixing is developed in [168]. This “log-linear” approach defines the mixing matrix elements  $M_{pi i'}$  as follows. The expected total numbers of partnerships between risk groups under random mixing are defined as:

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

Next, a matrix  $\Phi_{pi i'}$  is defined, representing the odds of a type- $p$  partnership forming between groups  $i$  and  $i'$ , compared to random mixing. The matrix  $\Phi$  must be symmetric, and can be estimated directly from the right kind of data (which is rarely available) [168]. Then, an initial estimate of  $M_{pi i'}$  is:

$$\begin{aligned} M_{pi i'}^{(0)} &= \exp \left[ \log \left( \Pi_{pi i'} \right) + \Phi_{pi i'} \right] \\ &= \Pi_{pi i'} \exp \left( \Phi_{pi i'} \right) \end{aligned} \quad (3.13)$$

However, this estimate changes the total numbers of partnerships formed by each group:  $M_{pi}^{(0)} \neq \Pi_{pi}$ , where  $M_{pi} = \sum_{i'} M_{pi i'}$  and  $\Pi_{pi} = \sum_{i'} \Pi_{pi i'}$ . There is no *a priori* definition of  $M_{pi i'}$  or adjustment to  $\Phi_{pi i'}$  that can guarantee the numbers of partnerships will not change.<sup>22</sup> However, an iterative proportional fitting procedure [169] can resolve an estimate  $M_{pi i'}^{(n)}$  that maintains the total numbers of partnerships:

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

Each step of this procedure can be understood as a re-scaling of the current estimate  $M_{pi i'}^{(n)}$  row-wise ( $i$ ) or column-wise ( $i'$ ) to match the numbers of partnerships offered by individuals ( $\Pi_{pi}$ ) or their partners ( $\Pi_{pi'}$ ). Each row-step re-introduces discrepancies in the columns, and vice versa, but overall convergence is guaranteed [170].

In practice, Eq. (3.14) adds approximately one decimal of precision per  $2n$  for the  $4 \times 4$  case, thus 15–20 iterations is often sufficient to come within computational precision limits. Since the partnerships matrix  $M_{pi i'}$  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  $\Phi_{pi i'}$ .

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

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  $\sum_j \omega_s M_{psj}$ , where  $\omega_s$  are weights such that  $\sum_s \omega_s = 1$ . Similar to the “compromise” parameter  $\theta$  in [166], 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.

### 3.2.11.3 Odds of Mixing

Despite the flexibility in the odds of mixing matrix  $\Phi_{pi i'}$ , limited data are available to inform specific elements, especially for Eswatini in particular. In Kenya [139], Benin, Guinea, and Senegal [141], and Uganda [164], a disproportionate fraction of non-paying partners of FSW were former and/or current clients. Given this fraction  $\psi$  and the proportion of all men who are clients  $\rho$ , the odds of these partnerships forming can be computed as:

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

Taking  $\psi \in (0.33, 0.70)$  [139, 141] and  $\rho \in (5, 20)\%$  [149], we obtain  $\Phi \in (2, 19)$ . As noted in § 3.2.8.4, it is 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:  $\Phi_{p_{12}i_{34}i'_{34}}$  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 [171], observed like-with-like sexual mixing preferences in numerous other contexts [168, 172, 173], and prior modelling work [174]. I sampled  $\Phi_{p_{1i_1}i'_1}$  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 parameter posterior distributions — 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.

### 3.3.1 Approach

I used a Bayesian approach for model calibration [175]. Let  $\theta$  denote the complete set of 74 calibrated model parameters (Table C.1), and  $T$  the complete set of 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 [5]; using this information, I defined a BAB distribution as the likelihood function for this calibration target  $p(T_i | \theta)$ . Thus, a parameter set  $\theta_{s_1}$  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  $\theta_{s_2}$  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 (57) calibrated parameters were sampled using Latin hypercube sampling [176]. The remaining 17 calibrated parameters were sampled randomly and iteratively until they satisfied a set of relational constraints (see § C.3.1).

Although several iterative methods exist to update the sampling distributions based on the likelihoods, and thereby characterize the posterior distribution more efficiently [175], I did not update the sampling distributions. Rather, I simply took the top 1% of parameter sets  $\theta_s$  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 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 [2], 2011 [3, 4], and 2016 [5] 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 [2] and Table C.2 in [5]). 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

Table 3.5: Estimates of HIV prevalence in Eswatini

Population <sup>a</sup>	Year	N	Raw	Adjusted		Used	Ref	Notes
			%	%	(95% CI)			
Overall	2006	8,187	25.9	—	(24.4, 27.3)	✓	[2]	b
	2011	18,172	32.1	28.0	(27.0, 29.0)	✓	[3]	cd
	2016	8,533	27.2	—	(25.8, 28.7)	✓	[5]	b
Women Overall	2006	4,424	31.1	—	(29.4, 32.9)	✓	[2]	b
	2011	9,843	38.8	34.2	(33.0, 35.4)	✓	[3]	cd
	2016	4,878	34.3	—	(32.6, 36.0)	✓	[5]	b
Men Overall	2006	3,763	19.7	—	(17.9, 21.4)	✓	[2]	b
	2011	8,329	24.1	20.7	(19.6, 21.8)	✓	[3]	cd
	2016	3,655	18.8	—	(17.3, 20.4)	✓	[5]	b
LR Overall	2006	7,589	24.9	—	—	✗	[2]	
	2011	16,145	31.9	—	—	✗	[3]	
	2016	7,887	32.2	—	—	✗	[5]	
Non-LR Overall	2006	579	38.3	—	—	✗	[2]	
	2011	1,887	33.3	29.0	(25.9, 32.2)	✗	[3]	cd
	2016	914	28.7	—	(25.8, 31.7)	*	[5]	f
LR Women	2006	4,346	30.7	26.8	(22.7, 28.7)	*	[2]	e
	2011	9,843	38.2	30.8	(28.9, 32.8)	*	[3]	ce
	2016	5,203	36.5	31.5	(30.0, 33.1)	*	[5]	e
Non-LR Women	2006	72	53.0	—	(41.5, 64.3)	*	[2]	f
	2011	373	54.5	48.1	(41.5, 54.8)	*	[3]	cd
	2016	263	45.3	—	(39.3, 51.3)	*	[5]	f
LR Men	2006	3,243	17.1	14.1	( 6.5, 16.7)	*	[2]	e
	2011	6,733	23.2	19.0	(18.0, 20.1)	*	[3]	ce
	2016	2,684	25.1	16.9	(15.7, 18.1)	*	[5]	e
Non-LR Men	2006	506	36.1	—	(32.0, 40.3)	*	[2]	f
	2011	1,515	28.1	24.1	(21.4, 26.9)	*	[3]	cd
	2016	651	22.8	—	(19.7, 26.1)	*	[5]	f
FSW Overall	2011	328	70.3	60.5	(52.1, 69.0)	✓	[33]	g
	2014	781	37.8	—	—	✗	[34]	h
	2021	676	60.8	58.8	(53.9, 63.6)	✓	[33]	g

<sup>a</sup> LR: lower risk, reporting 0-1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; <sup>b</sup> 95% CI as reported from sampling adjustment; <sup>c</sup> adjusted from ages 18-49 to 15-49 (see § 3.3.2.1); <sup>d</sup> 95% CI expanded via inferred sampling adjustment; <sup>e</sup> adjusted for biased reporting of risk behaviours (see § 3.2.8.2 and § 3.3.2.1); <sup>f</sup> 95% CI inferred from N; <sup>g</sup> RDS-adjusted; <sup>h</sup> self-reported; \* used within prevalence ratio only; all estimates used the BAB distribution.

Table 3.6: Estimated HIV prevalence ratios in Eswatini

Numerator <sup>a</sup>	Denominator <sup>a</sup>	Year	Ratio	(95% CI)	Used	Ref	Notes
Non-LR Women	LR Women	2006	2.02	(1.84, 2.34)	✓	[2]	b
		2011	1.54	(1.47, 1.66)	✓	[3]	b
		2016	1.42	(1.37, 1.51)	✓	[5]	b
Non-LR Men	LR Men	2006	2.57	(2.16, 5.28)	✓	[2]	b
		2011	1.24	(1.20, 1.34)	✓	[3]	b
		2016	1.32	(1.26, 1.45)	✓	[5]	b
FSW Overall	Women Overall	2011	2.16	(1.87, 2.50)	✓	[3, 33]	b
HR FSW	LR FSW	2011	1.46	(1.30, 1.63)	✓	[33]	c
		2014	2.30	(1.92, 2.75)	✗	[34]	cd

<sup>a</sup> 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 § 3.2.1; <sup>b</sup> mean and 95% CI estimated via Monte Carlo sampling; <sup>c</sup> per analysis in § 3.2.1.3; <sup>d</sup> self-reported; see Table 3.5 for more notes on data sources and adjustments.

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 [3].

**Biased Partner Number Reporting.** As discussed in § 3.2.8.2, 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 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 § 3.2.8.3.

**Respondent Ages.** The 2006 and 2016 surveys provide data for ages 15–49 (the age range intended to be captured by the model) while 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; so, I adjusted all 2011 HIV prevalence estimates in as follows. Drawing on age-stratified data in 2006 [2] and 2011 [3], 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%) [177]. 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

Table 3.7: Estimates of HIV incidence in Eswatini

Population <sup>a</sup>	Year	N	Raw	Adjusted		Used	Ref	Notes
			%	%	(95% CI)			
Overall	2016	9,476	1.48	—	(0.96, 1.99)	✓	[5]	bc
Women Overall	2011	5,486	3.1	2.94	(2.52, 3.47)	✓	[4]	de
	2016	5,227	1.99	—	(1.16, 2.80)	✓	[5]	bc
Men Overall	2011	5,746	1.7	1.50	(1.16, 1.84)	✓	[4]	de
	2016	4,249	0.99	—	(0.39, 1.59)	✓	[5]	bc
LR Women	2011	4,924	3.21	1.58	(0.40, 2.24)	*	[4]	def
Non-LR Women	2011	93	10.10	9.62	(4.76, 18.29)	*	[4]	de
LR Men	2011	3,855	1.64	0.76	(0.01, 1.17)	*	[4]	def
Non-LR Men	2011	874	3.87	3.42	(2.21, 4.94)	*	[4]	de
FSW Overall	2021	676	11.71	—	(8.31, 16.92)	✓	[35]	b

<sup>a</sup> LR: lower risk, reporting 0–1 partners p6m; Non-LR: lower risk, reporting 2+ partners p6m; FSW: female sex worker; <sup>b</sup> via HIV-1 Limiting Antigen recency testing; <sup>c</sup> 95% CI as reported from sampling adjustment; <sup>d</sup> via 6 month cohort (94.4% follow-up); <sup>e</sup> adjusted from ages 18–49 to 15–49 (see § 3.3.2.1); <sup>f</sup> adjusted for biased reporting of risk behaviours (see § 3.2.8.2 and § 3.3.2.1); \* used within incidence ratio only; all estimates used the skew normal distribution.

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).

### 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) [4, 62], 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) [178]; this LAg EIA incidence measure was validated during SHIMS1 [62]. Recency testing was also recently integrated into Eswatini standard of care [63].

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 [4]). 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).

Table 3.8: Estimated HIV incidence ratios in Eswatini

Numerator <sup>a</sup>	Denominator <sup>a</sup>	Year	Ratio	(95% CI)	Used	Ref	Notes
Non-LR Women	LR Women	2011	5.74	(2.47, 22.26)	✓	[3]	<sup>b</sup>
Non-LR Men	LR Men	2011	4.16	(1.69, 23.09)	✓	[3]	<sup>b</sup>

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

No study of FSW in Eswatini estimated incidence directly, but [35] reported that 30 of 676 prevalent HIV infections among FSW were identified as recent via LAg EIA per national guidelines [5, 63]. 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  $\rho \sim \text{Binom}(\rho = 4.44\%, N = 676)$  and  $T \in (118, 140)$ , yielding 95% CI for  $\lambda$  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 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 [179] 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 [5] 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 C.1 for definitions), and the modelled patterns of transmission among risk groups in Eswatini over time.

### 3.4.1 Posterior Parameter Distributions

Figure 3.6 illustrates the distributions of calibrated model parameters, stratified by top 1% (posterior) vs bottom 99% according to calibration likelihood. Many of the distributions do not significantly differ (Kolmogorov-Smirnov Test [181]), indicating that calibration did not reduce uncertainty in these parameters. While more advanced model calibration techniques might improve parameter inference [175], the overall model fit was judged to be sufficient for the downstream research questions (§ 1.4). A total of 19 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, C1m\_swr\_fsw\_l, dur\_acute, dur\_cas, F\_msp, F\_swr, PF\_ai\_mcx, PX\_w\_fsw, Rbeta\_acute, RC\_cas\_cli.wm, RF\_cas.msp

Table 3.9: Estimated HIV cascade of care in Eswatini

Step <sup>a</sup>	Population <sup>a</sup>	Year	N	%	(95% CI)	Used	Ref	Notes
Diagnosed among PLHIV	Overall	2011	5,807	62.6	(61.4, 63.8)	✓	[90]	bc
		2016	2,417	86.1	(84.7, 87.6)	✓	[5]	e
	Women overall	2011	3,810	69.1	(67.6, 70.6)	✓	[90]	b
		2016	1,690	90.2	(88.6, 91.8)	✓	[5]	e
	Men overall	2011	1,997	50.1	(47.9, 52.3)	✓	[90]	b
		2016	727	77.3	(74.0, 80.6)	✓	[5]	e
	FSW	2011	313	74.1	(61.7, 89.8)	✓	[180]	d
		2021	411	88.3	(85.1, 91.2)	✓	[35]	bf
On ART among Diagnosed	Overall	2011	3,635	52.1	(50.5, 53.7)	✓	[90]	bcd
		2016	2,113	87.8	(86.0, 89.6)	✓	[5]	e
	Women overall	2011	2,633	48.0	(46.1, 49.9)	✓	[90]	bd
		2016	1,532	87.5	(85.4, 89.6)	✓	[5]	e
	Men overall	2011	1,002	62.7	(59.7, 65.7)	✓	[90]	bd
		2016	581	88.4	(85.2, 91.6)	✓	[5]	e
	FSW	2011	174	36.9	(30.1, 44.2)	✓	[180]	
		2021	363	97.5	(95.7, 98.9)	✓	[35]	bf
On ART among PLHIV	Overall	2011	5,807	31.9	(30.7, 33.1)	✓	[90]	bc
		2016	2,417	75.6	(73.6, 77.5)	✓	[5]	e
	Women overall	2011	3,810	33.2	(31.7, 34.7)	✓	[90]	b
		2016	1,690	78.9	(76.8, 81.1)	✓	[5]	e
	Men overall	2011	1,997	31.4	(29.4, 33.4)	✓	[90]	b
		2016	727	68.3	(64.7, 72.0)	✓	[5]	e
	FSW	2011	313	27.4	(20.9, 35.7)	✓	[180]	d
		2021	411	86.1	(82.6, 89.3)	✓	[35]	bf
VLS among On ART	Overall	2016	1,858	90.3	(89.0, 91.6)	✓	[5]	e
	Women overall	2016	1,342	91.4	(89.9, 92.8)	✓	[5]	e
	Men overall	2016	516	87.6	(84.4, 90.9)	✓	[5]	e
VLS among PLHIV	Overall	2016	2,417	68.2	(66.1, 70.4)	✓	[5]	e
	Women overall	2016	1,690	72.1	(69.7, 74.5)	✓	[5]	e
	Men overall	2016	727	59.9	(56.1, 63.7)	✓	[5]	e

<sup>a</sup> PLHIV: people living with HIV; ART: antiretroviral therapy; VLS: HIV viral load suppressed, defined as  $\leq 1000$  RNA copies/mL in [5]; FSW: female sex worker; <sup>b</sup> 95% CI inferred from N; <sup>c</sup> estimated from combining women & men; <sup>d</sup> estimated from conditional steps, with 95% CI via simulation; <sup>e</sup> 95% CI as reported from sampling adjustment; <sup>f</sup> not RDS-adjusted; n.b. [2] did not provide any appropriate cascade data.



- **Mean decreased:** `dur_cli`, `dur_fsw_l`, `dx_wq_2011`, `Rdx_global`, `Rdx_m.wq_2011`

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 [182, 183].

Figure 3.7 further illustrates bivariate rank correlations among posterior parameter values (subset of parameters with at least one correlation  $\pm 0.1$ ). Of these 19 parameters, 12 were subject to relational constraints (§ C.3.1) and 11 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 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 (`beta_o`) 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 [185], although no parameters in the model are perfectly non-identifiable. Thus, the variance of posterior distributions may be inflated for these parameters [185], 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 § C.3.2, including: distribution of log-likelihoods (Figure C.4) total Eswatini population size aged 15–49 (Figure C.8), and condom use within each partnership type (Figure C.9).

#### 3.4.2.1 HIV Prevalence & Incidence

Figure 3.8 illustrates the modelled HIV prevalence (a) and incidence (b) among selected risk groups. Figures C.5 and C.6 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 C.3). 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

## 3.4 RESULTS

77

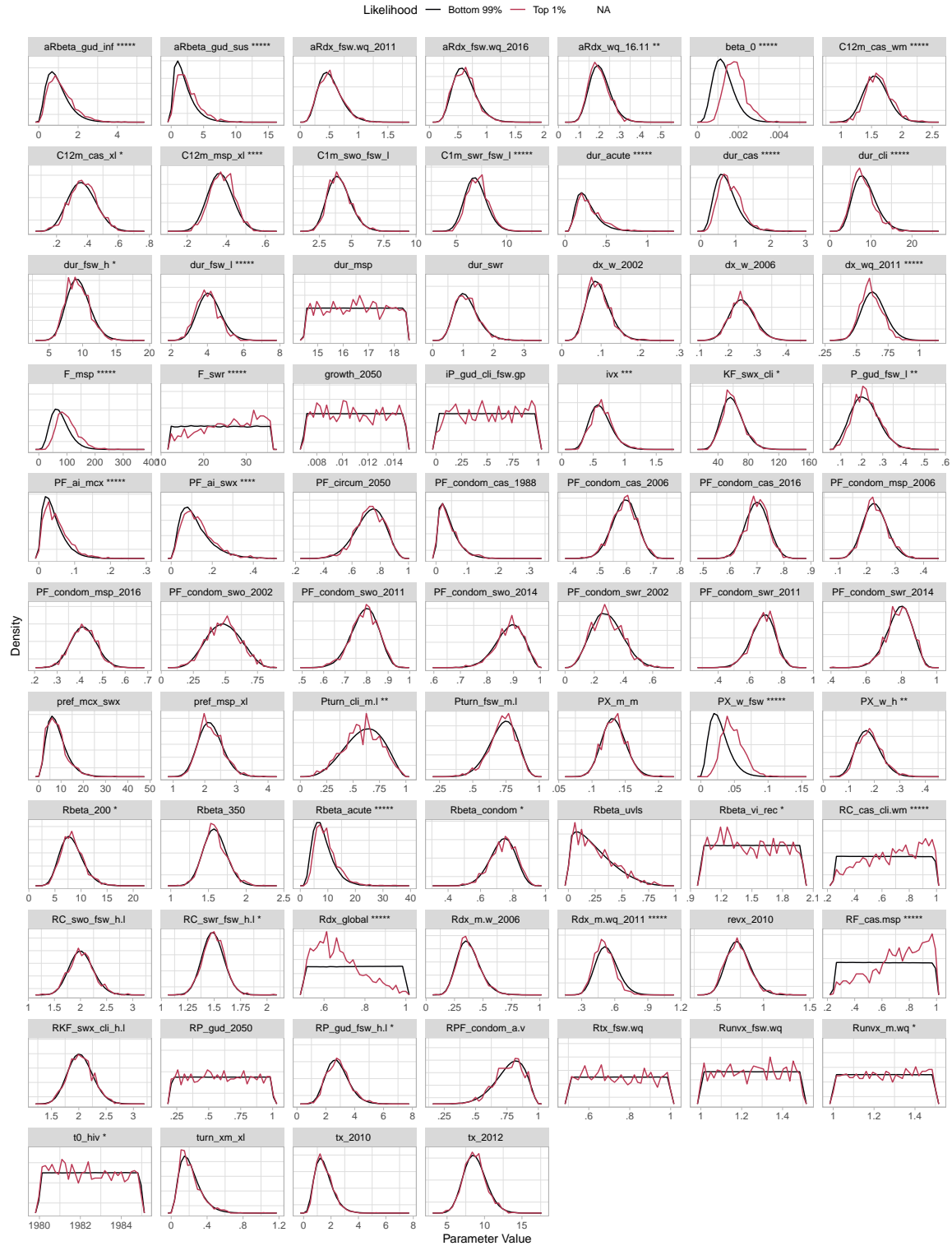


Figure 3.6: Distributions of calibrated model parameters, stratified by top 1% (posterior) vs bottom 99% according to calibration likelihood

Asterisks denote significance of Kolmogorov-Smirnov (KS) Test [184] for comparing distributions, where  $p < 0.1$ : \*,  $p < 0.01$ : \*\*, etc; see Table C.1 for parameter definitions

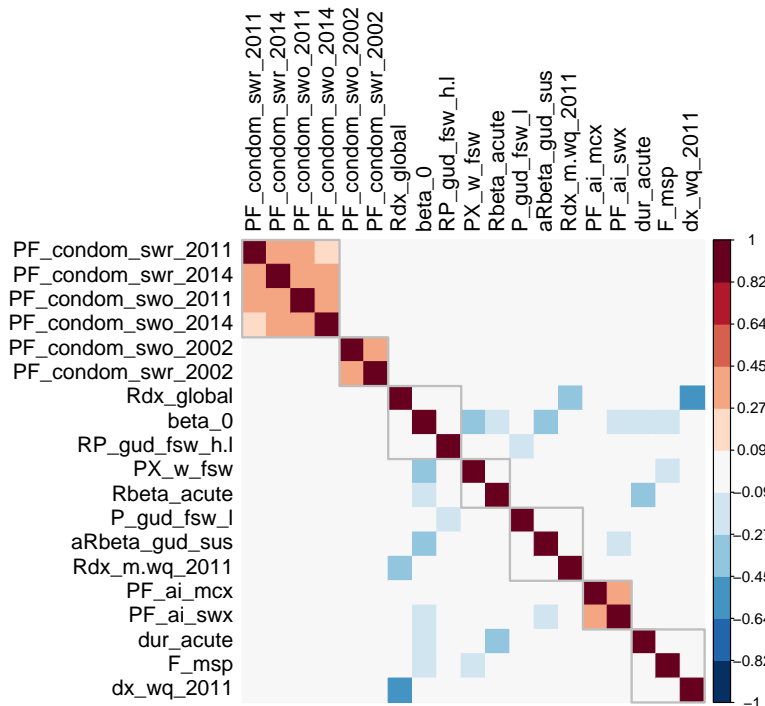


Figure 3.7: Rank correlations among selected posterior model parameters

Subset of parameters with at least one correlation  $\pm 0.1$ ; layout computed via hierarchical clustering using the Ward-2 criterion [181]; gray squares denote computed clusters; see Table C.1 for parameter definitions

that HIV prevalence among lower risk groups can be partially driven by turnover of infected individuals from higher risk groups [145].

Few data are available to validate the modelled early epidemic dynamics. Modelled incidence among women and men peaked rapidly after introduction of HIV (Figure 3.8b), 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 “partnership-level herd effects” (see § 4.3.3). These trends can be compared with HIV prevalence from Eswatini antenatal care clinics over the same period (Figure C.7), which suggest similar trends.<sup>23</sup> 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 C.9). 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.

<sup>23</sup> 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 [186, 187].

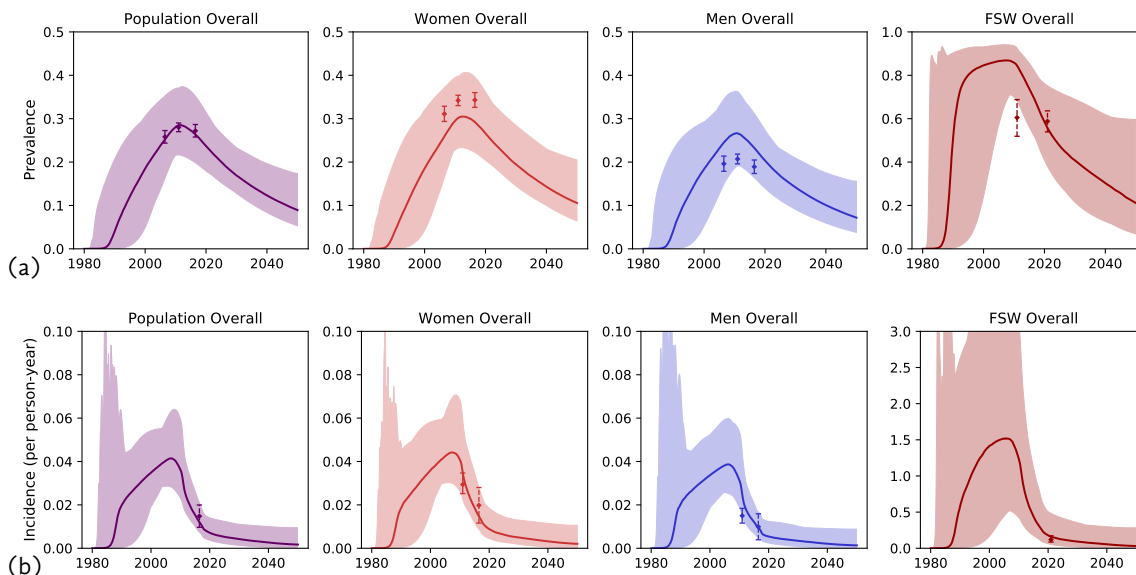


Figure 3.8: Modelled HIV prevalence and incidence among selected risk groups and associated calibration targets

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.

#### 3.4.2.2 ART Cascade

Figure 3.9 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 3.10 illustrates the total numbers and proportions of modelled yearly infections transmitted from (a) and acquired among (b) modelled risk groups. Figure 3.11 then gives the *ratio* of yearly infections transmitted vs. acquired. Figure 3.12 stratifies yearly infections by partnership type, while Figure 3.13 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

## 3.4 RESULTS

80

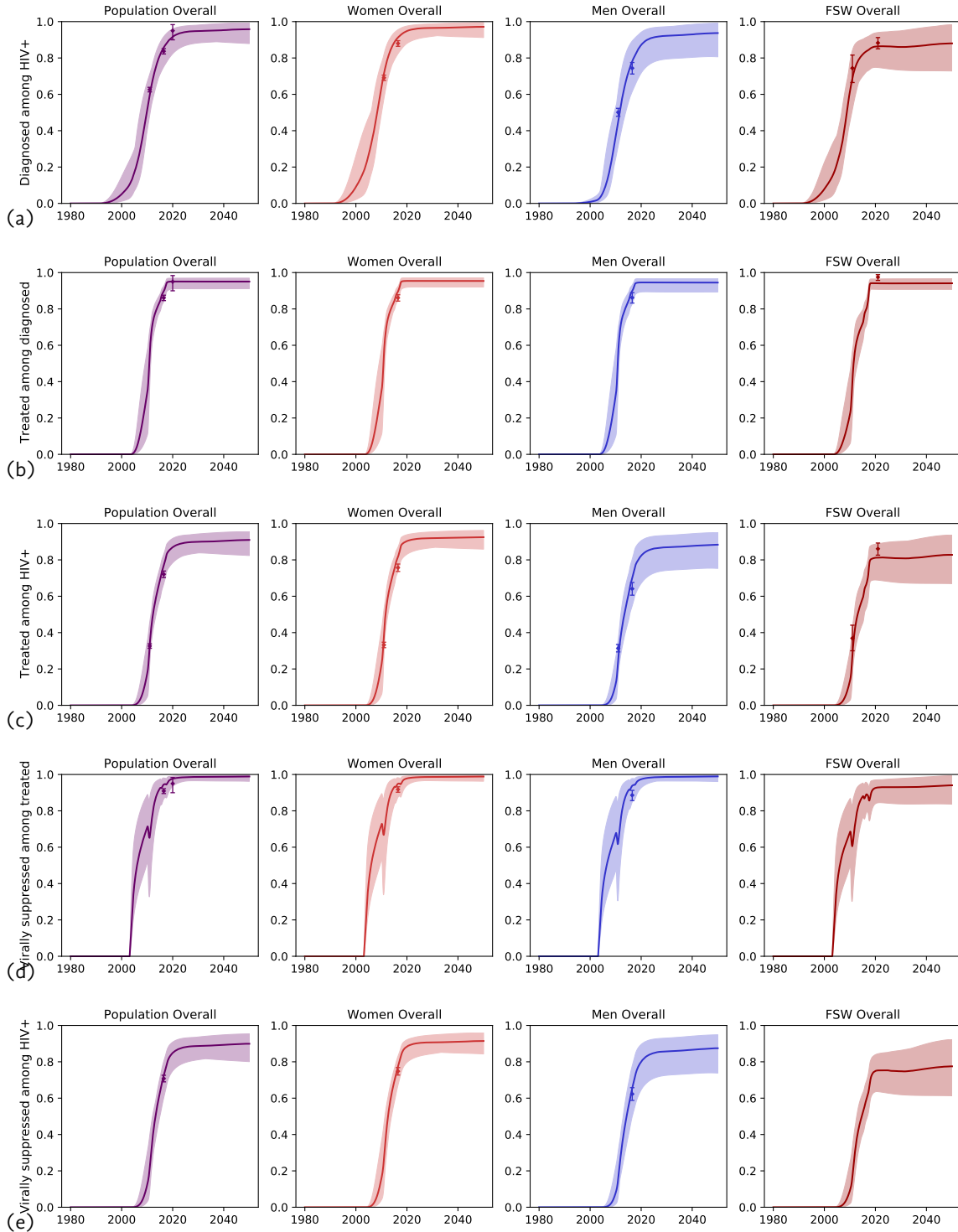


Figure 3.9: Modelled ART cascade among selected risk groups and associated calibration targets

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; PLHIV: people living with HIV.

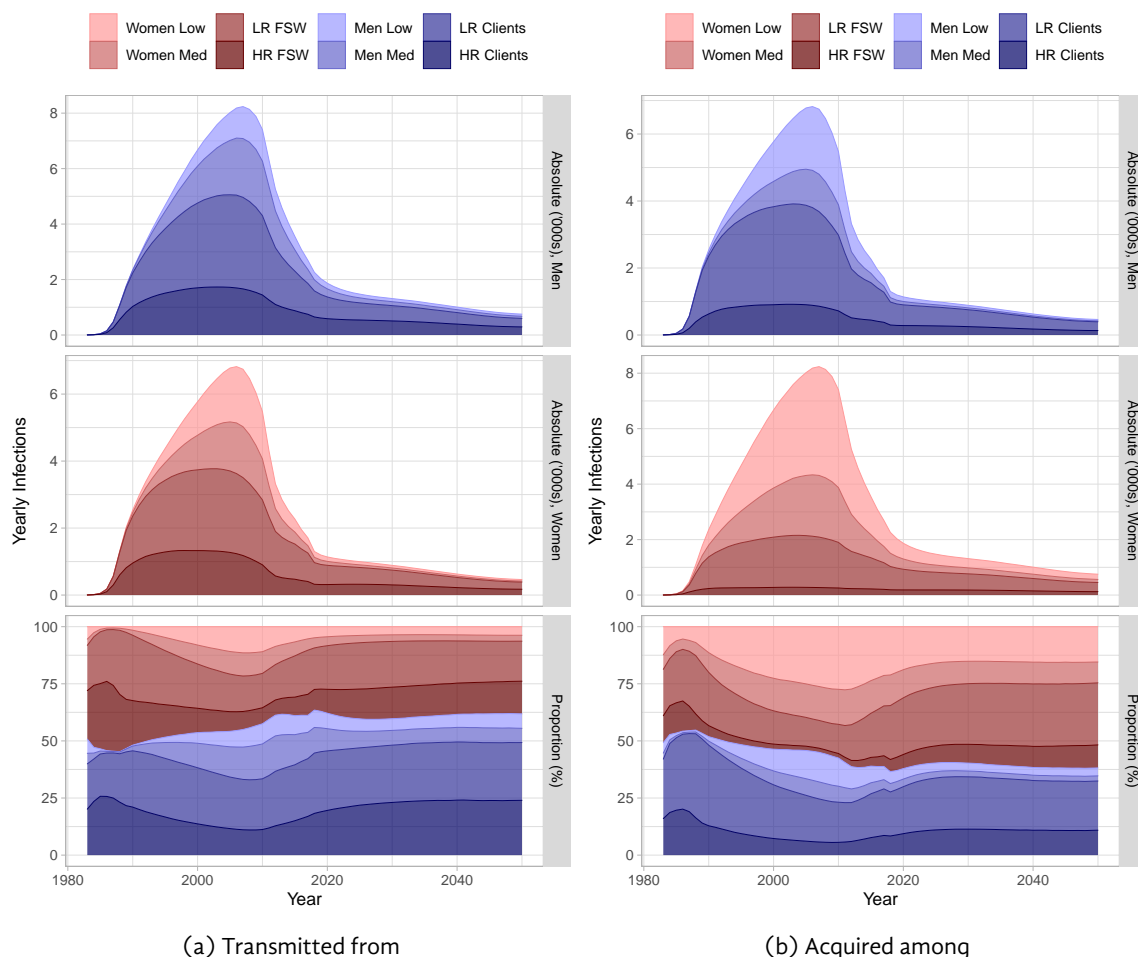


Figure 3.10: Absolute numbers and proportions of modelled yearly HIV infections (a) transmitted from and (b) acquired among risk groups in Eswatini

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.

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 [126, 142, 188], 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 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

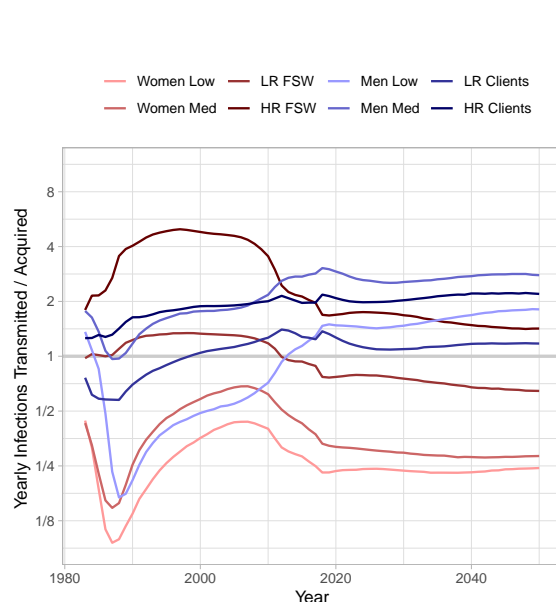


Figure 3.11: Ratio of modelled yearly infections transmitted from vs. acquired among risk groups in Eswatini

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.



Figure 3.12: Absolute numbers and proportions of modelled yearly HIV infections transmitted via different partnership types in Eswatini

“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 [189, 190], and likely threatens to undermine the anticipated prevention benefits of ART scale-up (as explored in Chapter 5) [191].

## 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, 192]. It’s not clear whether these supplementary materials are 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,<sup>1</sup> 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

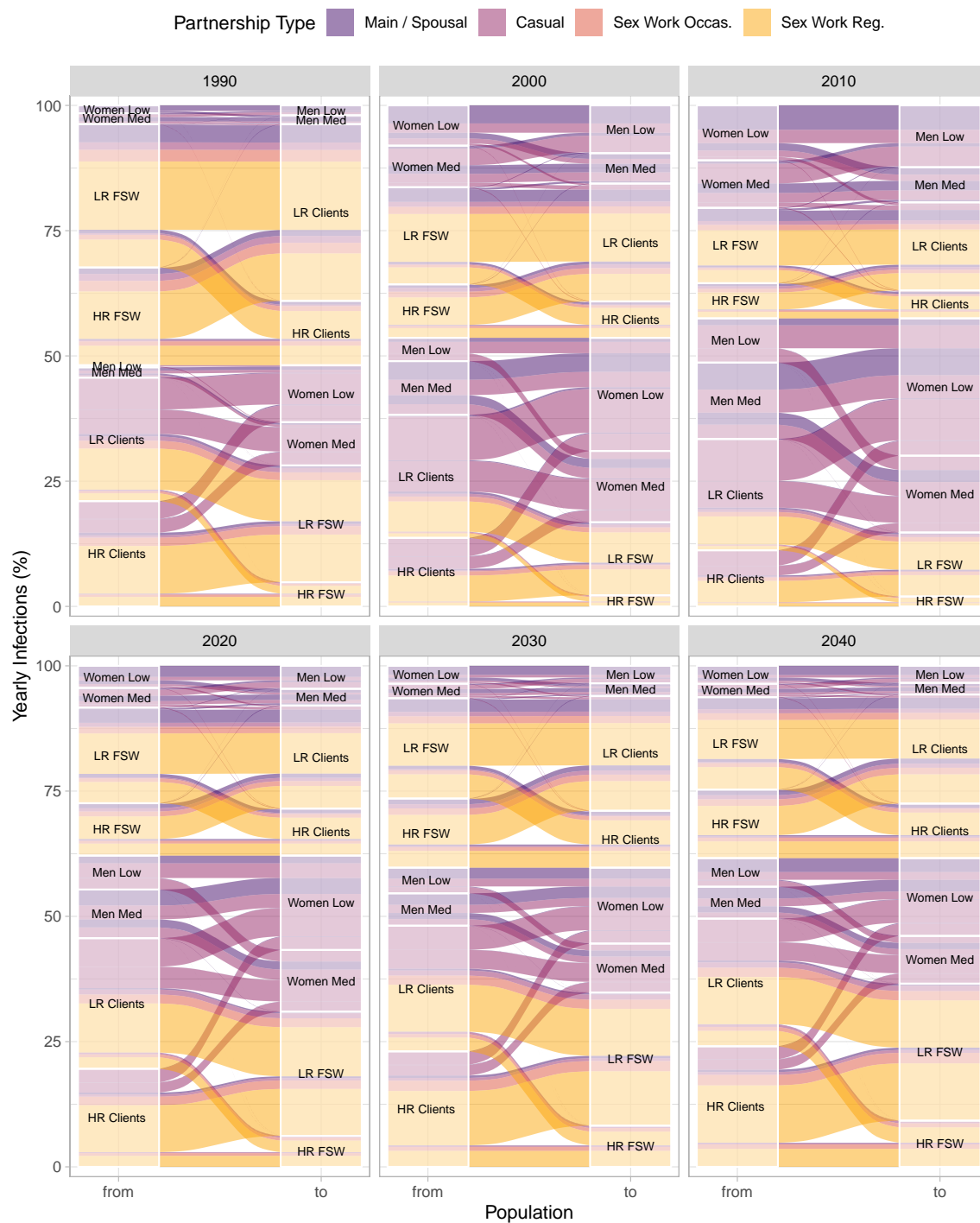


Figure 3.13: Alluvial diagram showing proportions of all yearly infections (ribbons) transmitted from (left) to (right) modelled risk groups, stratified by partnership type (color) and year (facets) in Eswatini

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.



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 [193]. 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 [194] 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 [195–198]. As such, household-based surveys are generally not recommended to collect data on stigmatized behaviour and/or key populations [122, 123].

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 [121, 137]. 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 [66] and 6–8 times higher in India [121]; reporting of genital ulcers was likewise 2–5 and 14–35 times higher, respectively; buying and selling sex was similarly biased [66, 121]. Qualitative data from Eswatini [133–136] 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., [199]. 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?*” [194] or “*past 1 month*”, etc. [33, 34, 68]. 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 § A.2.3, I showed that the correct interpretation is somewhere in between these extremes, and derived expressions for both the partnership formation rate Eq. (A.4) and numbers of concurrent partners Eq. (A.5), given a partnership duration. While partnership duration can also be challenging to measure [157], 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 [165, 200, 201]. 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 [200]. 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 ( $\epsilon$ ) approach [165, 174].<sup>24</sup> This approach assumes that a minimum proportion of partners ( $\epsilon$ ) are guaranteed to be from the same risk group, and that this proportion is fixed and equal for all risk groups.

By contrast, the log-linear approach proposed in [168] provides greater flexibility in conceptualizing and implementing mixing via the *odds* of any two groups mixing vs. random mixing. However, [168] 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 § 3.2.11.2, I developed a method to maintain fixed partnership formation rates for arbitrary mixing patterns using an iterative proportional fitting procedure [169]. 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 [202].

### 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 [144, 145]. 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 [145]. Turnover can be parameterized using, among other things, the average duration within a given risk group [145]. Within the model, these durations are implicitly assumed to be exponentially distributed, which appears reasonable for Swati FSWs [33, 34] (Figure C.2). 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 § 3.2.9.2 and A.2.2, 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 [147] (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”) [148]. 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 [147], and whether paid sex is driven by supply vs. demand [201, 203].

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

### 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 [15, 16, 19, 204]. The Eswatini model aims to represent this heterogeneity — albeit simply — by stratifying FSW into higher and lower risk groups. As explored in § 3.2.1, I parameterized these groups using individual-level data from FSW surveys in 2011 [33] and 2014 [34] 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 [204, 205] — 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 [33, 34]. While cross-sectional data can be used to estimate associations of factors with HIV status, which may be directly useful for recommending HIV testing [206], 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 [204, 205]. Regarding HIV status, self-reported status was historically considered unreliable due to low rates of HIV diagnosis and high rates of incidence among FSW [207, 208]; 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 [209].

## 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 [210, 211]. 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 [211]. In fact, HIV prevalence among Swati MSM has been estimated to be similar to among men aged 15–49 overall (approximately 20%) [5, 35, 211], likely because Swati MSM tend to skew younger, while HIV prevalence increases with age [5, 35]. The population size of MSM in Eswatini is estimated to be 1–2% of men aged 15–49 [14, 34, 35]. Thus, although unmet needs of MSM in other SSA countries are estimated to drive overall transmission [212, 213], including via overlapping MSM and heterosexual networks [214], 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 [2, 5, 62]. 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 [2, 5, 62].

Indeed, adolescent girls and young women are increasingly recognized as another key population in the HIV epidemic response [28], whose vulnerabilities include: higher biological susceptibility, gender-based violence, food/economic insecurity, and transactional relationships — defined in [215] as: “*non-commercial, non-marital sexual relationships motivated by the implicit assumption that sex will be exchanged for material support or other benefits*” [28, 216, 217]. Qualitative data highlight the prevalence of such factors in Eswatini, with roots in patriarchal norms and broader social pressures [133–136, 218].

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 [134, 136, 219] some infections can become “trapped” within age cohorts [220], whereas the model without age stratification implicitly assumes random age mixing throughout the population;<sup>25</sup> 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 (§ C.3.1). Additionally, the calibration approach used (selecting the top 1% of 100,000 parameter sets by likelihood) was similar to prior approaches [222], 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 3.7). The quality of parameter inference and model agreement with the calibration targets might be improved using more efficient calibration techniques [175], such as Sampling Importance Resampling (SIR) [223] or Incremental Mixture Importance Sampling (IMIS) [224].

<sup>25</sup> The importance of age-disparate partnerships for prevention remains controversial [171, 219, 221].

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.

**COVID-19.** Many health systems were disrupted by the COVID-19 pandemic, including in Eswatini [63]. 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 [63]. While rapid interventions designed to minimize ART interruption were largely successful, COVID-19 mortality was high among PLHIV in Eswatini [63]. Additionally, government restrictions aimed at reducing COVID-19 transmission — including closing bars, clubs, etc., imposing a nighttime curfew, and travel restrictions [35] — likely also reduced HIV incidence, especially among FSW [225].

**Civil Unrest.** As noted in § 1.2, democratic freedoms in Eswatini are severely limited by the absolute monarchy [226], and socioeconomic inequality remains high [227]. 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 [226, 227]. Such protests have been met with violence, including the assassination of prominent human rights lawyer and activist Thulani Maseko in 2023 January [228]. The trajectory of this unrest is not clear [229], 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 [230, 231], and aims to expand PrEP access nationally in the coming years, with a focus on adolescent girls and young women (AGYW) and FSW [63]. An estimated 25% of FSW (N = 264) and 8% of MSM (N = 303) were on PrEP by 2021 [35]. The success of these efforts will likely be further improved with the addition of long-acting injectable PrEP options [232, 233]. Similar improvements in viral suppression may also be gained in the coming years via long-acting injectable ART [234]. 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 [80, 81, 235, 236]. 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 [63, 237]. The current model does not currently include any of these emerging interventions, but they should be feasible to integrate in the future.

## References

- [1] S. Gill. "A process for the step-by-step integration of differential equations in an automatic digital computing machine". *Mathematical Proceedings of the Cambridge Philosophical Society* 47.1 (1951), pp. 96–108. <https://doi.org/10.1017/S0305004100026414>.
- [2] Central Statistical Office Swaziland. *Swaziland Demographic and Health Survey 2006–07*. Mbabane, Swaziland, 2008. <https://dhsprogram.com/>.
- [3] George T. Bicego et al. "Recent Patterns in Population-Based HIV Prevalence in Swaziland". *PLOS ONE* 8.10 (2013), e77101. <https://doi.org/10.1371/journal.pone.0077101>.
- [4] Jessica Justman et al. "Swaziland HIV Incidence Measurement Survey (SHIMS): a prospective national cohort study". *The Lancet HIV* 4.2 (2016), e83–e92. [https://doi.org/10.1016/S2352-3018\(16\)30190-4](https://doi.org/10.1016/S2352-3018(16)30190-4).
- [5] Eswatini Ministry of Health. *Swaziland HIV Incidence Measurement Survey 2 (SHIMS2) 2016–2017*. Mbabane, Eswatini, 2019.
- [6] Tara D. Mangal. "Joint estimation of CD4+ cell progression and survival in untreated individuals with HIV-1 infection". *AIDS* 31.8 (2017), pp. 1073–1082. <https://doi.org/10.1097/QAD.0000000000001437>.
- [7] Swaziland Ministry of Health. *National Guidelines for Antiretroviral Treatment and Post Exposure Prophylaxis*. Mbabane, Swaziland, 2006.
- [8] Swaziland Ministry of Health. *The National Guidelines on the Comprehensive HIV Package of Care for Adults and Adolescents in Swaziland*. Mbabane, Swaziland, 2010.
- [9] Swaziland Ministry of Health. *Swaziland Integrated HIV Management Guidelines*. Mbabane, Swaziland, 2015.
- [10] Swaziland Ministry of Health. *Swaziland Integrated HIV Management Guidelines*. Mbabane, Swaziland, 2018.
- [11] Marie Claude Boily et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". *The Lancet Infectious Diseases* 9.2 (2009), pp. 118–129. [https://doi.org/10.1016/S1473-3099\(09\)70021-0](https://doi.org/10.1016/S1473-3099(09)70021-0).
- [12] Alan Whiteside and Amy Whalley. *Reviewing Emergencies for Swaziland: Shifting the Paradigm in a New Era*. Mbabane, Swaziland: NERCHA, 2007.
- [13] John Iliffe. *The African AIDS Epidemic: A History*. Cape Town, South Africa: Ohio University Press, 2005. <https://isbnsearch.org/isbn/9780821442739>.
- [14] The World Bank. *World Bank Open Data*. 2020. <https://data.worldbank.org>.
- [15] James F. Blanchard and Stephen Moses. "Female Sex Workers and Their Clients in the Epidemiology and Control of Sexually Transmitted Diseases". *Sexually Transmitted Diseases*. Ed. by King K. Holmes et al. 4th ed. McGraw Hill, 2008. Chap. 12, pp. 187–201. <https://openlibrary.org/books/OL9792815M>.
- [16] Fiona Scorgie et al. "Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review". *AIDS and Behavior* 16.4 (2012), pp. 920–933. <https://doi.org/10.1007/s10461-011-9985-z>.
- [17] Ide Cremin et al. "PrEP for key populations in combination HIV prevention in Nairobi: a mathematical modelling study". *The Lancet HIV* 4.5 (2017), e214–e222. [https://doi.org/10.1016/S2352-3018\(17\)30021-8](https://doi.org/10.1016/S2352-3018(17)30021-8).
- [18] Andrea Low et al. "Potential impact of existing interventions and of antiretroviral use in female sex workers on transmission of HIV in Burkina Faso: A modeling study". *Journal of Acquired Immune Deficiency Syndromes* 68 (2015), S180–S188. <https://doi.org/10.1097/QAI.0000000000000441>.
- [19] Kate Shannon et al. "Global epidemiology of HIV among female sex workers: Influence of structural determinants". *The Lancet* 385.9962 (2015), pp. 55–71. [https://doi.org/10.1016/S0140-6736\(14\)60931-4](https://doi.org/10.1016/S0140-6736(14)60931-4).
- [20] Leigh F. Johnson et al. "The effect of changes in condom usage and antiretroviral treatment coverage on human immunodeficiency virus incidence in South Africa: A model-based analysis". *Journal of the Royal Society Interface* 9.72 (2012), pp. 1544–1554. <https://doi.org/10.1098/rsif.2011.0826>.
- [21] Mathieu Maheu-Giroux et al. "Population-level impact of an accelerated HIV response plan to reach the UNAIDS 90-90-90 target in Côte d'Ivoire: Insights from mathematical modeling". *PLOS Medicine* 14.6 (2017). Ed. by Nicola Low, e1002321. <https://doi.org/10.1371/journal.pmed.1002321>.

- [22] Mathias Aklilu et al. "Factors associated with HIV-1 infection among sex workers of Addis Ababa, Ethiopia". *AIDS* 15.1 (2001), pp. 87–96. <https://doi.org/10.1097/00002030-200101050-00013>.
- [23] K. L. Dunkle et al. "Risk factors for HIV infection among sex workers in Johannesburg, South Africa". *International Journal of STD and AIDS* 16.3 (2005), pp. 256–261. <https://doi.org/10.1258/0956462053420220>.
- [24] Anna Jonas et al. "HIV prevalence, risk factors for infection, and uptake of prevention, testing, and treatment among female sex workers in Namibia". *Journal of Epidemiology and Global Health* 10.4 (2020), pp. 351–358. <https://doi.org/10.2991/jegh.k.200603.001>.
- [25] Charlotte Watts et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". *Sexually Transmitted Infections* 86.S3 (2010), pp. iii85–iii92. <https://doi.org/10.1136/sti.2010.044602>.
- [26] Daphne A. van Wees et al. "Longitudinal Patterns of Sexually Transmitted Infection Risk Based on Psychological Characteristics and Sexual Behavior in Heterosexual Sexually Transmitted Infection Clinic Visitors". *Sexually Transmitted Diseases* 47.3 (2020), pp. 171–176. <https://doi.org/10.1097/OLQ.0000000000001110>.
- [27] Elizabeth Roberts et al. "Low program access despite high burden of sexual, structural, and reproductive health vulnerabilities among young women who sell sex in Mombasa, Kenya". *BMC Public Health* 20.1 (2020). <https://doi.org/10.1186/s12889-020-08872-6>.
- [28] Rachael C. Dellar, Sarah Dlamini, and Quarraisha Abdool Karim. "Adolescent girls and young women: Key populations for HIV epidemic control". *Journal of the International AIDS Society* 18.2 (2015), pp. 64–70. <https://doi.org/10.7448/IAS.18.2.19408>.
- [29] R. Scott McClelland et al. "HIV-1 acquisition and disease progression are associated with decreased high-risk sexual behaviour among Kenyan female sex workers". *AIDS* 20.15 (2006), pp. 1969–1973. <https://doi.org/10.1097/01.aids.0000247119.12327.e6>.
- [30] Lyle R. McKinnon et al. "Risk Factors for HIV Acquisition in a Prospective Nairobi-Based Female Sex Worker Cohort". *AIDS and Behavior* 19.12 (2015), pp. 2204–2213. <https://doi.org/10.1007/s10461-015-1118-7>.
- [31] Marcellin N Nouaman et al. "Incidence of HIV infection and associated factors among female sex workers in Côte d'Ivoire, results of the ANRS 12361 PrEP-CI study using recent infection assays". *PLOS ONE* 17.11 (2022). Ed. by Hamid Sharifi, e0271988. <https://doi.org/10.1371/journal.pone.0271988>.
- [32] Frances H. Priddy et al. "Anal sex, vaginal practices, and HIV incidence in female sex workers in Urban Kenya: Implications for the development of intravaginal HIV prevention methods". *AIDS Research and Human Retroviruses* 27.10 (2011), pp. 1067–1072. <https://doi.org/10.1089/aid.2010.0362>.
- [33] Stefan Baral et al. "Reconceptualizing the HIV epidemiology and prevention needs of female sex workers (FSW) in Swaziland". *PLOS ONE* 9.12 (2014), e115465. <http://doi.org/10.1371/journal.pone.0115465>.
- [34] PEPFAR. *Characterizing the HIV Prevention and Treatment Needs among Key Populations, including Men who Have Sex with Men and Female Sex Workers in Swaziland: From Evidence to Action*. Mbabane, Swaziland, 2015.
- [35] Eswatini Ministry of Health. *2020–2021 Integrated Biological-Behavioral Surveillance Survey among Female Sex Workers and Men Who Have sex with Men in Eswatini*. Mbabane, Eswatini, 2022.
- [36] Eileen A. Yam et al. "Association between condom use and use of other contraceptive methods among female sex workers in swaziland: A relationship-level analysis of condom and contraceptive use". *Sexually Transmitted Diseases* 40.5 (2013), pp. 406–412. <https://doi.org/10.1097/OLQ.0b013e318283c16d>.
- [37] Sharon Stucker Weir et al. *Priorities for Local AIDS Control Efforts: A Manual for Implementing the PLACE Method*. University of North Carolina at Chapel Hill, 2005. <https://www.measureevaluation.org/resources/publications/ms-05-13.html>.
- [38] J. F. Lawless and K. Singhal. "Efficient Screening of Nonnormal Regression Models". *Biometrics* 34.2 (1978), p. 318. <https://doi.org/10.2307/2530022>.
- [39] Ajit C. Tamhane and Brent R. Logan. *Finding the maximum safe dose level for heteroscedastic data*. 2004. <https://doi.org/10.1081/BIP-200035413>.
- [40] M. S. Saag et al. *HIV viral load markers in clinical practice*. 1996. <https://doi.org/10.1038/nm0696-625>.
- [41] Deborah Donnell et al. "Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis". *The Lancet* 375.9731 (2010), pp. 2092–2098. [https://doi.org/10.1016/S0140-6736\(10\)60705-2](https://doi.org/10.1016/S0140-6736(10)60705-2).
- [42] T. Déirdre Hollingsworth, Roy M. Anderson, and Christophe Fraser. "HIV-1 transmission, by stage of infection". *Journal of Infectious Diseases* 198.5 (2008), pp. 687–693. <https://doi.org/10.1086/590501>.



- [43] Myron S. Cohen et al. "Acute HIV-1 Infection". *New England Journal of Medicine* 364.20 (2011), pp. 1943–1954. <https://doi.org/10.1056/NEJMr1011874>.
- [44] Myron S. Cohen et al. "HIV treatment as prevention: Debate and commentary-will early infection compromise treatment-as-prevention strategies?" *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001232. <https://doi.org/10.1371/journal.pmed.1001232>.
- [45] Steve E. Bellan et al. "Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts". *PLOS Medicine* 12.3 (2015). Ed. by Marie-Louise Newell, e1001801. <https://doi.org/10.1371/journal.pmed.1001801>.
- [46] Maria J. Wawer et al. "Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda". *Journal of Infectious Diseases* 191.9 (2005), pp. 1403–1409. <https://doi.org/10.1086/429411>.
- [47] James P. Hughes et al. "Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples". *Journal of Infectious Diseases* 205.3 (2012), pp. 358–365. <https://doi.org/10.1093/infdis/jir747>.
- [48] Simon Gregson et al. "Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe". *The Lancet* 359.9321 (2002), pp. 1896–1903. [https://doi.org/10.1016/S0140-6736\(02\)00878-9](https://doi.org/10.1016/S0140-6736(02)00878-9).
- [49] Rebecca F. Baggaley et al. *Does per-act HIV-1 transmission risk through anal sex vary by gender? An updated systematic review and meta-analysis*. 2018. <https://doi.org/10.1111/aji.13039>.
- [50] Rebecca F. Baggaley et al. "Heterosexual Anal Intercourse: A Neglected Risk Factor for HIV?" *American Journal of Reproductive Immunology* 69.S1 (2013), pp. 95–105. <https://doi.org/10.1111/aji.12064>.
- [51] Pragna Patel et al. "Estimating per-act HIV transmission risk: A systematic review". *AIDS* 28.10 (2014), pp. 1509–1519. <https://doi.org/10.1097/QAD.0000000000000298>.
- [52] Charles Shey Wiysonge et al. "Male circumcision for prevention of homosexual acquisition of HIV in men". *Cochrane Database of Systematic Reviews* 6 (2011). <https://doi.org/10.1002/14651858.cd007496.pub2>.
- [53] Helen A. Weiss, Catherine A. Hankins, and Kim Dickson. *Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis*. 2009. [https://doi.org/10.1016/S1473-3099\(09\)70235-X](https://doi.org/10.1016/S1473-3099(09)70235-X).
- [54] Foteini K Giannou et al. "Condom effectiveness in reducing heterosexual HIV transmission: a systematic review and meta-analysis of studies on HIV serodiscordant couples". *Expert Review of Pharmacoeconomics and Outcomes Research* 16.4 (2016), pp. 489–499. <https://doi.org/10.1586/14737167.2016.1102635>.
- [55] Dawn K. Smith et al. "Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States". *Journal of Acquired Immune Deficiency Syndromes* 68.3 (2015), pp. 337–344. <https://doi.org/10.1097/QAI.0000000000000461>.
- [56] Francis A. Plummer et al. "Cofactors in male-female sexual transmission of human immunodeficiency virus type 1". *Journal of Infectious Diseases* 163.2 (1991), pp. 233–239. <https://doi.org/10.1093/infdis/163.2.233>.
- [57] Douglas T. Fleming and Judith N. Wasserheit. *From epidemiological synergy to public health policy and practice: The contribution of other sexually transmitted diseases to sexual transmission of HIV infection*. 1999. <http://doi.org/10.1136/sti.75.1.3>.
- [58] Jeanne S. Sheffield et al. "Effect of genital ulcer disease on HIV-1 coreceptor expression in the female genital tract". *Journal of Infectious Diseases* 196.10 (2007), pp. 1509–1516. <https://doi.org/10.1086/522518>.
- [59] Julie Fox and Sarah Fidler. "Sexual transmission of HIV-1". *Antiviral Research* 85.1 (2010), pp. 276–285. <https://doi.org/10.1016/j.antiviral.2009.10.012>.
- [60] Judith N. Wasserheit. "Epidemiological synergy: Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases". *Sexually Transmitted Diseases* 19.2 (1992), pp. 61–77. <https://doi.org/10.1097/00007435-199203000-00001>.
- [61] Ronald H Gray et al. "Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda". *The Lancet* 357.9263 (2001), pp. 1149–1153. [https://doi.org/10.1016/S0140-6736\(00\)04331-2](https://doi.org/10.1016/S0140-6736(00)04331-2).
- [62] Swaziland Ministry of Health. *Swaziland HIV Incidence Measurement Survey: First Findings Report*. Mbabane, Swaziland, 2012. <http://shims.icap.columbia.edu/>.
- [63] PEPFAR. *Eswatini Country Operational Plan 2021*. 2021.



- [64] Maria A. Carrasco, Joseph G. Rosen, and Ryan Phelps. "Left behind?: male clients of female sex workers in Zambia". *AIDS Care* 32.12 (2020), pp. 1498–1505. <https://doi.org/10.1080/09540121.2020.1718589>.
- [65] Julia Cordero-Coma and Richard Breen. "HIV Prevention and Social Desirability: Husband-Wife Discrepancies in Reports of Condom Use". *Journal of Marriage and Family* 74.3 (2012), pp. 601–613. <https://doi.org/10.1111/j.1741-3737.2012.00976.x>.
- [66] Luc Béhanzin et al. "Assessment of HIV-related risky behaviour: A comparative study of face-to-face interviews and polling booth surveys in the general population of Cotonou, Benin". *Sexually Transmitted Infections* 89.7 (2013), pp. 595–601. <https://doi.org/10.1136/sextrans-2012-050884>.
- [67] Swaziland Ministry of Health. *Swaziland 1988 Family Health Survey*. Mbabane, Swaziland, 1990.
- [68] Swaziland Ministry of Health. *Swaziland Behavioral Surveillance Survey*. Mbabane, Swaziland, 2002.
- [69] Anne-Marie; Marie Côté et al. "Transactional sex is the driving force in the dynamics of HIV in Accra, Ghana". *AIDS* 18.6 (2004), pp. 917–925. <https://doi.org/10.1097/00002030-200404090-00009>.
- [70] Branwen Nia Owen et al. "What Proportion of Female Sex Workers Practise anal Intercourse and How Frequently? A Systematic Review and Meta-analysis". *AIDS and Behavior* 24.3 (2020), pp. 697–713. <https://doi.org/10.1007/s10461-019-02477-w>.
- [71] F. N. Fritsch and R. E. Carlson. "Monotone Piecewise Cubic Interpolation". *SIAM Journal on Numerical Analysis* 17.2 (1980), pp. 238–246. <https://doi.org/10.1137/0717021>.
- [72] Caitlyn L. Jasumback et al. "Point-of-Care testing to guide treatment and estimate risk factors for sexually transmitted infections in adolescents and young people with human immunodeficiency virus in Eswatini". *Open Forum Infectious Diseases* 7.3 (2020), pp. 1–9. <https://doi.org/10.1093/ofid/ofaa052>.
- [73] Frances M. Cowan et al. "Is sexual contact with sex workers important in driving the HIV epidemic among men in rural Zimbabwe?" *Journal of Acquired Immune Deficiency Syndromes* 40.3 (2005), pp. 371–376. <https://doi.org/10.1097/01.qai.0000162420.93243.ff>.
- [74] M. E. Gomes Do Espirito Santo and G D Etheredge. "Male clients of brothel prostitutes as a bridge for HIV infection between high risk and low risk groups of women in Senegal". *Sexually Transmitted Infections* 81.4 (2005), pp. 342–344. <https://sti.bmj.com/content/81/4/342%20https://sti.bmj.com/content/81/4/342.abstract>.
- [75] Sara Lodi et al. "Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm3: Assessment of need following changes in treatment guidelines". *Clinical Infectious Diseases* 53.8 (2011), pp. 817–825. <http://doi.org/10.1093/cid/cir494>.
- [76] Motasim Badri, Stephen D. Lawn, and Robin Wood. "Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study". *The Lancet* 368.9543 (2006), pp. 1254–1259. [https://doi.org/10.1016/S0140-6736\(06\)69117-4](https://doi.org/10.1016/S0140-6736(06)69117-4).
- [77] Xavier Anglaret et al. "AIDS and non-AIDS morbidity and mortality across the spectrum of CD4 cell counts in HIV-infected adults before starting antiretroviral therapy in Côte d'Ivoire". *Clinical Infectious Diseases* 54.5 (2012), pp. 714–723. <https://doi.org/10.1093/cid/cir898>.
- [78] Melanie A. Thompson et al. "Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society—USA Panel". *JAMA* 308.4 (2012), pp. 387–402. <https://doi.org/10.1001/JAMA.2012.7961>.
- [79] Andrew Mujigira et al. "HIV transmission risk persists during the first 6 months of antiretroviral therapy". *Journal of Acquired Immune Deficiency Syndromes* 72.5 (2016), pp. 579–584. <https://doi.org/10.1097/QAI.0000000000001019>.
- [80] Thandeka T.T. Dlamini-Simelane and Eileen Moyer. "'Lost to follow up': Rethinking delayed and interrupted HIV treatment among married Swazi women". *Health Policy and Planning* 32.2 (2017), pp. 248–256. <https://doi.org/10.1093/heapol/czw117>.
- [81] Shona Horter et al. "'I don't want them to know': how stigma creates dilemmas for engagement with Treat-all HIV care for people living with HIV in Eswatini". *African Journal of AIDS Research* 18.1 (2019), pp. 27–37. <http://doi.org/10.2989/16085906.2018.1552163>.
- [82] Robert W. Eisinger, Carl W. Dieffenbach, and Anthony S. Fauci. "HIV viral load and transmissibility of HIV infection undetectable equals untransmittable". *Journal of the American Medical Association* 321.5 (2019), pp. 451–452. <https://doi.org/10.1001/jama.2018.21167>.

- [83] Myron S. Cohen et al. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission". *New England Journal of Medicine* 375.9 (2016), pp. 830–839. <https://doi.org/10.1056/nejmoa1600693>.
- [84] Manuel Battegay et al. "Immunological recovery and antiretroviral therapy in HIV-1 infection". *The Lancet Infectious Diseases* 6.5 (2006), pp. 280–287. [https://doi.org/10.1016/S1473-3099\(06\)70463-7](https://doi.org/10.1016/S1473-3099(06)70463-7).
- [85] Stephen D. Lawn et al. "CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa". *BMC Infectious Diseases* 6.1 (2006), pp. 1–8. <https://doi.org/10.1186/1471-2334-6-59>.
- [86] Delphine Gabillard et al. "Mortality, AIDS-morbidity, and loss to follow-up by current CD4 cell count among HIV-1-infected adults receiving antiretroviral therapy in Africa and Asia: Data from the ANRS 12222 collaboration". *Journal of Acquired Immune Deficiency Syndromes* 62.5 (2013), pp. 555–561. <https://doi.org/10.1097/QAI.0b013e3182821821>.
- [87] Andrew N. Phillips, James Neaton, and Jens D. Lundgren. "The role of HIV in serious diseases other than AIDS". *AIDS* 22.18 (2008), pp. 2409–2418. <https://doi.org/10.1097/QAD.0b013e3183174636>.
- [88] Jens D Lundgren et al. "Initiation of antiretroviral therapy in early asymptomatic HIV infection." *New England Journal of Medicine* 373.9 (2015), pp. 795–807. <https://doi.org/10.1056/NEJMoa1506816>.
- [89] T. Charles Witzel et al. "Uptake contexts and perceived impacts of HIV testing and counselling among adults in East and Southern Africa: A meta-ethnographic review". *PLOS ONE* 12.2 (2017). Ed. by Matthew P Fox, e0170588. <https://doi.org/10.1371/journal.pone.0170588>.
- [90] Swaziland Ministry of Health. *Swaziland HIV Incidence Measurement Survey (SHIMS): Descriptive Data Tables*. Mbabane, Swaziland, 2014.
- [91] Mathieu Maheu-Giroux et al. "National HIV testing and diagnosis coverage in sub-Saharan Africa: A new modeling tool for estimating the 'first 90' from program and survey data". *AIDS* 33 (2019), S255–S269. <https://doi.org/10.1097/QAD.0000000000002386>.
- [92] Government of Swaziland. *Policy Document on HIV/AIDS and STD Prevention and Control*. Mbabane, Swaziland, 1998.
- [93] Human Sciences Research Council. *An Audit of HIV/AIDS Policies in Botswana, Lesotho, Mozambique, South Africa, and Swaziland*. Ed. by Nompumelelo Zungu-Dirwayi et al. 1st ed. Cape Town, South Africa: HSRC Publishers, 2004.
- [94] Nokwazi Mathabela et al. *UNGASS 2010 Swaziland Progress Report*. Mbabane, Swaziland, 2010.
- [95] National Emergency Response Council on HIV and AIDS. *Swaziland Country Report On Monitoring The Political Declaration On HIV And AIDS*. Mbabane, Swaziland, 2012.
- [96] National Emergency Response Council on HIV and AIDS. *The Kingdom of Swaziland National AIDS Spending Assessment 2005/06 and 2006/07*. Mbabane, Swaziland, 2009.
- [97] National Emergency Response Council on HIV and AIDS. *National Multi-sectorial Strategic Framework for HIV and AIDS 2009-2014*. Mbabane, Swaziland, 2009.
- [98] Françoise Jenniskens. *Maximizing ART for Better Health and Zero New HIV Infections*. Mbabane, Eswatini, 2015.
- [99] WHO. *Scaling up antiretroviral therapy in resource-limited settings : treatment guidelines for a public health approach*. Geneva, Switzerland, 2013.
- [100] WHO. *Chronic HIV Care with ARV Therapy and Prevention*. Geneva, Switzerland, 2007.
- [101] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland, 2013.
- [102] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland, 2016. <https://www.who.int/hiv/pub/arv/arv-2016>.
- [103] MaxART Consortium. *MaxART Early Access to ART for All implementation study (2014-2018) Final Report*. Report. Mbabane, Eswatini, 2018.
- [104] National Emergency Response Council on HIV and AIDS. *Extended National Multisectorial HIV and AIDS Framework*. Mbabane, Swaziland, 2014.
- [105] Motasim Badri et al. "Initiating highly active antiretroviral therapy in sub-Saharan Africa". *AIDS* 18.8 (2004), pp. 1159–1168. <https://doi.org/10.1097/00002030-200405210-00009>.

- [106] Jameela Edathodu, Batool Ali, and Abdulrahman A. Alrajhi. "CD4 validation for the World Health Organization classification and clinical staging of HIV/AIDS in a developing country". *International Journal of Infectious Diseases* 13.2 (2009), pp. 243–246. <https://doi.org/10.1016/j.ijid.2007.12.017>.
- [107] US Centers for Disease Control and Prevention. "Differences between HIV-Infected men and women in antiretroviral therapy outcomes - six African countries, 2004-2012." *Morbidity and Mortality Weekly Report* 62.47 (2013), pp. 945–52. <https://pubmed.ncbi.nlm.nih.gov/24280913/>.
- [108] Swaziland Ministry of Health. *Annual HIV Programs Report*. Mbabane, Swaziland, 2015.
- [109] Kathryn E. Lancaster et al. "HIV care and treatment experiences among female sex workers living with HIV in sub-Saharan Africa: A systematic review". *African Journal of AIDS Research* 15.4 (2016), pp. 377–386. <https://doi.org/10.2989/16085906.2016.1255652>.
- [110] WHO. *HIV Drug Resistance Report 2021*. Geneva, Switzerland, 2021.
- [111] Anthony Hauser et al. "Bridging the gap between hiv epidemiology and antiretroviral resistance evolution: Modelling the spread of resistance in south africa". *PLOS Computational Biology* 15.6 (2019), e1007083. <https://doi.org/10.1371/journal.pcbi.1007083>.
- [112] National Emergency Response Council on HIV and AIDS. *Swaziland Global Aids Response Progress Reporting 2014*. 2014.
- [113] National Emergency Response Council on HIV and AIDS. *Extended National Multi-sectoral HIV and AIDS Framework 2014-2018: Final Evaluation Report*. Mbabane, Eswatini, 2018.
- [114] Matthew P. Fox et al. "Estimating retention in HIV care accounting for patient transfers: A national laboratory cohort study in South Africa". *PLoS Medicine* 15.6 (2018). <https://doi.org/10.1371/journal.pmed.1002589>.
- [115] Lynne S. Wilkinson et al. *Self-transfer and mortality amongst adults lost to follow-up in ART programmes in low- and middle-income countries: Systematic review and meta-analysis*. 2015. <https://doi.org/10.1111/tmi.12434>.
- [116] Kiran Jobanputra et al. "Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland". *PLOS ONE* 10.2 (2015), e0116144. <https://doi.org/10.1371/journal.pone.0116144>.
- [117] Giorgos Bakoyannis et al. "A semiparametric method for the analysis of outcomes during a gap in HIV care under incomplete outcome ascertainment". *Statistical Communications in Infectious Diseases* 12.s1 (2020). <https://doi.org/10.1515/SCID-2019-0013>.
- [118] Elke Konings et al. "Validating population surveys for the measurement of HIV/STD prevention indicators". *AIDS* 9.4 (1995), pp. 375–382. <https://doi.org/10.1097/00002030-199509040-00009>.
- [119] Simon Gregson et al. "Methods to reduce social desirability bias in sex surveys in low-development settings: Experience in Zimbabwe". *Sexually Transmitted Diseases* 29.10 (2002), pp. 568–575. <https://doi.org/10.1097/00007435-200210000-00002>.
- [120] S. Gregson et al. "Informal confidential voting interview methods and temporal changes in reported sexual risk behaviour for HIV transmission in sub-Saharan Africa". *Sexually Transmitted Infections*. Vol. 80. S2. 2004, pp. ii36–ii42. <https://doi.org/10.1136/sti.2004.012088>.
- [121] Catherine M. Lowndes et al. "Polling booth surveys: A novel approach for reducing social desirability bias in HIV-related behavioural surveys in resource-poor settings". *AIDS and Behavior* 16.4 (2012), pp. 1054–1062. <https://doi.org/10.1007/s10461-011-0004-1>.
- [122] UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. *Guidelines on Estimating the Size of Populations Most at Risk to HIV*. Geneva, Switzerland, 2010.
- [123] Abu S Abdul-Quader, Andrew L Baughman, and Wolfgang Hladik. *Estimating the size of key populations: Current status and future possibilities*. 2014. <http://doi.org/10.1097/COH.000000000000041>.
- [124] L. Morison et al. "Commercial sex and the spread of HIV in four cities in sub-Saharan Africa". *AIDS* 15.S4 (2001), S61–S69. <https://doi.org/10.1097/00002030-200108004-00007>.
- [125] Hélène A.C.M. Voeten et al. "Clients of female sex workers in Nyanza Province, Kenya: A core group in STD/HIV transmission". *Sexually Transmitted Diseases* 29.8 (2002), pp. 444–452. <https://doi.org/10.1097/00007435-200208000-00003>.
- [126] J. K.B. Matovu and B N Ssebadduka. "Sexual risk behaviours, condom use and sexually transmitted infection treatment-seeking behaviours among female sex workers and truck drivers in Uganda". *International Journal of STD and AIDS* 23.4 (2012), pp. 267–273. <https://doi.org/10.1258/ijsa.2011.011313>.

- [127] Leigh F. Johnson and Rob E. Dorrington. *Thembisa version 3.2: A model for evaluating the impact of HIV/AIDS in South Africa*. University of Cape Town, 2017. [https://thembisa.org/content/downloadPage/Thembisa3\\_2report](https://thembisa.org/content/downloadPage/Thembisa3_2report).
- [128] M. L. Plummer et al. "'A bit more truthful': The validity of adolescent sexual behaviour data collected in rural northern Tanzania using five methods". *Sexually Transmitted Infections* 80.S2 (2004), pp. ii49–ii56. <https://doi.org/10.1136/sti.2004.011924>.
- [129] J. Todd et al. "Reported number of sexual partners: Comparison of data from four African longitudinal studies". *Sexually Transmitted Infections* 85.S1 (2009), pp. i72–i80. <https://doi.org/10.1136/sti.2008.033985>.
- [130] Jenny A. Higgins, Susie Hoffman, and Shari L. Dworkin. "Rethinking gender, heterosexual men, and women's vulnerability to HIV/AIDS". *American Journal of Public Health* 100.3 (2010), pp. 435–445. <https://doi.org/10.2105/AJPH.2009.159723>.
- [131] Soori Nnko et al. "Secretive females or swaggering males? An assessment of the quality of sexual partnership reporting in rural Tanzania". *Social Science and Medicine* 59.2 (2004), pp. 299–310. <https://doi.org/10.1016/j.socscimed.2003.10.031>.
- [132] Shelley Clark, Caroline Kabiru, and Eliya Zulu. "Do men and women report their sexual partnerships differently? Evidence from Kisumu, Kenya". *International Perspectives on Sexual and Reproductive Health* 37.4 (2011), pp. 181–190. <https://doi.org/10.1363/3718111>.
- [133] Allison Ruark et al. "Love, lust and the emotional context of multiple and concurrent sexual partnerships among young Swazi adults". *African Journal of AIDS Research*. Vol. 13. 2. Routledge, 2014, pp. 133–143. <https://www.tandfonline.com/doi/abs/10.2989/16085906.2014.927781>.
- [134] Rebecca Fielding-Miller et al. "The feminine ideal and transactional sex: Navigating respectability and risk in Swaziland". *Social Science and Medicine* 158 (2016), pp. 24–33. <https://doi.org/10.1016/j.socscimed.2016.04.005>.
- [135] Allison Ruark et al. "Navigating intimate sexual partnerships in an era of HIV: dimensions of couple relationship quality and satisfaction among adults in Eswatini and linkages to HIV risk". *Sahara J* 16.1 (2019), pp. 10–24. <https://doi.org/10.1080/17290376.2019.1604254>.
- [136] J. Pulerwitz et al. "'A man without money getting a sexual partner? It doesn't exist in our community': male partners' perspectives on transactional sexual relationships in Uganda and Eswatini". *Culture, Health and Sexuality* (2021). <https://doi.org/10.1080/13691058.2021.1904521>.
- [137] Lisa F. Langhaug, Lorraine Sherr, and Frances M. Cowan. "How to improve the validity of sexual behaviour reporting: Systematic review of questionnaire delivery modes in developing countries: Systematic Review". *Tropical Medicine and International Health* 15.3 (2010), pp. 362–381. <https://doi.org/10.1111/j.1365-3156.2009.02464.x>.
- [138] Cassia Wells et al. "Characterizing the patterns of HIV disclosure to clients among South African female sex workers in Port Elizabeth". *AIDS and Behavior* 22.12 (2018), pp. 3924–3932. <https://doi.org/10.1007/s10461-018-2199-x>.
- [139] H. A.C.M. Voeten et al. "Female sex workers and unsafe sex in urban and rural Nyanza, Kenya: Regular partners may contribute more to HIV transmission than clients". *Tropical Medicine and International Health* 12.2 (2007), pp. 174–182. <http://doi.org/10.1111/j.1365-3156.2006.01776.x>.
- [140] Catherine M. Lowndes et al. "Management of sexually transmitted diseases and HIV prevention in men at high risk: Targeting clients and nonpaying sexual partners of female sex workers in Benin". *AIDS* 14.16 (2000), pp. 2523–2534. <https://doi.org/10.1097/00002030-200011100-00015>.
- [141] Gaston Godin et al. "Correlates of condom use among sex workers and their boyfriends in three West African countries". *AIDS and Behavior* 12.3 (2008), pp. 441–451. <https://doi.org/10.1007/s10461-007-9296-6>.
- [142] M. Carael et al. "Clients of sex workers in different regions of the world: Hard to count". *Sexually Transmitted Infections* 82.S3 (2006), pp. iii26–iii33. <https://doi.org/10.1136/sti.2006.021196>.
- [143] United Nations. *World Population Prospects*. Report. 2019. <https://population.un.org/wpp>.
- [144] Christopher J. Henry and James S. Koopman. "Strong influence of behavioral dynamics on the ability of testing and treating HIV to stop transmission". *Scientific Reports* 5.1 (2015), p. 9467. <http://www.doi.org/10.1038/srep09467>.
- [145] Jesse Knight et al. "Contribution of high risk groups' unmet needs may be underestimated in epidemic models without risk turnover: A mechanistic modelling analysis". *Infectious Disease Modelling* 5 (2020), pp. 549–562. <https://doi.org/10.1016/j.idm.2020.07.004>.
- [146] Mick Roberts et al. "Nine challenges for deterministic epidemic models". *Epidemics* 10 (2015), pp. 49–53. <https://doi.org/10.1016/j.epidem.2014.09.006>.

- [147] Eve Cheuk et al. "Transitions: Novel Study Methods to Understand Early HIV Risk Among Adolescent Girls and Young Women in Mombasa, Kenya, and Dnipro, Ukraine". *Frontiers in Reproductive Health* 2 (2020), p. 10. <https://doi.org/10.3389/frph.2020.00007>.
- [148] Erika Fazito et al. "Analysis of duration of risk behaviour for key populations: a literature review." *Sexually transmitted infections* 88.S2 (2012), pp. i24–i32. <https://doi.org/10.1136/sextrans-2012-050647>.
- [149] Caroline Hodgins et al. "Population sizes, HIV prevalence, and HIV prevention among men who paid for sex in sub-Saharan Africa (2000–2020): A meta-analysis of 87 population-based surveys". *PLOS Medicine* 19.1 (2022). Ed. by Marie-Louise Newell, e1003861. <https://doi.org/10.1371/JOURNAL.PMED.1003861>.
- [150] Huiting Ma et al. "Venue-Based HIV Testing at Sex Work Hotspots to Reach Adolescent Girls and Young Women Living with HIV: A Cross-sectional Study in Mombasa, Kenya". *Journal of Acquired Immune Deficiency Syndromes* 84.5 (2020), pp. 470–479. <https://doi.org/10.1097/QAI.0000000000002363>.
- [151] Despina Learmonth, Suvi Hakala, and Marike Keller. "'I can't carry on like this': barriers to exiting the street-based sex trade in South Africa". *Health Psychology and Behavioral Medicine* 3.1 (2015), pp. 348–365. <https://doi.org/10.1080/21642850.2015.1095098>.
- [152] Wim Delva et al. "Coital frequency and condom use in monogamous and concurrent sexual relationships in Cape Town, South Africa". *Journal of the International AIDS Society* 16.1 (2013). <https://doi.org/10.7448/IAS.16.1.18034>.
- [153] Olive Shisana and Leickness Simbayi. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005*. Cape Town, South Africa, 2005.
- [154] Martina Morris, Helen Epstein, and Maria Wawer. "Timing Is Everything: International Variations in Historical Sexual Partnership Concurrency and HIV Prevalence". *PLOS ONE* 5.11 (2010), e14092. <https://doi.org/10.1371/journal.pone.0014092>.
- [155] Gita Ramjee, Amy E Weber, and Neetha S Morar. "Recording sexual behavior: Comparison of recall questionnaires with a coital diary". *Sexually Transmitted Diseases* 26.7 (1999), pp. 374–380. <https://doi.org/10.1097/00007435-199908000-00002>.
- [156] Branwen N. Owen et al. *How common and frequent is heterosexual anal intercourse among South Africans? A systematic review and meta-analysis*. 2017. <https://doi.org/10.7448/IAS.20.1.21162>.
- [157] Bart Burington et al. "Estimating duration in partnership studies: Issues, methods and examples". *Sexually Transmitted Infections* 86.2 (2010), pp. 84–89. <https://doi.org/10.1136/sti.2009.037960>.
- [158] Ben Malinga John and Vissého Adjiwanou. "Fertility decline in sub-Saharan Africa: Does remarriage matter?" *Population Studies* 76.2 (2022), pp. 213–233. <https://doi.org/10.1080/00324728.2021.1933148>.
- [159] Abigail Harrison, John Cleland, and Janet Frohlich. "Young people's sexual partnerships in KwaZulu-Natal, South Africa: Patterns, contextual influences, and HIV risk". *Studies in Family Planning* 39.4 (2008), pp. 295–308. <https://doi.org/10.1111/j.1728-4465.2008.00176.x>.
- [160] James R. Hargreaves et al. "Characteristics of sexual partnerships, not just of individuals, are associated with condom use and recent HIV infection in rural South Africa". *AIDS Care* 21.8 (2009), pp. 1058–1070. <https://doi.org/10.1080/09540120802657480>.
- [161] Nadia L. Nguyen et al. "Sexual partnership patterns among South African adolescent girls enrolled in STI preventions trial network 068: Measurement challenges and implications for HIV/STI transmission". *Sexually Transmitted Diseases* 42.11 (2015), pp. 612–618. <https://doi.org/10.1097/OLQ.0000000000000357>.
- [162] B. Ferry et al. "Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection". *AIDS* 15.S4 (2001). <https://doi.org/10.1097/00002030-200108004-00005>.
- [163] Leigh F. Johnson et al. "Sexual behaviour patterns in South Africa and their association with the spread of HIV: Insights from a mathematical model". *Demographic Research* 21 (2009), pp. 289–340. <https://doi.org/10.4054/DemRes.2009.21.11>.
- [164] Martin Mbonye, Godfrey Siu, and Janet Seeley. "Marginal men, respectable masculinity and access to HIV services through intimate relationships with female sex workers in Kampala, Uganda". *Social Science & Medicine* 296 (2022), p. 114742. <https://doi.org/10.1016/j.socscimed.2022.114742>.
- [165] Annett Nold. "Heterogeneity in disease-transmission modeling". *Mathematical Biosciences* 52.3-4 (1980), pp. 227–240. [https://doi.org/10.1016/0025-5564\(80\)90069-3](https://doi.org/10.1016/0025-5564(80)90069-3).

- [166] Geoffrey P. Garnett and Roy M. Anderson. "Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations". *Mathematical Medicine and Biology* 11.3 (1994), pp. 161–192. <https://doi.org/10.1093/imammb/11.3.161>.
- [167] Ide Cremin et al. "The new role of antiretrovirals in combination HIV prevention: A mathematical modelling analysis". *AIDS* 27.3 (2013), pp. 447–458. <https://doi.org/10.1097/QAD.0b013e32835ca2dd>.
- [168] M Morris. "A log-linear modeling framework for selective mixing." *Mathematical biosciences* 107.2 (1991), pp. 349–77. [https://doi.org/10.1016/0025-5564\(91\)90014-a](https://doi.org/10.1016/0025-5564(91)90014-a).
- [169] Ludger Ruschendorf. "Convergence of the Iterative Proportional Fitting Procedure". *The Annals of Statistics* 23.4 (1995), pp. 1160–1174. <https://doi.org/10.1214/aos/1176324703>.
- [170] Richard Sinkhorn. "A Relationship Between Arbitrary Positive Matrices and Doubly Stochastic Matrices". *Annals of Mathematical Statistics* 35.2 (1964), pp. 876–879. <https://doi.org/10.1214/aoms/1177703591>.
- [171] Suzanne Leclerc-Madlala. "Age-disparate and intergenerational sex in southern Africa: The dynamics of hypervulnerability". *AIDS* 22.S4 (2008). <https://doi.org/10.1097/01.aids.0000341774.86500.53>.
- [172] Geoffrey P Garnett and Roy M Anderson. "Contact tracing and the estimation of sexual mixing patterns: The epidemiology of gonococcal infections". *Sexually Transmitted Diseases* 20.4 (1993), pp. 181–191. <https://doi.org/10.1097/00007435-199307000-00001>.
- [173] Ryan Admiraal and Mark S. Handcock. "Modeling concurrency and selective mixing in heterosexual partnership networks with applications to sexually transmitted diseases". *Annals of Applied Statistics* 10.4 (2016), pp. 2021–2046. <https://doi.org/10.1214/16-AOAS963>.
- [174] Jesse Knight, Rupert Kaul, and Sharmistha Mishra. "Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review". *Epidemics* 40 (2022), p. 100608. <https://doi.org/10.1016/j.epidem.2022.100608>.
- [175] Nicolas A Menzies et al. "Bayesian Methods for Calibrating Health Policy Models: A Tutorial". *PharmacoEconomics* 35.6 (2017), pp. 613–624. <https://doi.org/10.1007/s40273-017-0494-4>.
- [176] Michael Stein. "Large Sample Properties of Simulations Using Latin Hypercube Sampling". *Technometrics* 29.2 (1987), pp. 143–151.
- [177] The World Bank. *DataBank: World Development Indicators*. 2022. <https://databank.worldbank.org/> (visited on 08/23/2018).
- [178] Yen T. Duong et al. "Detection of recent HIV-1 infection using a new limiting-antigen avidity assay: Potential for HIV-1 incidence estimates and avidity maturation studies". *PLOS ONE* 7.3 (2012), e33328. <https://doi.org/10.1371/journal.pone.0033328>.
- [179] Nirali Soni et al. "Under-Reporting of Known HIV-Positive Status Among People Living with HIV: A Systematic Review and Meta-analysis". *AIDS and Behavior* 25.12 (2021), pp. 3858–3870. <https://link.springer.com/article/10.1007/s10461-021-03310-z>.
- [180] PEPFAR. *HIV among Female Sex Workers and Men Who Have Sex with Men in Swaziland*. Mbabane, Swaziland, 2014.
- [181] Fionn Murtagh and Pierre Legendre. "Ward's Hierarchical Agglomerative Clustering Method: Which Algorithms Implement Ward's Criterion?" *Journal of Classification* 31.3 (2014), pp. 274–295. <https://doi.org/10.1007/s00357-014-9161-z>.
- [182] Alan Whiteside et al. *What is driving the HIV/AIDS epidemic in Swaziland, and what more can we do about it?* NERCHA, 2003.
- [183] James D. Shelton. "Two-component generalised HIV epidemics - Author's reply". *The Lancet* 376.9734 (2010), p. 22. [https://doi.org/10.1016/S0140-6736\(10\)61048-3](https://doi.org/10.1016/S0140-6736(10)61048-3).
- [184] George Marsaglia, Wai Wan Tsang, and Jingbo Wang. "Evaluating Kolmogorov's distribution". *Journal of Statistical Software* 8 (2003), pp. 1–4. <https://doi.org/10.18637/jss.v008.i18>.
- [185] Andreas Raue et al. "Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood". *Bioinformatics* 25.15 (2009), pp. 1923–1929. <https://doi.org/10.1093/bioinformatics/btp358>.
- [186] Eleanor Gouws, V. Mishra, and T. B. Fowler. "Comparison of adult HIV prevalence from national population-based surveys and antenatal clinic surveillance in countries with generalised epidemics: Implications for calibrating surveillance data". *Sexually Transmitted Infections* 84.S1 (2008), pp. 17–23. <https://doi.org/10.1136/sti.2008.030452>.



- [187] Kimberly Marsh et al. *Assessing and adjusting for differences between HIV prevalence estimates derived from national population-based surveys and antenatal care surveillance, with applications for Spectrum* 2013. 2014. <https://doi.org/10.1097/QAD.0000000000000453>.
- [188] Nosipho Faith Makhakhe et al. "Sexual transactions between long distance truck drivers and female sex workers in South Africa". *Global Health Action* 10.1 (2017), pp. 1–9. <https://doi.org/10.1080/16549716.2017.1346164>.
- [189] Tim Brown and Wiwat Peerapatanapokin. "Evolving HIV epidemics: The urgent need to refocus on populations with risk". *Current Opinion in HIV and AIDS* 14.5 (2019), pp. 337–353. <https://doi.org/10.1097/COH.0000000000000571>.
- [190] Katrina F. Ortblad et al. *The arc of HIV epidemics in sub-Saharan Africa: New challenges with concentrating epidemics in the era of 90-90-90*. 2019. <https://doi.org/10.1097/COH.0000000000000569>.
- [191] Stefan Baral et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment". *The Lancet HIV* 6 (2019), e632–638. [http://doi.org/10.1016/s2352-3018\(19\)30226-7](http://doi.org/10.1016/s2352-3018(19)30226-7).
- [192] Wim Delva et al. "HIV treatment as prevention: Principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001239. <https://doi.org/10.1371/journal.pmed.1001239>.
- [193] K. A. Fenton et al. "Measuring sexual behaviour: Methodological challenges in survey research". *Sexually Transmitted Infections* 77.2 (2001), pp. 84–92. <https://sti.bmj.com/content/77/2/84%20https://sti.bmj.com/content/77/2/84.abstract>.
- [194] USAID. *The DHS Program*. Rockville, Maryland, USA, 1984. <https://www.dhsprogram.com>.
- [195] Jesús M. García Calleja et al. "Lessons learned in the conduct, validation, and interpretation of national population based HIV surveys". *AIDS* 19.S2 (2005). <https://doi.org/10.1097/01.aids.0000172872.88347.f3>.
- [196] Vinod Mishra et al. "Evaluation of bias in HIV seroprevalence estimates from national household surveys". *Sexually Transmitted Infections* 84.S1 (2008), pp. i63–i70. <http://sti.bmj.com/info/unlocked.dtl>.
- [197] Susan Cassels, Samuel M. Jenness, and Aditya S. Khanna. "Conceptual Framework and Research Methods for Migration and HIV Transmission Dynamics". *AIDS and Behavior* 18.12 (2014), pp. 2302–2313.
- [198] Carol S. Camlin et al. "Men "missing" from population-based HIV testing: insights from qualitative research". *AIDS Care* 28.sup3 (2016), pp. 67–73. <http://www.tandfonline.com/doi/full/10.1080/09540121.2016.1164806>.
- [199] Sarah Jane Anderson et al. "Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study". *The Lancet* 384.9939 (2014), pp. 249–256. [https://doi.org/10.1016/S0140-6736\(14\)61053-9](https://doi.org/10.1016/S0140-6736(14)61053-9).
- [200] John A. Jacquez et al. "Modeling and analyzing HIV transmission: the effect of contact patterns". *Mathematical Biosciences* 92.2 (1988), pp. 119–199. [https://doi.org/10.1016/0025-5564\(88\)90031-4](https://doi.org/10.1016/0025-5564(88)90031-4).
- [201] G P Garnett and R M Anderson. "Factors controlling the spread of HIV in heterosexual communities in developing countries: Patterns of mixing between different age and sexual activity classes". *Philosophical Transactions of the Royal Society B: Biological Sciences* 342.1300 (1993), pp. 137–159. <http://www.ncbi.nlm.nih.gov/pubmed/7904355>.
- [202] Jesse Knight and Sharmistha Mishra. "Contact Matrices in Compartmental Disease Transmission Models". *Mathematics of Public Health*. Ed. by Jummy David and Jianhong Wu. Springer. <https://github.com/mishra-lab/contact-chapter/>.
- [203] Richard Steen et al. "Economy, migrant labour and sex work: Interplay of HIV epidemic drivers in Zimbabwe over three decades". *AIDS* 33.1 (2019), pp. 123–131. <https://pmc/articles/PMC6415983/?report=abstract%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6415983/>.
- [204] Alexandra C. Willcox et al. "Derivation of an HIV Risk Score for African Women Who Engage in Sex Work". *AIDS and Behavior* 25.10 (2021), p. 3. <https://doi.org/10.1007/s10461-021-03235-7>.
- [205] Sarah Gabrielle Ayton, Martina Pavlicova, and Quarraisha Abdool Karim. "Identification of adolescent girls and young women for targeted HIV prevention: a new risk scoring tool in KwaZulu Natal, South Africa". *Scientific Reports* 10.1 (2020), pp. 1–10. <https://doi.org/10.1038/s41598-020-69842-x>.
- [206] Corrina Moucheraud et al. "Screening Adults for HIV Testing in the Outpatient Department: An Assessment of Tool Performance in Malawi". *AIDS and Behavior* 26.2 (2022), pp. 478–486. <https://link.springer.com/article/10.1007/s10461-021-03404-8>.

- [207] Elisa Mountain et al. "Antiretroviral therapy uptake, attrition, adherence and outcomes among hiv-infected female sex workers: A systematic review and meta-analysis". *PLOS ONE* 9.9 (2014). Ed. by Nicolas Sluis-Cremer, e105645. <https://doi.org/10.1371/journal.pone.0105645>.
- [208] Avi Joseph Hakim et al. "Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response". *Journal of the International AIDS Society* 21 (2018), e25119. <http://doi.org/10.1002/jia2.25119>.
- [209] Yiqing Xia et al. "Accuracy of self-reported HIV-testing history and awareness of HIV-positive status in four sub-Saharan African countries". *AIDS* 35.3 (2021), pp. 503–510. [https://journals.lww.com/aidsonline/Fulltext/2021/03010/Accuracy\\_of\\_self\\_reported\\_HIV\\_testing\\_history\\_and.17.aspx](https://journals.lww.com/aidsonline/Fulltext/2021/03010/Accuracy_of_self_reported_HIV_testing_history_and.17.aspx).
- [210] Chris Beyrer et al. "Global epidemiology of HIV infection in men who have sex with men". *The Lancet* 380.9839 (2012), pp. 367–377. [https://doi.org/10.1016/S0140-6736\(12\)60821-6](https://doi.org/10.1016/S0140-6736(12)60821-6).
- [211] P. H. Septime Hessou et al. "Comparison of the prevalence rates of HIV infection between men who have sex with men (MSM) and men in the general population in sub-Saharan Africa: A systematic review and meta-analysis". *BMC Public Health* 19.1 (2019), pp. 1–10. <https://doi.org/10.1186/s12889-019-8000-x>.
- [212] Jack Stone et al. "Estimating the contribution of key populations towards HIV transmission in South Africa". *Journal of the International AIDS Society* 24.1 (2021), e25650. <https://doi.org/10.1002/jia2.25650>.
- [213] Romain Silhol et al. "Quantifying the Evolving Contribution of HIV Interventions and Key Populations to the HIV Epidemic in Yaoundé, Cameroon". *Journal of Acquired Immune Deficiency Syndromes* 86.4 (2021), pp. 396–405. <https://doi.org/10.1097/QAI.0000000000002580>.
- [214] Chris Beyrer et al. "Bisexual concurrency, bisexual partnerships, and HIV among Southern African men who have sex with men". *Sexually Transmitted Infections* 86.4 (2010), pp. 323–327. <https://doi.org/10.1136/sti.2009.040162>.
- [215] Kirsten Stoebe et al. *Revisiting the understanding of "transactional sex" in sub-Saharan Africa: A review and synthesis of the literature*. 2016.
- [216] Tae Joon Yi et al. "Genital immunology and HIV susceptibility in young women". *American Journal of Reproductive Immunology* 69.S1 (2013), pp. 74–79. <http://doi.wiley.com/10.1111/aji.12035>.
- [217] Joyce Wamoyi et al. "Transactional sex and risk for HIV infection in sub-Saharan Africa: a systematic review and meta-analysis". *Journal of the International AIDS Society* 19.1 (2016), p. 20992. <https://doi.org/10.7448/IAS.19.1.20992>.
- [218] Lynne Jones. "Sexual discourse and decision-making by urban youth in AIDS-afflicted Swaziland". *African Journal of AIDS Research* 5.2 (2006), pp. 145–157. <https://doi.org/10.2989/16085900609490375>.
- [219] Guy Harling et al. "Do age-disparate relationships drive HIV incidence in young women? Evidence from a population cohort in Rural KwaZulu-Natal, South Africa". *Journal of Acquired Immune Deficiency Syndromes* 66.4 (2014), pp. 443–451. <http://journals.lww.com/00126334-201408010-00015>.
- [220] Roxanne Beauclair, Niel Hens, and Wim Delva. "The role of age-mixing patterns in HIV transmission dynamics: Novel hypotheses from a field study in Cape Town, South Africa". *Epidemics* 25 (2018), pp. 61–71. <https://doi.org/10.1016/j.epidem.2018.05.006>.
- [221] Miles Q. Ott et al. "Age-gaps in sexual partnerships: Seeing beyond 'sugar daddies'". *AIDS* 25.6 (2011), pp. 861–863. <https://doi.org/10.1097/QAD.0b013e32834344c9>.
- [222] Leigh F. Johnson, Leontine Alkema, and Rob E. Dorrington. "A Bayesian approach to uncertainty analysis of sexually transmitted infection models". *Sexually Transmitted Infections* 86.3 (2010), pp. 169–174. <https://doi.org/10.1136/sti.2009.037341>.
- [223] Donald B. Rubin. "The Calculation of Posterior Distributions by Data Augmentation: Comment: A Noniterative Sampling/Importance Resampling Alternative to the Data Augmentation Algorithm for Creating a Few Imputations When Fractions of Missing Information Are Modest: The SIR". *Journal of the American Statistical Association* 82.398 (1987), p. 543. <https://doi.org/10.2307/2289460>.
- [224] Adrian E. Raftery and Le Bao. "Estimating and Projecting Trends in HIV/AIDS Generalized Epidemics Using Incremental Mixture Importance Sampling". *Biometrics* 66.4 (2010), pp. 1162–1173. <http://doi.org/10.1111/j.1541-0420.2010.01399.x>.
- [225] Jack Stone et al. "Impact and cost-effectiveness of the national scale-up of HIV pre-exposure prophylaxis among female sex workers in South Africa: a modelling analysis". *Journal of the International AIDS Society* 26.2 (2023), e26063. <https://doi.org/10.1002/jia2.26063>.



- [226] Maxwell Vusumuzi Mthembu. "Pro-democracy protests in the Kingdom of Eswatini 2018–2019". *Popular Protest, Political Opportunities, and Change in Africa*. Ed. by Edalina Rodrigues Sanches. Routledge, 2022. Chap. 12, pp. 200–217. <https://doi.org/10.4324/9781003177371-12>.
- [227] Moeketsi Kali. "A comparative analysis of the causes of the protests in Southern Africa". *SN Social Sciences* 3.2 (2023), pp. 1–22. <https://doi.org/10.1007/s43545-023-00613-x>.
- [228] Human Rights Watch. *Eswatini: Activist, Rights Lawyer Brutally Killed*. Johannesburg, South Africa, 2023. <https://www.hrw.org/news/2023/01/25/eswatini-activist-rights-lawyer-brutally-killed>.
- [229] Nothando Maphalala. *Kingdom of Eswatini: Conflict Insights*. Addis Ababa, Ethiopia: Institute for Peace and Security Studies, 2021. <https://www.africaportal.org/publications/kingdom-eswatini-conflict-insights/>.
- [230] National Emergency Response Council on HIV and AIDS. *Eswatini National Multisectoral HIV and AIDS Strategic Framework 2018–2023*. Mbabane, Eswatini, 2018.
- [231] Kate E. Bärnighausen et al. "This is mine, this is for me : Preexposure prophylaxis as a source of resilience among women in Eswatini". *AIDS* 33 (2019), S45–S52. [https://journals.lww.com/aidsonline/Fulltext/2019/06011/\\_This\\_is\\_mine,\\_this\\_is\\_for\\_me\\_\\_preexposure.6.aspx](https://journals.lww.com/aidsonline/Fulltext/2019/06011/_This_is_mine,_this_is_for_me__preexposure.6.aspx).
- [232] Meredith E. Clement, Ryan Kofron, and Raphael J. Landovitz. "Long-acting injectable cabotegravir for the prevention of HIV infection". *Current Opinion in HIV and AIDS* 15.1 (2020), pp. 19–26. <https://doi.org/10.1097/COH.0000000000000597>.
- [233] Jennifer Smith et al. "Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study". *The Lancet HIV* 10.4 (2023), e254–e265. [https://doi.org/10.1016/S2352-3018\(22\)00365-4](https://doi.org/10.1016/S2352-3018(22)00365-4).
- [234] Paul Thouelle et al. "Long-acting antiretrovirals: a new era for the management and prevention of HIV infection". *Journal of Antimicrobial Chemotherapy* 77.2 (2022), pp. 290–302. <https://doi.org/10.1093/jac/dkab324>.
- [235] Nozipho Becker et al. "Individual, household, and community level barriers to ART adherence among women in rural Eswatini". *PLOS ONE* 15.4 (2020). Ed. by Catherine E. Oldenburg, e0231952. <https://dx.plos.org/10.1371/journal.pone.0231952>.
- [236] Kate Bärnighausen et al. "Qualitative accounts of PrEP discontinuation from the general population in Eswatini". *Culture, Health and Sexuality* (2020), pp. 1–17. <https://doi.org/10.1080/13691058.2020.1770333>.
- [237] Janet Saul et al. *The DREAMS core package of interventions: A comprehensive approach to preventing HIV among adolescent girls and young women*. Ed. by Linda-Gail Bekker. 2018. <https://dx.plos.org/10.1371/journal.pone.0208167>.

## Chapter 4

# Modelling HIV Transmission in Sexual Partnerships: Equations and Assumptions

A key equation in transmission models defines the force of infection  $\lambda$ : the instantaneous rate at which susceptible individuals acquire infection. In the simplest compartmental transmission models — i.e., without any population stratification, repeated contacts, etc. — this rate is defined as:<sup>1</sup>

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

where:  $C$  is the average contact rate per-person;  $\beta$  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:

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

where:  $C_{p i i'}$  is the average rate of type- $p$  contacts per-person among group  $i$  with group  $i'$ ,  $\beta_{p h'}$  is the average probability of transmission per type- $p$  contact given infection stage  $h'$ , and  $I_{i' h'}/N_{i'}$  is the 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”.<sup>2</sup> With repeated vs. random contacts, it is more likely that individuals who recently acquired or transmitted infection will continue to contact the same person, resulting in “wasted

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

<sup>2</sup> Sex involving vaginal and anal intercourse would be modelled as two sex acts.

contacts” (in terms of transmission),<sup>3</sup> and slower infection spread through the contact/partnership network.

This chapter explores different mathematical approaches to modelling HIV transmission within sexual partnerships in compartmental models, considering these “wasted contacts”. In particular, I review prior approaches (§ 4.1), develop a new approach (§ 4.2), and compare the influence of each approach on selected model outputs (§ 4.3). A preliminary version of this approach was presented in [2].

## 4.1 Prior Approaches

The earliest HIV transmission models [3] were adapted from models of other sexually transmitted diseases, especially gonorrhea [4–6]. These early HIV transmission models did not explicitly model individual sex acts, but instead assumed an overall probability of transmission per partnership [7]. This assumption was initially justified via data suggesting that the probability of HIV transmission per partnership increased quickly and then saturated [8]. 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.) [9–11]. As this heterogeneity was quantified [9] and incorporated into HIV transmission models [12], the probability of transmission was increasingly parameterized per act vs. per partnership.

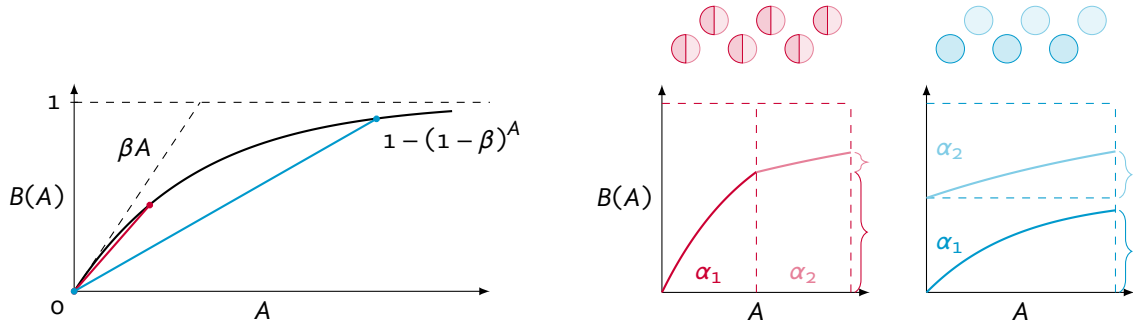
The shift to per-act vs. per-partnership parameterization highlighted a fundamental limitation of compartmental models (see § 4.1.5): compartmental models cannot model individual partnerships, because each “compartment” reflects a group of individuals whose characteristics are assumed to be homogeneous [13]. 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 [14]. 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.

### 4.1.1 Aggregating Sex Acts within a Partnership

To account for repeated sex acts with the same partner, the per-partnership probability of transmission  $B$  was conceptualized as follows [15]. Let  $A$  denote the total number of sex acts in the partnership, and  $\beta$  denote the probability of transmission per act. For now,  $\beta$  is assumed to be equal for all acts. With equal and independent  $\beta$ , the theoretical probability of  $n$  transmissions after  $A$  acts can be described by a

<sup>3</sup> Another conception of “wasted contacts” is “within-partnership competing risks”.



(a) Probability of transmission per partnership  $B$  vs. number of sex acts  $A$ , comparing shorter (red) vs. longer (blue) partnerships

(b) Average accumulation of transmission probability for within-partnership heterogeneity (red) vs. between-partnership heterogeneity (blue)

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

$B$ : probability of transmission per partnership;  $\beta$ : probability of transmission per act;  $A$ : total acts per partnership;  $\alpha$ : fraction of total acts (within or between partnerships).

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:<sup>4</sup>

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

We can show that  $B \leq \beta A$ . Thus, a model with partnerships using Eq. (4.4) reduces transmission vs. a model without partnerships by adjusting for “wasted contacts”. Figure 4.1a illustrates the shape of  $B(A)$  (curve) and the corresponding effective probabilities of transmission per act  $B/A$  (tangent slopes) for a shorter (red) vs. longer (blue) partnership. Although  $B(A)$  is monotonic, the effective probability of transmission per act decreases with the number of acts because, on average, more and more acts are “wasted” — occurring after transmission.

#### 4.1.2 Heterogeneity in the Per-Act Probability of Transmission

As noted above, the per-act probability of transmission  $\beta$  is heterogeneous, varying with factors like: HIV infection stage, genital ulcer disease, condom use, etc. [11, 16]. The next step in developing a force of infection equation is to extend Eq. (4.4) to allow heterogeneity in  $\beta$  [15]. Let  $\beta_f$  denote the probability of transmission associated with a particular factor (or combination of factors)  $f$ ; and let  $\alpha_f$  denote the

<sup>4</sup> Eq. (4.4) can also be reasonably approximated via the Poisson distribution  $B = 1 - e^{-\beta A}$  for small  $\beta$ .

proportion of acts  $A$  in an average partnership having transmission probability  $\beta_f$  (thus  $\sum_f \alpha_f = 1$ ). There are two main approaches to aggregating  $\beta_f$ , reflecting different interpretations of  $\alpha_f$ :<sup>5 6</sup>

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

$$B_{\text{WPH}} = 1 - \prod_f (1 - \beta_f)^{A\alpha_f} \quad (4.5)$$

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

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

Figure 4.1b illustrates these approaches for a simple case with two factors. For WPH (red), each factor  $f$  marginally contributes to the probability of escaping infection in every partnership. For BPH (blue), 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 § A.3.1) [17]. Intuitively, this inequality arises because any large probability of transmission  $\beta_f$  has disproportionate influence in Eq. (4.5), even for a small proportion of acts affected  $\alpha_f$ , whereas this influence is bounded by  $\alpha_f$  in Eq. (4.6), as shown in Figure 4.1b.

The decision to use WPH vs. BPH for aggregating specific types of heterogeneity in  $\beta$  should be driven by the factor(s) in question. To this end, it is possible to combine Eq. (4.5) and Eq. (4.6) as follows to aggregate both types of factors simultaneously:

$$B_{\text{wb}} = 1 - \sum_g \gamma_g \prod_f (1 - \beta_{fg})^{A\alpha_{fg}} \quad (4.7)$$

where:  $f$  denotes WPH factor(s);  $g$  denotes BPH factor(s); and  $\gamma_g$  replaces  $\alpha_f$  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,<sup>7</sup> with  $\gamma_g$  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  $\gamma_g$  is replaced by the unconditional prevalence of stage/status  $g$  among *all* partners.

<sup>5</sup> 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.

<sup>6</sup> In fact, further variations on Eqs. (4.5) and (4.6) have also been used.

<sup>7</sup> 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 the partnership, but this future trajectory is not explicitly modelled — which only serves to highlight the limitations of either approach to aggregating heterogeneity in  $\beta$ .

### 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 [15].

As in § 4.1.2, there are two main approaches to aggregating partnerships — indeed having similar equations to Eqs. (4.5) and (4.6). This time, the distinction may be more familiar:

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

$$\lambda_i^{\text{IR}} = \sum_{p i' h'} Q_{p i i'} B_{p i i' h'} \frac{I_{i' h'}}{N_{i'}} \quad (4.8)$$

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

$$\lambda_i^{\text{IP}} = 1 - \prod_{p i' h'} \left( 1 - B_{p i i' h'} \frac{I_{i' h'}}{N_{i'}} \right)^{Q_{p i i'} \Delta_t} \quad (4.9)$$

where:  $Q_{p i i'}$  is the rate of type- $p$  partnership formation between groups  $i$  and  $i'$ ,<sup>8</sup>  $B_{p i i' h'}$  is the average per-partnership probability of transmission from group/infection stage  $i' h'$  to group  $i$  via partnership type  $p$ , and  $I_{i' h'}/N_{i'}$  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 § A.3.1).

By definition, the force of infection is a rate [18]. Yet in principle, incidence proportion could be more precise than incidence rate *over a given time period*  $\Delta_t$ . Since most models are now solved computationally, the period  $\Delta_t$  could be matched to the timestep of the numerical solver. However, the added precision may be insignificant, as  $\Delta_t$  should be small.<sup>9</sup> Moreover, some applications of this approach have used a period of  $\Delta_t = 1$  year in the equation, but then applied the resulting incidence proportion  $\lambda_i^{\text{IP}}$  as a rate over smaller timesteps. Such applications then erroneously reduce *current* transmission due to *future* “wasted contacts” across multiple partnerships. This reduction is then redundant because “wasted contacts” *within* partnerships are already captured via the per-partnership probability of transmission, while “wasted contacts” *between* partnerships are already captured via multiple opportunities for transmission over successive timesteps. In sum, unless the period  $\Delta_t$  can be matched to the numerical solver timestep, incidence rate Eq. (4.8) is preferred over incidence proportion Eq. (4.9) as the force of infection equation.

<sup>8</sup> This fully stratified partnership formation rate  $Q_{p i i'}$  is often broken down into a per-person partnership formation rate  $Q_{p i}$  and a mixing matrix  $\rho_{p i i'}$ , as in § 3.2.11.1.

<sup>9</sup> Also, many popular numerical solvers do not pass the timestep  $\Delta_t$  (only the current time  $t$ ) to the derivative computing function, and may use adaptive timestep sizes for precision while solving — including: `scipy.integrate.odeint` in Python, `deSolve::lsoda` in R, and `ode45` in MATLAB.

#### 4.1.4 Revisiting Partnership Duration

A final issue in constructing the force of infection equation relates to parameterization. In Eqs. (4.3)–(4.9), partnership durations  $\delta$  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 § A.2.3). 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 “wasted”, 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  $\delta$  is further related to the average partnership formation rate  $Q$  and the average number of concurrent partners  $K$  by  $Q = K/\delta$ .<sup>10</sup> 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

Evidently, prior approaches to modelling HIV transmission in sexual partnerships have several limitations (see also [13]). These limitations, and their implications for existing model-based evidence, can be summarized as follows.

**Instantaneous Partnerships.** Eqs. (4.8) and (4.9) 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 has likely been systematically overestimated by compartmental models, while the contribution of shorter partnerships has likely been underestimated. This point was directly illustrated in a comparison of compartmental vs. network-based models [19]. This bias has substantial implications for which types of interventions and populations have been prioritized using compartmental model-based evidence.

**Aggregating Past/Future Sex Acts.** The instantaneous partnerships assumption is in fact directly related to the “wasted contacts” issue, because the delay in onward transmission risk that is missing under instantaneous partnerships reflects the same post-transmission period within partnerships wherein contacts are “wasted”. The prevailing solution to this issue is to define the per-partnership probability of

<sup>10</sup> Gaps between partnerships do not result in  $Q < K/\delta$ , because the average  $K$  would be reduced if some individuals are “between partnerships”.

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 “wasted contacts” in longer partnerships (using the true partnership duration  $\delta$ ) 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, with broader implications as described above. 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., § 3.2.1.3), 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  $\lambda^{\text{IP}}$  via Eq. (4.9). As described in § 4.1.3, this approach is not inherently wrong, but the specification of time period  $\Delta_t = 1$  often is. This  $\Delta_t$  *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  $\lambda^{\text{IP}}$  saturates at 1 — similar to  $B(A)$  in Figure 4.1a — transmission to higher risk groups is disproportionately reduced. Thus, this error may *further* underestimate the importance of prevention among higher risk groups.

**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. (4.5) and (4.6) — 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  $B_{\text{WPH}} \geq B_{\text{BPH}}$ , 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. A more detailed system for classifying modelling frameworks is also given in Appendix 1 of [19].

**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 [14]. In pair-based models, the fundamental population stratification reflects different partnership configurations and health states [20], 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 partnerships where transmission is vs. is not possible, thereby avoiding the instantaneous partnership



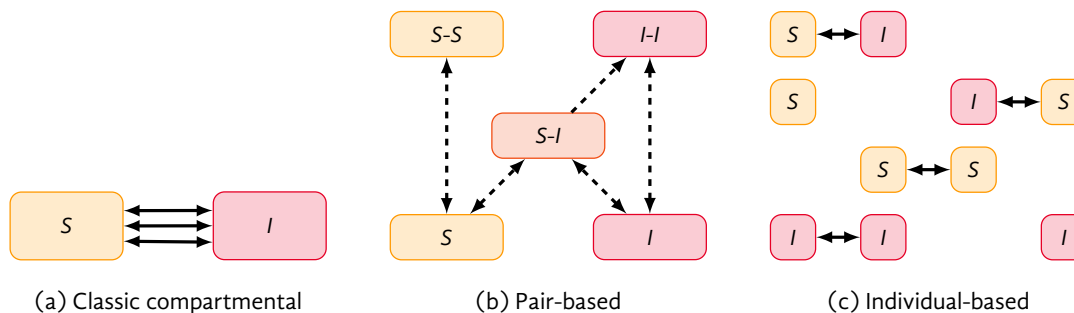


Figure 4.2: Representations of health states and sexual partnerships under three different STI modelling frameworks

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

assumption. Pair-based models have been applied to a variety of STIs [20]. However, the numbers of compartments required to reflect all possible partnership configurations *and* all possible health states among connected partners quickly become impractical [13, 20]. 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  $2 \times 2$  (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 [21]. As such, pair-based models have seen little widespread adoption for STI or HIV transmission modelling [13].

**Individual-Based Models.** Individual-based models, also known as agent-based, network-based, or microsimulation models, explicitly simulate unique individuals (Figure 4.2c), representing a fundamental change in the model unit from groups of individuals — i.e., the “compartments” of compartmental models [13]. 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 [13, 22]. 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 [19, 23]. Evidently, many of the limitations of compartmental and pair-based models do not apply to individual-based models [13]. Yet these limitations are replaced with new challenges, especially related to implementing, parameterizing, and calibrating these powerful models [13, 22, 24]. For example, much effort has been dedicated to formalizing the statistical properties of dynamic networks via temporal exponential family random graph models (tERGM) [25] or latent order logistic models (LOLOG) [26], 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 [13].

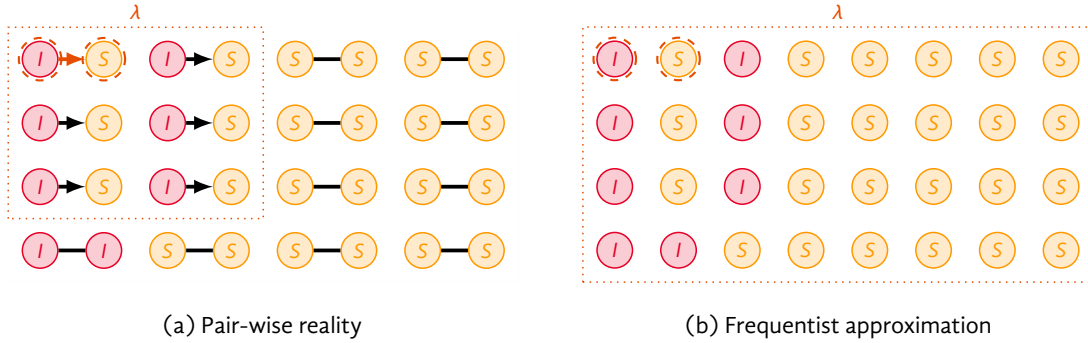


Figure 4.3: Comparison of pair-based reality and frequentist approximation for a population of 16 pairs with 25% infection prevalence, at the moment of one transmission event

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

## 4.2 Proposed Approach

In this section, I propose a new approach to modelling HIV transmission within sexual partnerships in compartmental models. The approach overcomes the limitations of prior approaches described in § 4.1.5, without the need to change modelling frameworks.

### 4.2.1 Illustrative Toy 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. Evidently, this assumption is worse for longer partnerships.

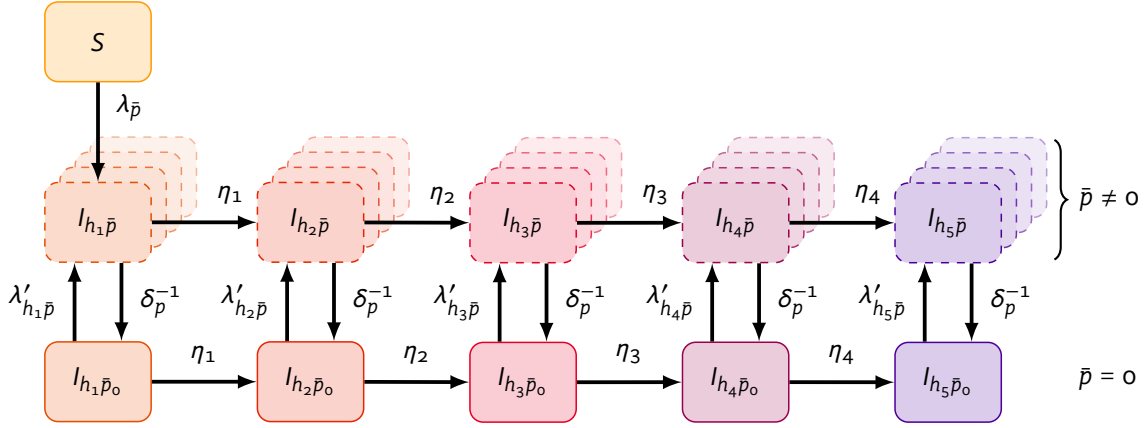


Figure 4.4: Modelled states and transitions related to HIV infection, and a new stratification  $\bar{p}$  to track the proportions of individuals in partnerships where transmission already occurred

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

#### 4.2.2 Conceptual Development

The toy scenario highlights how any partnership where transmission has occurred 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 effective numbers of partners 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 can then be applied until the individuals change partners — at an effective rate inversely related to partnership duration:  $\delta^{-1}$ . 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) partners. 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:  $\lambda_{ip}$ . Individuals may then transition from  $\bar{p} \neq 0$  to  $\bar{p} = 0$  upon forming a new partnership, at a rate  $\delta_p^{-1}$ . 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  $\lambda'_{ip}$ , representing the per-person rate of *transmission*, not *acquisition* as in  $\lambda_{ip}$ . This rate  $\lambda'_{ip}$  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 Equations<sup>11</sup>

Since partnership duration is now considered separately and explicitly, I do not define any adjusted 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  $\beta$ . However, the mixing is now slightly more complicated, since the effective number of partnerships “offered” depends on infection status. In addition, these partnerships are now defined as numbers of concurrent partners  $K$ , rather than partnership formation rates  $Q$ .

Let  $M_{pii'}$  be the total (population-level, not per-person) number of type- $p$  partnerships between group  $i$  and group  $i'$ . As described § 3.2.11, this “mixing matrix”  $M_{pii'}$  can be defined in several ways, based on the total numbers of partnerships “offered” by each group:  $M_{pi}$ ,  $M_{pi'}$ , plus some parameter(s) specifying mixing patterns (e.g.,  $\Phi$ ). Working backwards, I start by defining  $M_{pi}$  (and likewise  $M_{pi'}$ ) via the sum across health statuses — i.e., susceptible, and different stages of infection  $h$ :

$$M_{pi} = M_{S,pi} + \sum_h M_{I,pih} \quad (4.10)$$

I then define the total numbers of partnerships “offered” by susceptible individuals as:

$$M_{S,pi} = S_i K_{pi} \quad (4.11)$$

and likewise for individuals in infection stage  $h$ :

$$M_{I,pih} = I_{ih,\bar{p}=p} (K_{pi} - 1) + \sum_{\bar{p} \neq p} I_{ih\bar{p}} K_{pi} \quad (4.12)$$

Eq. (4.12) is the key equation whereby the effective numbers of type- $p$  partnerships “offered” by 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:

$$\Lambda_{pii'h'} = F_p \beta_{pii'h'} M_{pii'} \left( \frac{M_{S,pi}}{M_{pi}} \right) \left( \frac{M_{I,pi'h'}}{M_{pi'}} \right) \quad (4.13)$$

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:

$$\lambda_{pi} = \sum_{i'h'} \Lambda_{pii'h'} S_i^{-1} \quad (4.14)$$

$$\lambda'_{pi'h'} = \sum_i \Lambda_{pii'h'} I_{i'h'}^{-1} \quad (4.15)$$

<sup>11</sup> “Enough talk. Show me the \$” — L<sup>A</sup>T<sub>E</sub>X users.

For the purposes of solving the model, we can skip division by  $S_i$  and  $l'_{ih'}$  in Eqs. (4.14) and (4.15), since  $\lambda'_{pi}$  and  $\lambda'_{pi'h'}$  are immediately multiplied by  $S_i$  and  $l'_{ih'}$ , respectively, in the system of differential equations. Finally, and to reiterate from above, infected individuals in stratum  $l_{ih\bar{p}}$  are assumed to form new partnerships at a rate  $\delta_{\bar{p}}^{-1}$ , and thereby transition to stratum  $l_{ih\bar{p}_0}$  (“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 approach (i.e., new stratification and equations), 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 [20]. 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  $l_{ih\bar{p}_0}$  to  $l_{ih\bar{p}_1}$  and  $l_{ih\bar{p}_2}$  (one each) under the  $P + 1$  stratification, instead of just one individual from  $l_{ih\bar{p}_0}$  to  $l_{ih\bar{p}_{12}}$  under any of the exponential  $x^P$  the stratifications.

In fact,  $l_{ih\bar{p}_0}$  can be *negative* (but only for  $\bar{p} = 0$ ), because the dimension  $\bar{p}$  is only relevant to Eq. (4.12); in all other contexts and equations, we use  $l_{ih} = \sum_{\bar{p}} l_{ih\bar{p}}$ , which must be positive as usual. Moreover, we can also have  $l_{ih\bar{p}} > l_{ih}$ , provided that:

$$l_{ih\bar{p}} \leq l_{ih} K_{pi} \quad (4.16)$$

reflecting the situation where 100% of  $l_{ih}$  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  $l_{ih\bar{p}} > l_{ih}$ , then  $l_{ih\bar{p}_0}$  must be negative, but it can be shown that Eq. (4.12) still yields the correct value of  $M_{l,pih}$ . With this perspective, the constraint in Eq. (4.16) may be intuitive: we cannot “remove” more than the total number of partnerships “offered”. This constraint should also be easy to guarantee for small enough timesteps, because  $M_{l,pih}$  approaches zero as  $l_{ih\bar{p}}$  approaches  $l_{ih} K_{pi}$  — i.e. all type- $p$  partnerships become HIV+ concordant, and no more transmission can occur via these partnerships until partners change.

### 4.3 Experiments

In this section, I describe some simple experiments (methods and results) to highlight differences in the various equations and approaches to modelling HIV transmission in sexual partnerships.

#### 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. (4.5) vs. Eq. (4.6) as modelling within-partnership heterogeneity (WPH) vs. between-partnership heterogeneity (BPH), respectively. As shown in § A.3.1 (proof),  $B_{WPH} \geq B_{BPH}$ . Here I explore

under what conditions the ratio  $B_{\text{WPH}} / B_{\text{BPH}}$  is maximized — i.e., when does choosing the correct 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  $B_{\text{WPH}}$  and  $B_{\text{BPH}}$  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 [11].

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  $(\alpha, A)$  for a given  $R$ , including  $\alpha > \frac{1}{2}$  for  $R < 1$ , and  $\alpha < \frac{1}{2}$  for  $R > 1$

The specific values of  $(\alpha, A)$  which maximize the difference between approaches for a given  $R$  and  $\beta$  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  $\beta$ . 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 “wasted contacts” Eq. (4.4) would have less effect. This reduced effect can be quantified via the effective probability of transmission per sex act  $\beta'$  — i.e., tangent slopes in Figure 4.1a — defined as:

$$\beta' = \frac{B}{A} = \frac{1 - (1 - \beta)^A}{A} \quad (4.17)$$

Figure 4.7 illustrates the 1-year  $\beta'_1$  vs. true-duration  $\beta'_\delta$ , 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.

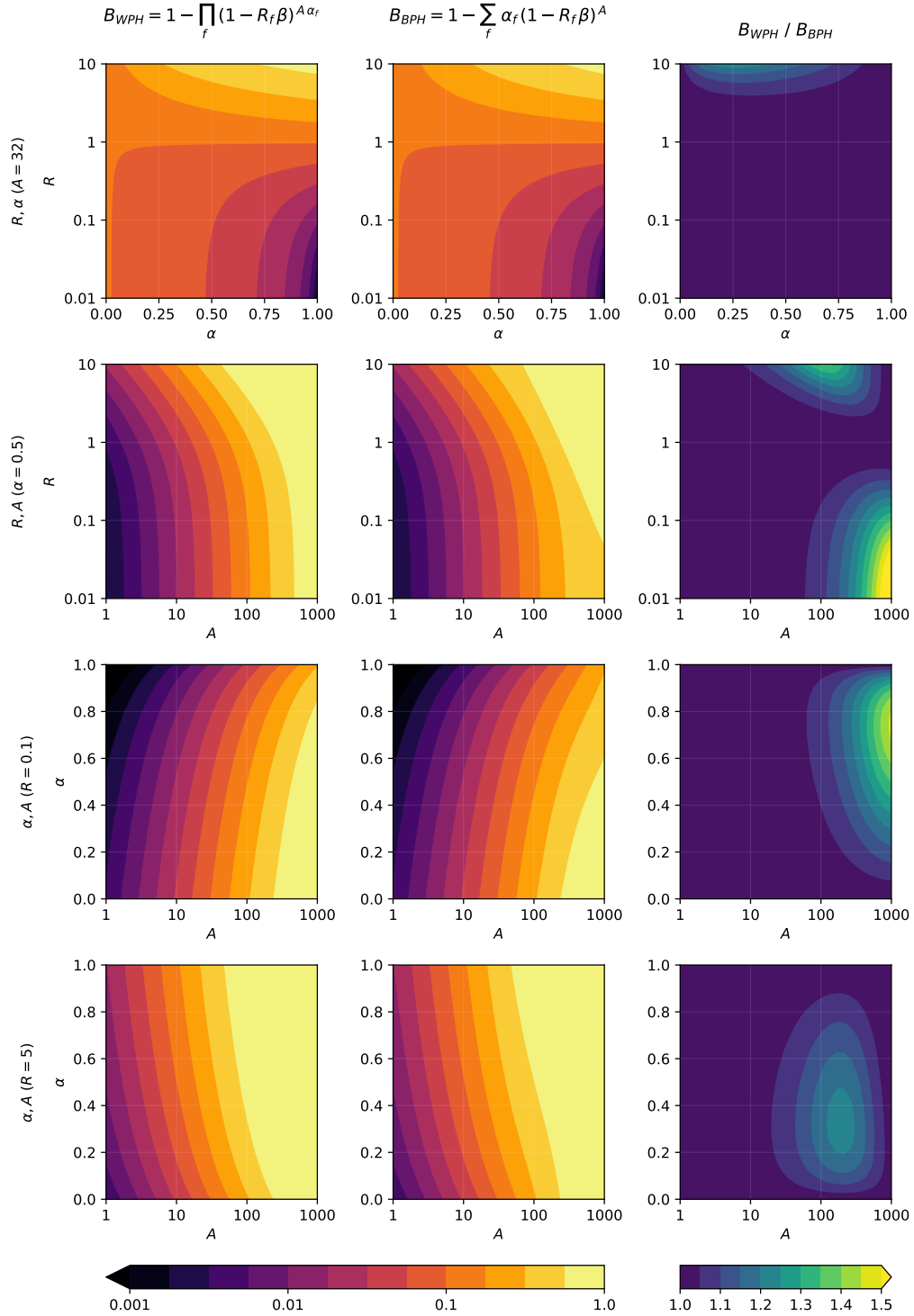


Figure 4.5: Average per-partnership probability of transmission  $B$  given heterogeneity in the per-act probability of transmission  $\beta$  within vs. between partnerships

$B$ : probability of transmission per partnership (log scale colourmap);  $\beta = 0.34\%$ : probability of transmission per sex act (fixed) [11];  $A$ : total sex acts per partnership (log scale);  $\alpha_f$ : proportion of sex acts affected by factor  $f$  (linear scale);  $R_f$ : relative  $\beta$  given factor  $f$  (log scale); WPH: within-partnership heterogeneity; BPH: between-partnership heterogeneity.

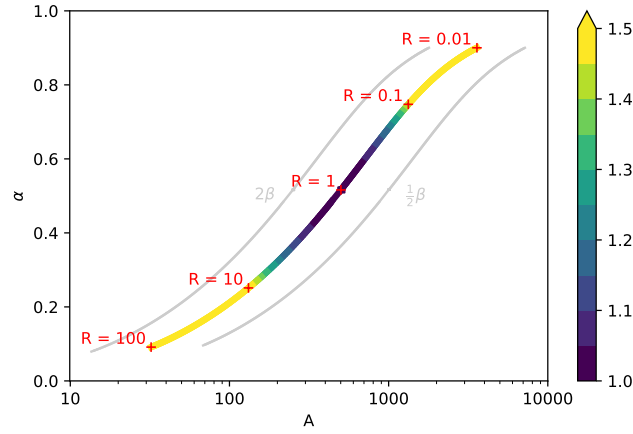


Figure 4.6: Parameter values ( $\alpha, A$ ) which maximize the difference between the average per-partnership probability of transmission given within- vs. between-partnership heterogeneity

$B_{WPH} / B_{BPH}$ : line colour;  $\beta = 0.34\%$ : probability of transmission per sex act (fixed) [11];  $A$ : total sex acts per partnership (log scale);  $\alpha_f$ : proportion of sex acts affected by factor  $f$  (linear scale);  $R_f$ : relative  $\beta$  given factor  $f$  (log scale); gray lines denote equivalent contours for  $2\beta$  and  $\frac{1}{2}\beta$ .

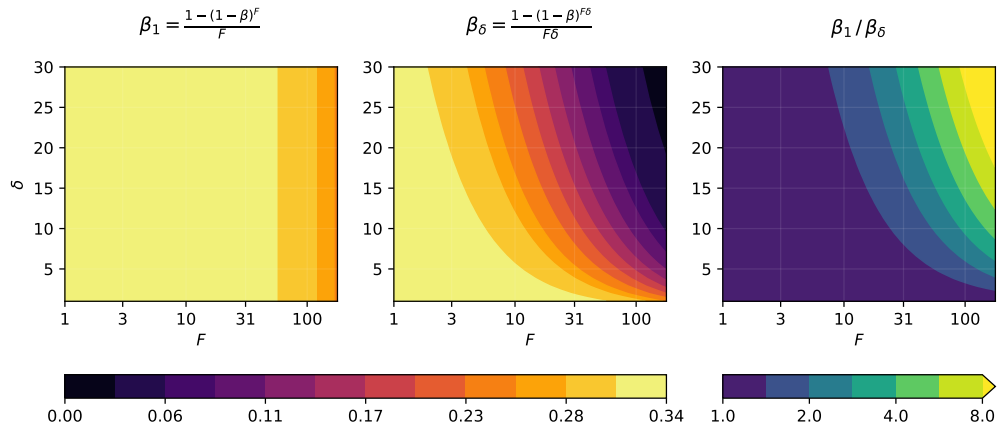


Figure 4.7: Effective probability of transmission per sex act over 1 year vs. total partnership duration

$\beta = 0.34\%$ : probability of transmission per sex act (fixed) [11];  $F$ : frequency of sex per partnership (per year, log scale);  $\delta$ : partnership duration (years, linear scale);  $\beta_1, \beta_\delta$ : effective probability of transmission per sex act, for 1 year vs. total partnership duration, respectively.



### 4.3.3 Comparing Approaches in a Complete Model

Next, I sought to explore how different approaches to modelling HIV transmission via sexual partnerships — i.e., the force of infection — influence key outputs from a complete model. For this analysis, I focused on two aspects of prior approaches: whether incidence is aggregated across partnerships as a rate vs. proportion (§ 4.1.3), and whether or not partnership durations are effectively capped at 1 year (§ 4.1.4). Thus, I considered 4 prior approaches, plus the new proposed approach from § 4.2 (Table 4.1). I integrated each approach within the model from Chapter 3.

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

ID	Name	Key Eqs.	Key Parameters
NP	New Proposed	(4.10)–(4.15)	$K, F, \delta$
RD	Rate-Duration	(4.6), (4.8)	$A, Q$
RY	Rate-1-Year	(4.6), (4.8)	$A_1, Q_1$
PD	Proportion-Duration	(4.6), (4.9)	$A, Q$
PY	Proportion-1-Year	(4.6), (4.9)	$A_1, Q_1$

$K$ : number of concurrent partners;  $F$ : frequency of sex per partnership;  $\delta$ : 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 5 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. For aim 2, I compared the transmission population attributable fraction (TPAF, details in § 4.3.3.2) of several transmission pathways, using *approach-specific* model parameters (recalibrated). 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 models using each approach.

**Equal vs. Approach-Specific Parameters.** The new proposed (NP) approach uses the numbers of concurrent partnerships  $K$ , frequency of sex per partnership  $F$ , and partnership duration  $\delta$ , while 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 NP (see § 3.4.1), and converted  $A = F\delta$  and  $Q = K/\delta$  for all 4 prior approaches (RD, RY, PD, PY), with the additional adjustment  $\delta_1 = \min(\delta, 1)$  for the 1-year approaches (RY, PY). For *approach-specific* parameters, I repeated the methods in § 3.3, yielding 1000 unique model fits (parameter sets) for each prior approach.

#### 4.3.3.1 Transmission Dynamics using Equal Parameters

Figure 4.8 illustrates HIV incidence under each approach among FSW, clients, and everybody else (“lower risk”). Specifically, Figure 4.8a illustrates incidence per person-year (NP repeated for comparison) and

Figure 4.8b illustrates relative differences vs. the NP approach.<sup>12</sup> I made the following observations — and *hypothesized* explanations, drawing on the complete network of modelled transmission under NP (Figure 3.13):

- Incidence among lower risk was generally much higher under 1-year approaches (RY, PY) — underestimation of “wasted contacts” 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-width-like mixing (see § 3.2.11.3).
- Incidence differences between the 1-year approaches (RY, PY) vs. NP grew over time — NP explicitly models the accumulation of seroconcordant partnerships wherein contacts are “wasted”, or “partnership-level herd effects”; thus, by underestimating “wasted contacts” throughout the epidemic, the 1-year approaches are initially less biased vs. NP, but later overestimate incidence.
- Incidence among all risk groups was lower under full-duration approaches (RD, PD) — complete and instantaneous accounting of “wasted contacts” under these approaches effectively delays transmission in all partnership types, and contributes to a lower HIV prevalence feedback loop.
- Incidence among FSW and clients was much lower under “incidence proportion” approaches (PD, PY) — incidence proportion Eq. (4.9) treats all transmission risks as competing, and notably forces incidence  $\lambda^{\text{IP}} \leq 1$ , disproportionately reducing incidence among those at highest risk.
- Incidence among FSW and clients under RY approximately matched NP — competing biases due to underestimation of some “wasted contacts” (delays transmission), but not all “wasted contacts” (overestimates transmission) coincidentally yielded incidence roughly matching NP.

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

Figure 4.9 further illustrates the proportions of modelled yearly HIV infections transmitted via different partnership types under each approach using equal parameters (top) and approach-specific parameters for comparison (bottom). As hypothesized above, for equal parameters, the 1-year approaches (RY, PY) featured the greatest proportions of transmission via main/spousal partnerships, and the least via sex work. By contrast, the full-duration approaches (RD, PD) featured the smallest proportions transmitted via main/spousal partnerships, and the most via sex work. The distribution under the proposed approach (NP) was in between these two extremes. Interestingly, there were minimal differences in Figure 4.9 between incidence rate (RD, RY) and incidence proportion (PD, PY) approaches.

#### 4.3.3.2 Prevention Priorities using Approach-Specific Parameters

Many models applied to assess HIV prevention priorities explicitly model specific intervention scenarios, often with a cost dimension [27–29]. 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.

**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

<sup>12</sup> Relative differences were “paired” according to each parameter set  $k$ , and computed as  $(xx_k - NP_k)/NP_k$ .

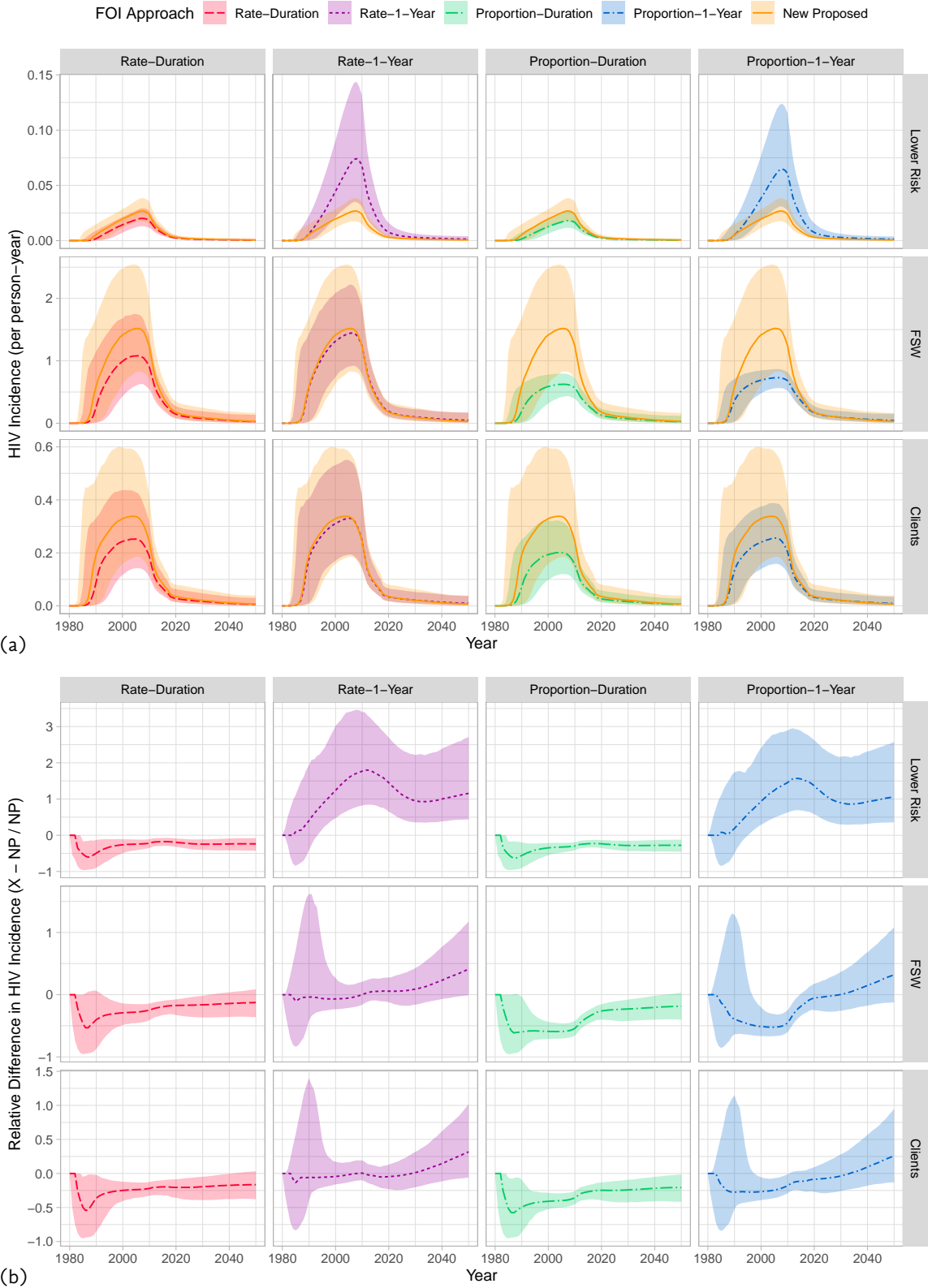


Figure 4.8: HIV incidence among selected risk groups, estimated under different prior force of infection approaches (colours) vs. the new proposed approach using equal model parameters

See Table 4.1 for approach definitions; 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.



Figure 4.9: 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)

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

outcomes with vs. without the factor [30, 31]. 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 [32]. 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 [33–35].

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

$$\text{TPAF}_{jk}(t) = \frac{\Omega_j(t) - \Omega_{jk}(t)}{\Omega_j(t)}, \quad \Omega_{jk}(t) = \int_{t_0}^t \Lambda_{j,M_k=0}(\tau) d\tau, \quad t = t_0 + \Delta_t \quad (4.18)$$

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% [36, 37].

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  $M_{piir}$ , after resolving the values per § 3.2.11, such that mixing patterns were not affected.

**TPAFs of Partnership Types.** Figure 4.10 illustrates the TPAFs for partnership types. TPAFs generally increased over longer time horizons  $\Delta_t$  but decreased with calendar year  $t_0$  (n.b. vertical scales), especially for sex work. Such trends are consistent with prior work showing that TPAFs typically decrease as epidemics become more widespread, especially for key populations [38–40].

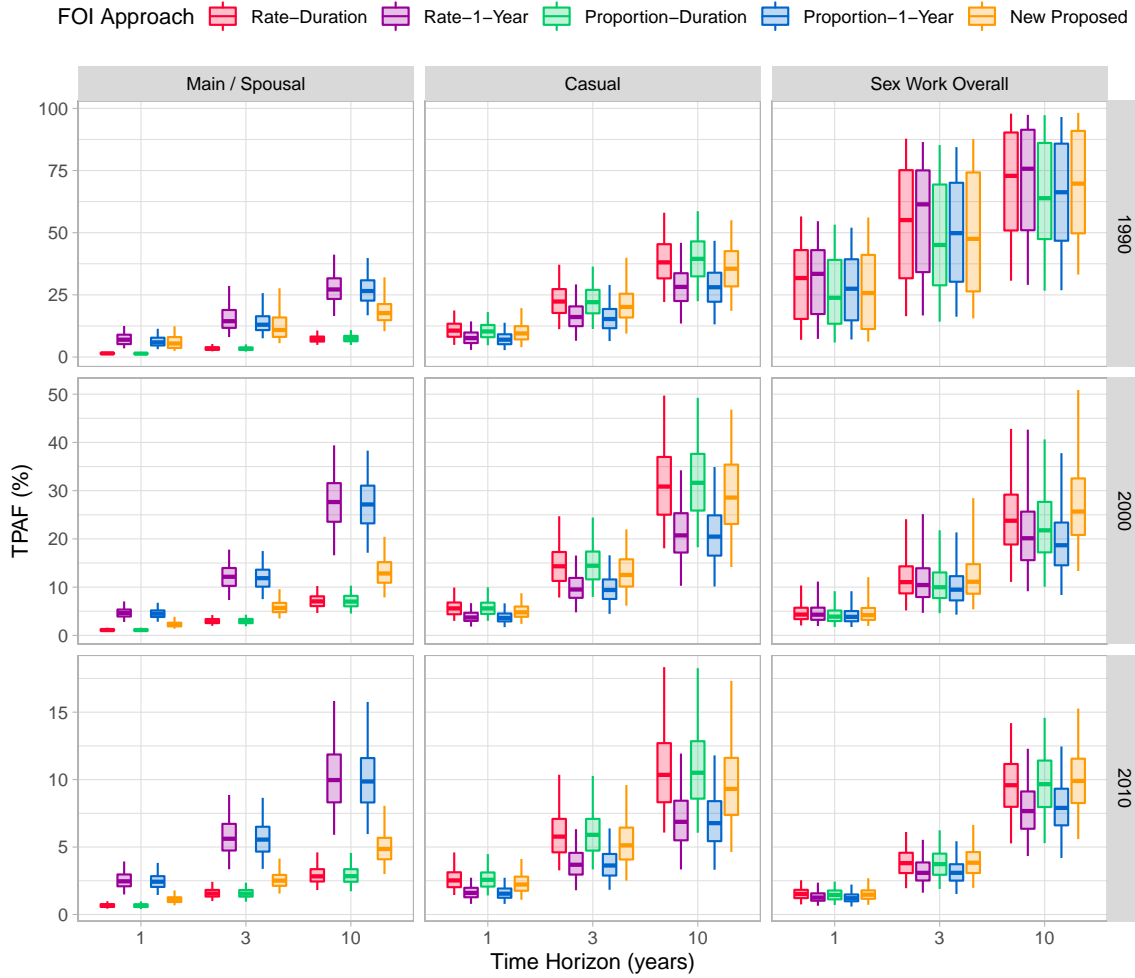


Figure 4.10: TPAF of transmission via different partnership types (horizontal facets), starting from different  $t_0$  (vertical facets), estimated under different force of infection approaches (colours)

TPAF: transmission population attributable fraction, § 4.3.3.2; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

TPAF differences across force of infection approaches were largest for main/spousal partnerships, with 1-year approaches (RY, PY) significantly larger than full-duration approaches (RD, PD). Main/spousal TPAFs under NP were similar to RY and PY from 1990 over short time horizons, beyond which TPAFs tended towards RD and PD; similar to incidence differences in § 4.3.3.1, these findings reflect reduced transmission via longer partnerships over time due to the accumulation of “partnership-level herd effects”, which are only captured under NP. 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 RD and PD, while main/spousal TPAFs were almost always greater than casual TPAFs under RY and PY. There were minimal differences in TPAFs for main/spousal or casual partnerships *between* 1-year approaches (RY vs. PY) or between full-duration approaches (RD vs. PD).

The TPAFs of sex work were the largest of all partnership types in 1990, reflecting the disproportionate role of sex work in early transmission (Figure 3.12). In 2000 and 2010, the size of sex work TPAFs

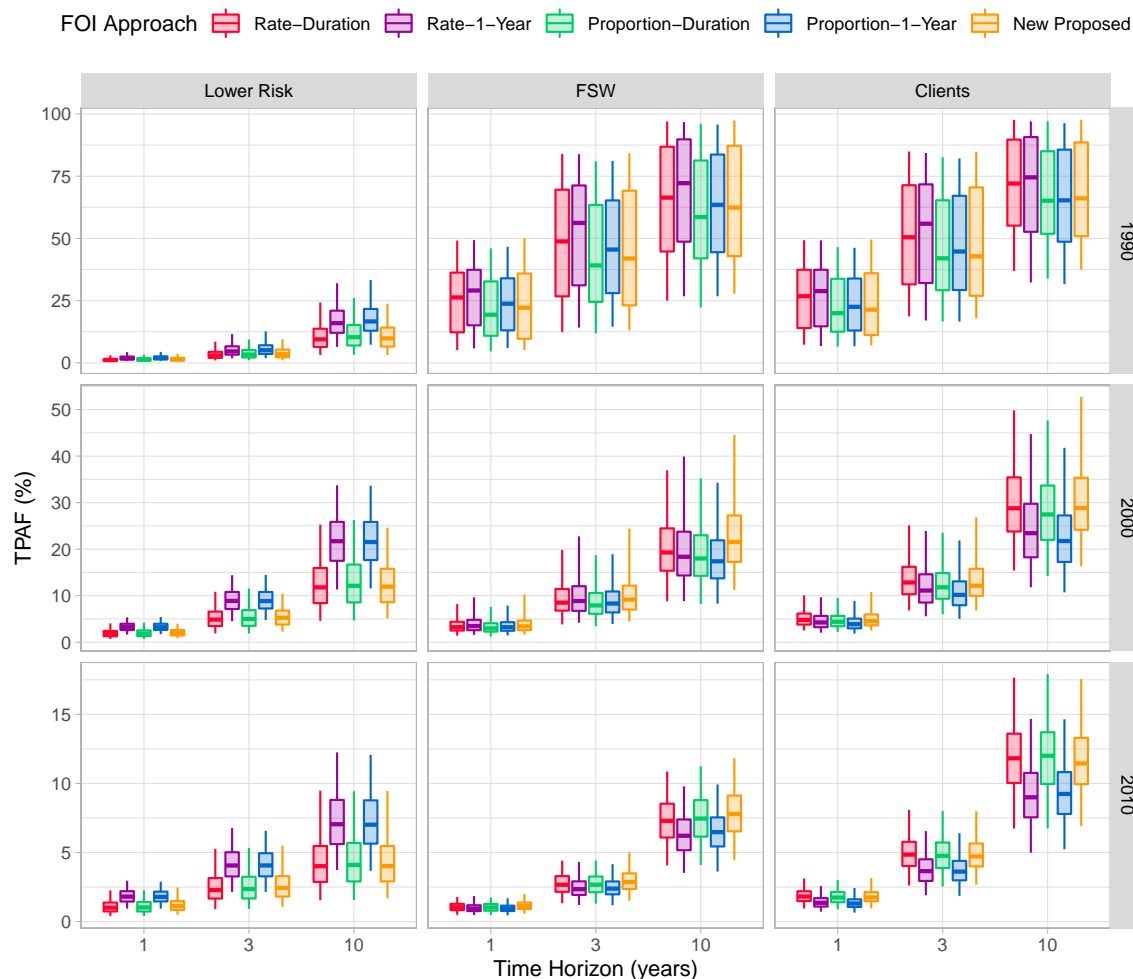


Figure 4.11: TPAF of transmission from different risk groups (horizontal facets), starting from different  $t_0$  (vertical facets), estimated under different force of infection approaches (colours)

TPAF: transmission population attributable fraction, § 4.3.3.2; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.

remained similar to those of casual partnerships. 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 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 § 3.2.10.3 and Figure 3.6). By 2010, clearer differences across approaches in sex work TPAFs emerged, which were similar to differences for casual partnerships.

**TPAFs of Risk Groups.** Figure 4.11 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 3.13). 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 RY, PY) on the contribution of lower risk groups to overall transmission.

## 4.4 Discussion

Compartmental models of sexual HIV transmission continue to support HIV epidemic response globally, including the Spectrum suite of models [41, 42], the Optima HIV model [28, 43], the Asian Epidemic Model [44], the Thembisa model for South Africa [45–47], and numerous others (e.g., Chapter 2). Such models usually simulate sexual HIV transmission within risk- and/or age-stratified populations, possibly considering multiple partnership types and/or transmission modifiers. As I have shown in § 4.1, several existing approaches (model structures and equations) are used to define rates of HIV transmission via sexual partnerships in these models — especially with respect to heterogeneous populations, partnerships, and sex acts — each with implicit assumptions. In § 4.3, I explored the potential influence of these approaches/assumptions on: the computed probability of transmission per partnership, modelled epidemic dynamics, and on model-estimated prevention priorities. Yet, many of these assumptions can be avoided altogether using a new approach I developed in § 4.2, representing an exciting opportunity to improve the quality of compartmental model-based evidence for HIV response going forward.

### 4.4.1 Heterogeneity in Per-Act Probability of Transmission

In § 4.1.2 and 4.3.1, I introduced and explored the distinction between *within*-partnership heterogeneity (WPH) vs. *between*-partnership heterogeneity (BPH) in the per-act probability of transmission  $\beta$ . Whereas WPH reflects an assumption that all partnerships are identical, but comprise heterogeneous acts, BPH reflects an assumption that partnerships are different, but each comprise identical acts. This distinction — i.e., all of Eqs. (4.4)–(4.7) and variants thereof — is unnecessary under the proposed approach.

Numerous variations on Eqs. (4.4)–(4.9) have been used in prior models. For example, the Optima [28] and Goals [48] models aggregate heterogeneity due to HIV infection stage *before* aggregating sex acts within each partnership or applying transmission modifiers. Such an approach is difficult to justify, because the prevalence of each infection stage evidently reflects distinct individuals — *not* the distribution of infection stages within a given partnership (see also footnote 7.) This approach then does not allow for the *multiplicative* interaction of infection stage and other modifiers, while simultaneously allowing a high-infectivity stage with low prevalence (e.g., acute HIV) to increase transmission risk across all partnerships (see Figure 4.1b). As a result, this approach yields intermediate  $B_{WPH} \geq B' \geq B_{BPH}$  (see § A.3.1). It's not clear whether these variations have systematically biased existing model-based evidence, but improved understanding of the assumptions and potential biases of each approach can help guide interpretation of existing results, and design of future models which do not adopt the proposed approach.

In some cases, modellers have noted the discrepancies between equations between models, but dismissed the differences as inconsequential because  $\beta$  is usually small [28]. This justification is fair when  $\beta$  is indeed

small. However, several combinations of transmission modifiers (e.g., condomless anal sex with GUD and acute HIV infection) [11, 49] can easily yield larger  $\beta$ , for which the discrepancies are *not* inconsequential (e.g., Figure 4.5). In fact, it is precisely these contexts of rapid transmission which define key epidemic dynamics, as reflected in core group theory [50]. Moreover, since the prevalence of such modifiers often varies across risk groups and transmission pathways, differences in how heterogeneous  $\beta$  is aggregated may ultimately yield differences in the modelled contribution of risk groups and transmission pathways to overall transmission — although some differences might be reduced via model calibration.

Lastly, statistical inference on modifiers of per-act transmission probability — e.g., relative risk with condoms, GUD, etc. — typically uses exposure-stratified individual-level data [9, 11, 51, 52]. Thus, these statistical models do not consider what *proportion* of sex acts are exposed, and need not distinguish between within vs. between partnership heterogeneity. Yet, relative risks estimated from *per-act* data have been applied to the *per-partnership* transmission probability in several models [TOOD]. Such an approach would then underestimate the impact of risk-reducing modifiers (e.g., condoms) and overestimate the impact of risk-increasing modifiers (e.g., GUD).<sup>13</sup>

#### 4.4.2 Beyond Instantaneous Partnerships

The 2021 review by Rao et al. [13] summarizes frameworks that have been used to simulate partnership dynamics for modelling sexually transmitted infections (see also § 4.1.6 and Appendix 1 of [19]). Besides pair-based models, the review does not identify another approach which has extended the compartmental modelling framework beyond instantaneous partnerships. Pair-based models have not seen widespread adoption, likely due to exponential complexity (i.e., numbers of required compartments) [20]. However, several hybrid models have been developed [53, 54] 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 likely offer substantial improvements over fully instantaneous partnerships [55–57]. However, the high number of *regular* clients reported by Swati FSW (§ 3.2.1) reflects precisely the kind of dense, persistent sexual network — i.e., high concurrency — which is difficult to model via a pair-based approach. The importance of partnership concurrency in HIV transmission has been debated extensively [21, 58–61]. Thus, the proposed approach offers an alternative to hybrid / pair-based models for such networks, and thereby solves a 30-year old modelling challenge [14].

##### 4.4.2.1 Prior Comparisons of Models with vs. Without Instantaneous Partnerships

The potential biases associated with instantaneous partnerships have been explored previously, via comparison with deterministic pair-based models [55–57], a stochastic pair-based model [56], a stochastic static network-based model [56], and a stochastic dynamic network-based model [19].

Kretzschmar and Dietz [55] highlight how biases associated with instantaneous partnership increase with the true partnership durations, and conclude that: “*the number of new partners per unit time is not sufficient to predict the course of the epidemic, but that partnership duration is a quantity that is equally influential.*” I agree and regret that data to directly inform sexual partnership durations, especially for

<sup>13</sup> 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  $R > 1$ .



non-marital partnerships, remain lacking (see § 3.2.10.3). Efforts to fill this data gap will likely benefit from careful consideration of different measurement approaches and sources of error [62], perhaps in conjunction with efforts to better quantify partnership formation rates, as explored in § A.2.3.

Eames and Keeling [56] and Lloyd-Smith, Getz, and Westerhoff [57] both show that instantaneous partnerships can result in overestimation of the initial epidemic growth rate and equilibrium prevalence. Such findings seem intuitive. However, in § 4.3.3 (Figure 4.8), I showed how the rate of epidemic growth under instantaneous partnerships strongly depends on the effective partnership duration used for the “wasted contacts” adjustment — if such an adjustment is applied at all. That is, when durations were capped at 1 year (approaches **RY**, **PY**), this adjustment likely had little effect, and modelled incidence was indeed overestimated relative to the proposed approach; by contrast, when full partnership durations were used (approaches **RD**, **PD**), this adjustment reduced transmission immediately in anticipation of future “wasted contacts”, and modelled incidence was *underestimated* relative to the proposed approach. No adjustments for “wasted contacts” were described in [56, 57], reflecting the former case.

**Johnson and Geffen [19].** This landmark study compared modelling frameworks across 6 STIs.<sup>14</sup> The models explored were more complex than previous works, including: population stratification by sex, age, and risk, and three partnership types within a dynamic sexual network, in a South African context. Although an adjustment for “wasted contacts” for instantaneous partnerships was applied, the adjustment considered different time period across partnership types: 1 month for main/spousal, 6 months for casual, and none for sex work partnerships; thus, regular sex work partnerships were not considered. Similar to experiments in § 4.3.3, [19] first compared model outputs from frameworks with equal parameters, and then again with recalibrated parameters.

With equal parameters, findings echoed those above [56, 57], although differences between frameworks were larger for curable STIs with faster transmission, and smaller for HIV. After recalibrating models to the same STI data in, the best-fitting parameters differed significantly across modelling frameworks, as expected — e.g., lower transmission probabilities were inferred with instantaneous partnerships. More importantly, the relative impact (infections averted after 10 years) of several illustrative intervention strategies also differed substantially. These differences were summarized as: “[instantaneous partnership 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” [19]. Such findings are similar to those in § 4.3.3.2, where the TPAFs of lower risk populations and main/spousal partnerships were overestimated, while the TPAFs of casual partnerships were underestimated under 1-year approaches (**RY**, **PY**) vs. the new proposed approach (**NP**). However, while [19] observed that instantaneous partnerships “may underestimate the contribution of commercial sex”, the TPAFs of FSW, clients, and sex work partnerships were similar across approaches in § 4.3.3.2. These different findings could be explained by the fact that [19] only modelled one-off sex work partnerships, whereas transmission via sex work in the Eswatini model was dominated by regular partnerships (Figure 4.9). Indeed, many HIV models have yet to incorporate longer partnerships between higher risk groups (see § 2.3.2.3). Thus, I would offer to rephrase the conclusions of [19] as: “without complete adjustment for ‘wasted contacts’, models with instantaneous partnerships may overestimate the contribution of longer partnerships, and underestimate the contribution of shorter partnerships.”

<sup>14</sup> The term “frequency-dependent” in [19] is synonymous with “instantaneous partnerships” here.

#### 4.4.2.2 Implications for Existing Model-Based Evidence

The vast majority of existing compartmental HIV transmission models have used an instantaneous partnerships approach, with adjustments for “wasted contacts” of 1-year or less. The results in § 4.3.3.2 suggest that such models have likely *systematically* and *significantly* overestimated the relative contributions of longer vs. shorter partnerships to overall transmission. Such results are corroborated by [19], and have substantial implications for the existing body of model-based evidence. That is, models continue to help inform which interventions are prioritized and for whom, and existing evidence may overestimate the importance of prevention within longer partnerships for reducing overall transmission. For example:

**Anderson et al.** [27, 63, 64] These works explore “optimal” combinations of PrEP, early ART, behaviour change, and VMMC for MSM, other men, FSW, and other women in Kenya, under various cost constraints. Their modelling analyses indicate that early ART for non-MSM men is usually more cost effective than PrEP for FSW. Yet, for lowest risk men — modelled median [IQR] 53 [37, 70]% of non-MSM men — effective partnership duration was 4 [2.6, 6.2] years.<sup>15</sup> If longer partnership durations were more accurately modelled, the relative impact of PrEP for FSW vs. early ART for non-MSM would likely increase.

**Optima HIV Model.** [28, 43, 65, 66] As the name suggests, this model has similarly been applied to “optimize resource allocation” in over 20 countries. Recommended allocations have generally increased resources for key populations over current spending. However, the force of infection equation is defined as an incidence proportion [66] — Eq. (4.9) — wherein all sex acts over a given time period (default  $\Delta_t = 0.2$  years)<sup>16</sup> are modelled as competing risks, and so partnership durations are *completely ignored*. Thus, the relative impact of prioritizing key populations has likely been underestimated via both: overestimation of transmission via longer partnerships due to ignoring partnership durations, underestimation of transmission to higher risk groups due to the incidence proportion equation.

**Goals Model.** [41, 48] The Goals Model is part of the Spectrum suite of policy modelling tools [42], which have been widely applied in consultation with national ministries of health to estimate yearly new infections and the impact of various interventions [41]. The Goals model includes mechanistic HIV transmission among 11 total risk groups, including FSW, their clients, MSM, and PWID, without age stratification [48].<sup>17</sup> Yet, as in the Optima model, the force of infection is defined as an incidence proportion — using a transformation of Eq. (4.9) — with  $\Delta_t = 1$  year. Thus, for the same reasons as Optima (and worse with  $\Delta_t = 1$  vs. 0.2 years), the relative impact of prioritizing shorter partnerships and key populations for prevention have likely been systematically underestimated by the Goals Model.

In sum, decades of model-based HIV prevention evidence — for multiple countries and resource allocation questions — are built upon the instantaneous partnerships assumption and associated equations. I have shown that this assumption and these equations can significantly bias model-estimated contributions of different populations and partnerships to overall transmission, and thus the model-estimated importance of different prevention strategies. Specifically, the common practice of only adjusting for up to 1-year of “wasted contacts” (or equivalently: assuming that all individuals change partners at least once per year)

<sup>15</sup> Median [IQR] estimated via Monte Carlo sampling of  $\bar{c}$ ,  $R$ ,  $\varpi$  from uniform prior distributions in Table S7; posterior parameter distribution were not given in [27].

<sup>16</sup> From: [github.com/optimamodel/optimamodel/blob/master/optimamodel/parameters.py](https://github.com/optimamodel/optimamodel/blob/master/optimamodel/parameters.py)

<sup>17</sup> 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) [41]. To confuse matters further, a Goals “Age-Risk-Stratified Model” is also being developed.

overestimates the importance of prevention in longer partnerships, and underestimates the importance of prevention in shorter partnerships. Moreover, defining the force of infection as an incidence proportion (vs. rate) disproportionately reduces modelled incidence among populations at higher risk, and thus underestimates the importance of prevention among these populations. Finally, I illustrated these potential biases in the context of a high prevalence HIV epidemic (Eswatini), but these biases and implications for prevention could be even greater elsewhere.

### 4.4.3 Transmission-Driven Emergence of Serosorting Patterns

HIV serosorting is a controversial harm reduction strategy defined as preferential selection of sexual partners with matching (perceived) HIV serostatus; related strategies can involve modified sexual practices with a given partner on the same basis [67–69]. Serosorting is often quantified using cross-sectional data, using the odds or excess fraction of seroconcordant partnerships vs. random mixing by serostatus [70, 71]. However, using an illustrative toy scenario (§ 4.2.1, Figure 4.3), I have highlighted how transmission naturally generates a disproportionate number of seroconcordant (*I-I*) partnerships as compared to random mixing by serostatus. This emergent property was also noted in [56], therein described as “*correlation of infection statuses of neighboring individuals*”. This disproportionate seroconcordance would be correlated with partnership duration. Failure to consider this dynamic could then lead to overestimation of the degree to which serosorting is intentional (from cross-sectional data). Such biases in quantifying serosorting could be mitigated using longitudinal data or consideration of only new partnerships [72].

### 4.4.4 Future Work

Hopefully I have made a convincing case for the value added by the proposed approach. Thus, an obvious area for future work would be to integrate this approach into new and existing compartmental HIV transmission models, including widely-used models like Spectrum Goals, Optima, Asian Epidemic Model, and Thembisa. To this end, the complete implementation of the proposed approach in the Eswatini model is available online,<sup>18</sup> although perhaps it would also be useful to develop a simpler example model with vs. without the proposed approach to illustrate the essential differences. It may also be useful to compare key model outputs before vs. after integrating the proposed approach in existing models and highlight notable differences, similar to the experiments in § 4.3.3. Similar work could compare and indeed validate the proposed approach vs. individual-based models, similar to the experiments in [19].

Additionally, while I developed the proposed approach in the context of HIV, accurate simulation of partnership dynamics is also relevant for compartmental models of other sexually transmitted infections [13], including gonorrhea, chlamydia, syphilis, trichomoniasis, herpes, hepatitis, papillomavirus, and mpox. However, the approach should be carefully adapted for curable infections, as I have not considered how transitions *out* of the newly proposed infected strata (stratification  $\bar{p}$  in Figure 4.4) should be conceptualized and parameterized.

<sup>18</sup> See: [github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/foi.py](https://github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/foi.py), where `foi_mode='base'`.

## References

- [1] M. Begon et al. "A clarification of transmission terms in host-microparasite models: Numbers, densities and areas". *Epidemiology and Infection* 129.1 (2002), pp. 147–153. <https://doi.org/10.1017/S0950268802007148>.
- [2] Jesse Knight and Sharmistha Mishra. "Beyond instantaneous partnerships: capturing partnership-level herd effects in compartmental models of sexually transmitted infections". *SMDM 44th North American Meeting*. Seattle, Washington, 2023. <https://github.com/mishra-lab/hiv-fsw-art/tree/master/docs/conf/smdm>.
- [3] R. M. Anderson et al. "A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS". *Mathematical Medicine and Biology* 3.4 (1986), pp. 229–263. <https://doi.org/10.1093/imammb/3.4.229>.
- [4] James A Yorke, Herbert W Hethcote, and Annett Nold. "Dynamics and control of the transmission of gonorrhea". *Sexually Transmitted Diseases* 5.2 (1978), pp. 51–56. <http://doi.org/10.1097/00007435-197804000-00003>.
- [5] Annett Nold. "Heterogeneity in disease-transmission modeling". *Mathematical Biosciences* 52.3-4 (1980), pp. 227–240. [https://doi.org/10.1016/0025-5564\(80\)90069-3](https://doi.org/10.1016/0025-5564(80)90069-3).
- [6] Herbert W. Hethcote, James A. Yorke, and Annett Nold. "Gonorrhea modeling: a comparison of control methods". *Mathematical Biosciences* 58.1 (1982), pp. 93–109. [https://doi.org/10.1016/0025-5564\(82\)90053-0](https://doi.org/10.1016/0025-5564(82)90053-0).
- [7] Valerie Isham. "Mathematical Modelling of the Transmission Dynamics of HIV Infection and AIDS: A Review". *Journal of the Royal Statistical Society. Series A: Statistics in Society* 151.1 (1988), p. 5. <https://doi.org/10.2307/2982179>.
- [8] Edward H. Kaplan. "Modeling HIV infectivity: Must sex acts be counted?" *Journal of Acquired Immune Deficiency Syndromes* 3.1 (1990), pp. 55–61. <https://pubmed.ncbi.nlm.nih.gov/2293643/>.
- [9] Ronald H Gray et al. "Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda". *The Lancet* 357.9263 (2001), pp. 1149–1153. [https://doi.org/10.1016/S0140-6736\(00\)04331-2](https://doi.org/10.1016/S0140-6736(00)04331-2).
- [10] John Arne Røttingen and Geoffrey P. Garnett. "The epidemiological and control implications of HIV transmission probabilities within partnerships". *Sexually Transmitted Diseases* 29.12 (2002), pp. 818–827. <https://doi.org/10.1097/00007435-200212000-00014>.
- [11] Marie Claude Boily et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". *The Lancet Infectious Diseases* 9.2 (2009), pp. 118–129. [https://doi.org/10.1016/S1473-3099\(09\)70021-0](https://doi.org/10.1016/S1473-3099(09)70021-0).
- [12] Seyed M. Moghadas et al. "Could condoms stop the AIDS epidemic?" *Journal of Theoretical Medicine* 5.3-4 (2003), pp. 171–181. <https://doi.org/10.1080/10273660412331315147>.
- [13] Darcy White Rao et al. "Partnership dynamics in mathematical models and implications for representation of sexually transmitted infections: a review". *Annals of Epidemiology* 59 (2021), pp. 72–80. <https://doi.org/10.1016/j.annepidem.2021.04.012>.
- [14] K. Dietz and K. P. Hadeler. "Epidemiological models for sexually transmitted diseases". *Journal of Mathematical Biology* 26.1 (1988), pp. 1–25. <https://doi.org/10.1007/BF00280169>.
- [15] Robert Allard. "A family of mathematical models to describe the risk of infection by a sexually transmitted agent". *Epidemiology* 1.1 (1990), pp. 30–33. <https://doi.org/10.1097/00001648-199001000-00007>.
- [16] Foteini K Giannou et al. "Condom effectiveness in reducing heterosexual HIV transmission: a systematic review and meta-analysis of studies on HIV serodiscordant couples". *Expert Review of Pharmacoeconomics and Outcomes Research* 16.4 (2016), pp. 489–499. <https://doi.org/10.1586/14737167.2016.1102635>.
- [17] J. M. Aldaz. "Self-improvement of the inequality between arithmetic and geometric means". *Journal of Mathematical Inequalities* 2 (2009), pp. 213–216. <https://doi.org/10.7153/jmi-03-21>.
- [18] Roy M Anderson and Robert M May. *Infectious diseases of humans: dynamics and control*. Oxford University Press, 1991.
- [19] Leigh F. Johnson and Nathan Geffen. "A Comparison of two mathematical modeling frameworks for evaluating sexually transmitted infection epidemiology". *Sexually Transmitted Diseases* 43.3 (2016), pp. 139–146. <http://doi.org/10.1097/OLQ.0000000000000412>.
- [20] Mirjam Kretzschmar and Janneke C.M. Heijne. "Pair formation models for sexually transmitted infections: A primer". *Infectious Disease Modelling* 2.3 (2017), pp. 368–378. <https://doi.org/10.1016/j.idm.2017.07.002>.

- [21] Larry Sawers. "Measuring and modelling concurrency". *Journal of the International AIDS Society* 16.1 (2013), p. 17431. <http://doi.wiley.com/10.7448/IAS.16.1.17431>.
- [22] Lorenzo Pellis et al. "Eight challenges for network epidemic models". *Epidemics* 10 (2015), pp. 58–62. <https://www.sciencedirect.com/science/article/pii/S1755436514000334#bib0190>.
- [23] Jan A.C. C. Hontelez et al. "Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study". *PLOS Medicine* 10.10 (2013). Ed. by Nathan Ford, e1001534. <http://doi.org/10.1371/journal.pmed.1001534>.
- [24] C. Marijn Hazelbag et al. "Calibration of individual-based models to epidemiological data: A systematic review". *PLOS Computational Biology* 16.5 (2020). Ed. by Roger Dimitri Kouyos, e1007893. <https://doi.org/10.1371/journal.pcbi.1007893>.
- [25] Samuel M. Jenness, Steven M. Goodreau, and Martina Morris. "EpiModel: An R package for mathematical modeling of infectious disease over networks". *Journal of Statistical Software* 84 (2018). [/pmc/articles/PMC5931789/%20/pmc/articles/PMC5931789/?report=abstract%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5931789/](https://pmc/articles/PMC5931789/%20/pmc/articles/PMC5931789/?report=abstract%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5931789/).
- [26] Duncan A. Clark and Mark S. Handcock. "Comparing the real-world performance of exponential-family random graph models and latent order logistic models for social network analysis". *Journal of the Royal Statistical Society. Series A: Statistics in Society* 185.2 (2022), pp. 566–587. <https://doi.org/10.1111/rssa.12788>.
- [27] Sarah Jane Anderson et al. "Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study". *The Lancet* 384.9939 (2014), pp. 249–256. [https://doi.org/10.1016/S0140-6736\(14\)61053-9](https://doi.org/10.1016/S0140-6736(14)61053-9).
- [28] Cliff C. Kerr et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376. <https://doi.org/10.1097/QAI.0000000000000605>.
- [29] Mathieu Maheu-Giroux et al. "Cost-Effectiveness of Accelerated HIV Response Scenarios in Cote d'Ivoire". *Journal of Acquired Immune Deficiency Syndromes* 80.5 (2019), pp. 503–512. <https://doi.org/10.1097/QAI.0000000000001956>.
- [30] B. Rockhill, B. Newman, and C. Weinberg. "Use and misuse of population attributable fractions." *American Journal of Public Health* 88.1 (1998), pp. 15–19. <https://doi.org/10.2105/AJPH.88.1.15>.
- [31] Charles Poole. "A history of the population attributable fraction and related measures". *Annals of Epidemiology* 25.3 (2015), pp. 147–154. <https://doi.org/10.1016/j.annepidem.2014.11.015>.
- [32] Sharmistha Mishra and Stefan D. Baral. "Rethinking the population attributable fraction for infectious diseases". *The Lancet Infectious Diseases* 20.2 (2020), pp. 155–157. <https://doi.org/10.1016/S1473-3099>.
- [33] Kathleen N. Deering et al. "The impact of out-migrants and out-migration on the HIV/AIDS epidemic: A case study from south-west India". *AIDS* 22.S5 (2008). [https://pubmed.ncbi.nlm.nih.gov/19098476/%20https://journals.lww.com/aidsonline/Fulltext/2008/12005/The\\_impact\\_of\\_out\\_migrants\\_and\\_out\\_migration\\_on.15.aspx](https://pubmed.ncbi.nlm.nih.gov/19098476/%20https://journals.lww.com/aidsonline/Fulltext/2008/12005/The_impact_of_out_migrants_and_out_migration_on.15.aspx).
- [34] Sharmistha Mishra et al. "Distinguishing sources of HIV transmission from the distribution of newly acquired HIV infections: Why is it important for HIV prevention planning?" *Sexually Transmitted Infections* 90.1 (2014), pp. 19–25. <http://doi.org/10.1136/sextrans-2013-051250>.
- [35] Sharmistha Mishra et al. "Data and methods to characterize the role of sex work and to inform sex work programs in generalized HIV epidemics: evidence to challenge assumptions". *Annals of Epidemiology* 26.8 (2016), pp. 557–569. <https://doi.org/10.1016/j.annepidem.2016.06.004>.
- [36] Alexander K. Rowe, Kenneth E. Powell, and W.Dana Dana Flanders. "Why population attributable fractions can sum to more than one". *American Journal of Preventive Medicine* 26.3 (2004), pp. 243–249. <https://www.sciencedirect.com/science/article/pii/S0749379703003775>.
- [37] Sharmistha Mishra et al. "Estimating the epidemic consequences of HIV prevention gaps among key populations". *Journal of the International AIDS Society* 24.S3 (2021), e25739. <https://doi.org/10.1002/jia2.25739>.
- [38] Leigh F. Johnson and Peter J. White. "A review of mathematical models of HIV/AIDS interventions and their implications for policy". *Sexually Transmitted Infections* 87.7 (2011), pp. 629–634. <https://doi.org/10.1136/sti.2010.045500>.
- [39] Sharmistha Mishra et al. "Impact of High-Risk Sex and Focused Interventions in Heterosexual HIV Epidemics: A Systematic Review of Mathematical Models". *PLOS ONE* 7.11 (2012), e50691. <http://doi.org/10.1371/journal.pone.0050691>.

- [40] Marie Claude Boily et al. "What really is a concentrated HIV epidemic and what does it mean for West and Central Africa? Insights from mathematical modeling". *Journal of Acquired Immune Deficiency Syndromes* 68 (2015), S74–S82. <https://doi.org/10.1097/QAI.0000000000000437>.
- [41] John Stover et al. "Modeling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030". *PLOS Medicine* 18.10 (2021), e1003831. <https://doi.org/10.1371/journal.pmed.1003831>.
- [42] Avenir Health. *Spectrum Models*. M, 2022. <https://avenirhealth.org/software-spectrum.php>.
- [43] Optima Consortium for Decision Science. *Optima HIV User Guide Vol. VI: Parameter Data Sources*. 2021. <http://optimamodel.com/user-guide>.
- [44] T. Brown and W. Peerapatnapokin. *The Asian Epidemic Model: A process model for exploring HIV policy and programme alternatives in Asia*. 2004. <https://doi.org/10.1136/sti.2004.010165>.
- [45] Leigh F. Johnson and Rob E. Dorrington. "Modelling the demographic impact of HIV/AIDS in South Africa and the likely impact of interventions". *Demographic Research* 14.22 (2006), pp. 541–574. <https://doi.org/10.4054/DemRes.2006.14.22>.
- [46] Leigh F. Johnson et al. "Prospects for HIV control in South Africa: a model-based analysis". *Global Health Action* 9.1 (2016). <https://doi.org/10.3402/gha.v9.30314>.
- [47] Leigh F. Johnson et al. "The effect of HIV programmes in South Africa on national HIV incidence trends, 2000–2019". *JAIDS Journal of Acquired Immune Deficiency Syndromes* (2022). <https://doi.org/10.1097/qai.0000000000002927>.
- [48] John Stover et al. "How Can We Get Close to Zero? The Potential Contribution of Biomedical Prevention and the Investment Framework towards an Effective Response to HIV". *PLOS ONE* 9.11 (2014), e111956. <https://doi.org/10.1371/journal.pone.0111956>.
- [49] Julie Fox et al. "Quantifying sexual exposure to HIV within an HIV-serodiscordant relationship: Development of an algorithm". *AIDS* 25.8 (2011), pp. 1065–1082. <https://doi.org/10.1097/QAD.0b013e328344fe4a>.
- [50] Charlotte Watts et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". *Sexually Transmitted Infections* 86.S3 (2010), pp. iii85–iii92. <https://doi.org/10.1136/sti.2010.044602>.
- [51] Nicholas P. Jewell and Stephen C. Shiboski. "Statistical Analysis of HIV Infectivity Based on Partner Studies". *Biometrics* 46.4 (1990), p. 1133. <https://doi.org/10.2307/2532454>.
- [52] Maria J. Wawer et al. "Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda". *Journal of Infectious Diseases* 191.9 (2005), pp. 1403–1409. <https://doi.org/10.1086/429411>.
- [53] Maria Xiridou et al. "The contribution of steady and casual partnerships to the incidence of HIV infection among homosexual men in Amsterdam". *AIDS* 17.7 (2003), pp. 1029–1038. <https://doi.org/10.1097/00002030-200305020-00012>.
- [54] Kimberly A. Powers et al. "The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: A modelling study". *The Lancet* 378.9787 (2011), pp. 256–268. [https://doi.org/10.1016/S0140-6736\(11\)60842-8](https://doi.org/10.1016/S0140-6736(11)60842-8).
- [55] Mirjam Kretzschmar and Klaus Dietz. "The effect of pair formation and variable infectivity on the spread of an infection without recovery". *Mathematical Biosciences* 148.1 (1998), pp. 83–113.
- [56] Ken T.D. Eames and Matt J. Keeling. "Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases". *Proceedings of the National Academy of Sciences of the United States of America* 99.20 (2002), pp. 13330–13335. <https://www.pnas.org/content/99/20/13330%20https://www.pnas.org/content/99/20/13330.abstract>.
- [57] James O. Lloyd-Smith, Wayne M. Getz, and Hans V. Westerhoff. "Frequency-dependent incidence in models of sexually transmitted diseases: Portrayal of pair-based transmission and effects of illness on contact behaviour". *Proceedings of the Royal Society B: Biological Sciences* 271.1539 (2004), pp. 625–634. <https://doi.org/10.1098/rspb.2003.2632>.
- [58] Timothy L. Mah and Daniel T. Halperin. "Concurrent sexual partnerships and the HIV epidemics in Africa: Evidence to move forward". *AIDS and Behavior* 14.1 (2010), pp. 11–16. <https://doi.org/10.1007/s10461-008-9433-x>.
- [59] Frank Tanser et al. "Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: A cohort study". *The Lancet* 378.9787 (2011), pp. 247–255. [https://doi.org/10.1016/S0140-6736\(11\)60779-4](https://doi.org/10.1016/S0140-6736(11)60779-4).
- [60] Steven M. Goodreau et al. "Concurrent partnerships, acute infection and HIV epidemic dynamics among young adults in Zimbabwe". *AIDS and Behavior* 16.2 (2012), pp. 312–322. <https://link-springer-com.myaccess.library.utoronto.ca/article/10.1007/s10461-010-9858-x>.

- [61] Marie Claude Boily, Michel Alary, and Rebecca F. Baggageley. "Neglected issues and hypotheses regarding the impact of sexual concurrency on HIV and sexually transmitted infections". *AIDS and Behavior* 16.2 (2012), pp. 304–311. <https://doi.org/10.1007/s10461-011-9887-0>.
- [62] Bart Burington et al. "Estimating duration in partnership studies: Issues, methods and examples". *Sexually Transmitted Infections* 86.2 (2010), pp. 84–89. <https://doi.org/10.1136/sti.2009.037960>.
- [63] Sarah-Jane Anderson et al. "HIV prevention where it is needed most: Comparison of strategies for the geographical allocation of interventions: Comparison". *Journal of the International AIDS Society* 20.4 (2017), e25020. <https://doi.org/10.1002/jia2.25020>.
- [64] Sarah-Jane Anderson et al. "Frontloading HIV financing maximizes the achievable impact of hiv prevention". *Journal of the International AIDS Society* 21.3 (2018), e25087. <https://doi.org/10.1002/jia2.25087>.
- [65] Robyn M. Stuart et al. *How should HIV resources be allocated? Lessons learnt from applying optima HIV in 23 countries*. 2018. <https://doi.org/10.1002/jia2.25097>.
- [66] Cliff C. Kerr et al. "Optima HIV Methodology and Approach". *Tackling the World's Fastest-Growing HIV Epidemic: More Efficient HIV Responses in Eastern Europe and Central Asia*. Ed. by Feng Zhao, Clemens Benedikt, and David Wilson. Washington, DC: The World Bank, 2020. [https://doi.org/10.1596/978-1-4648-1523-2\\_ch13](https://doi.org/10.1596/978-1-4648-1523-2_ch13).
- [67] Kelly Jean Heymer and David P. Wilson. *Available evidence does not support serosorting as an HIV risk reduction strategy*. 2010. <https://doi.org/10.1097/QAD.0b013e328337b029>.
- [68] Susan Cassels et al. "Available evidence does not support serosorting as an HIV risk reduction strategy: Author's reply". *AIDS* 24.6 (2010), pp. 936–938. <http://www.ncbi.nlm.nih.gov/pubmed/24850995>.
- [69] Susan Cassels and David A Katz. "Seroadaptation among men who have sex with men: Emerging research themes". *Current HIV/AIDS Reports* 10.4 (2013), pp. 305–313. <http://doi.org/10.1007/s11904-013-0188-2>.
- [70] Susan Cassels et al. "HIV serosorting as a harm reduction strategy: Evidence from Seattle, Washington". *AIDS* 23.18 (2009), pp. 2497–2506. <http://www.ncbi.nlm.nih.gov/pubmed/19834319>.
- [71] Linwei Wang et al. "Population-level sexual mixing according to hiv status and preexposure prophylaxis use among men who have sex with men in montreal, canada: Implications for hiv prevention". *American Journal of Epidemiology* 189.1 (2020), pp. 44–54. <https://doi.org/10.1093/aje/kwz231>.
- [72] Hae Young Kim et al. "HIV seroconcordance among heterosexual couples in rural KwaZulu-Natal, South Africa: a population-based analysis". *Journal of the International AIDS Society* 23.1 (2020), e25432. <https://doi.org/10.1002/jia2.25432>.



## Chapter 5

# Modelling Intersections of Differential Risk and ART Coverage

### 5.1 Introduction

TODO: more background ... [1, 2]

As explored in Chapter 2, numerous modelling studies have sought to estimate the prevention impacts of ART scale-up in Sub-Saharan Africa [3–6]. Prevention impacts are usually quantified as incidence reduction or cumulative infections averted in scenarios with higher cascade attainment vs. scenarios with lower attainment [6]. Such studies often stratify modelled populations by risk, including key populations like FSW and their clients, to capture important epidemic dynamics related to risk heterogeneity [7–9]. However, these studies almost always assume that cascade attainment (i.e., proportions diagnosed, treated, and virally suppressed) or progression (i.e., rates of diagnosis, treatment initiation, and treatment failure/discontinuation) are equal across modelled risk groups (§ 2.3.2.4).

In fact, there is growing evidence of differential ART cascade across population strata, including across age, gender, mobility, and risk [10, 11]. These differences can be driven by unique barriers to engagement in care faced by vulnerable populations, which intersect with drivers of HIV risk [12–14]. These intersections of risk and cascade heterogeneity could potentially undercut the prevention impacts of ART scale-up anticipated from model-based evidence [15]. Therefore, I sought to examine the following question in an illustrative modelling analysis:

*How are projections of ART prevention impacts influenced by differences in ART cascade across risk groups?*

I examined this question 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) [16, 17]; thus, I used observed ART scale-up in Eswatini as a base case reflecting what is possible, and explored counterfactual scenarios in which scale-up was slower, and where specific risk groups could have been “left behind”.



Table 5.1: Modelling scenarios defined by 2020 calibration targets

Scenario	ART cascade in 2020 <sup>a</sup>			Re-scaled cascade rates <sup>b</sup>		
	FSW	Clients	Overall	FSW	Clients	Lower Risk
<i>Base Case</i>	95-95-95	—	95-95-95	—	—	—
<i>Leave Behind: FSW</i>	60-40-80	—	80-80-90	✓	✗	✓
<i>Leave Behind: Clients</i>	—	60-40-80	80-80-90	✗	✓	✓
<i>Leave Behind: FSW &amp; Clients</i>	60-40-80	60-40-80	80-80-90	✓	✓	✓
<i>Leave Behind: Neither</i>	—	—	80-80-90	✗	✗	✓

<sup>a</sup> Cascade: % diagnosed among PLHIV; % on ART among diagnosed; % virally suppressed among on ART; <sup>b</sup> 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 E.1 plots the modelled cascades over time.

## 5.2 Methods

### 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 in Chapter 4 was used throughout. Briefly, the model includes 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.

### 5.2.2 Scenarios & Analyses

As noted above, I defined the *base case* scenario to reflect observed cascade scale-up in Eswatini, reaching 95-95-95 by 2020 [17]. 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 [17]. In these counterfactual scenario, 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 ( $R_f \in [1, 20]$ ). When FSW and/or clients had reduced cascade, I calibrated their  $R$ s so that these populations achieved approximately 60-40-80 by 2020. By contrast, I calibrated  $R$ s for the lower risk population so that the Swazi population *overall* achieved 80-80-90 in all 4 counterfactual scenarios, thus ensuring that a consistent proportion of the population overall experienced reduced cascade. Table 5.1 summarizes these scenarios, while Figure E.1 plots the modelled cascades over 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 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 (AI) in the counterfactual scenarios ( $k$ ) vs. the base case ( $o$ ), over multiple time horizons up to 2030, starting from  $t_0 = 2000$ :

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

For each scenario, I computed relative additional infections for each model fit, and reported median (95% CI) values across model fits, reflecting uncertainty.

## 5.3 Results

Figure 5.1 illustrates cumulative additional infections and additional incidence in each counterfactual scenario (80-80-90 overall by 2020) versus the base case (95-95-95 overall by 2020). 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. However, who acquired these additional infections differed (Figure E.2c), with more additional infections among clients when FSW were left behind, versus among lower risk risk women when clients were left behind. The majority of additional infections were transmitted via casual partnerships in all scenarios (Figure E.2a).

## 5.4 Discussion

We sought to explore how intersections of risk heterogeneity and differential ART coverage may influence model-estimated prevention impacts of ART. We showed 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.

Although our analysis only considered Eswatini, our findings are likely generalizeable to other epidemic contexts. In fact, HIV prevalence ratios between key populations and the population overall are relatively low in Eswatini versus elsewhere [18, 19]; thus, the transmission impact of cascade gaps among key populations in other contexts would likely be even greater than we found for Eswatini. Moreover, as HIV incidence declines in many settings, epidemics may become re-concentrated among key populations [20, 21], further magnifying the transmission impact of cascade disparities.

To our knowledge, our study is the first to explore the transmission impact of heterogeneity in ART coverage across risk groups, within consistent population-overall coverage. In a previous review of mathematical modelling of ART scale-up in Sub-Saharan Africa, we found that few studies have considered any cascade differences by risk group, but that such differences likely mediate ART prevention impacts [6]. Cascade gaps have been observed among men versus women [11, 22], younger versus older populations [11, 23], key populations versus the population overall [10], and within key populations themselves

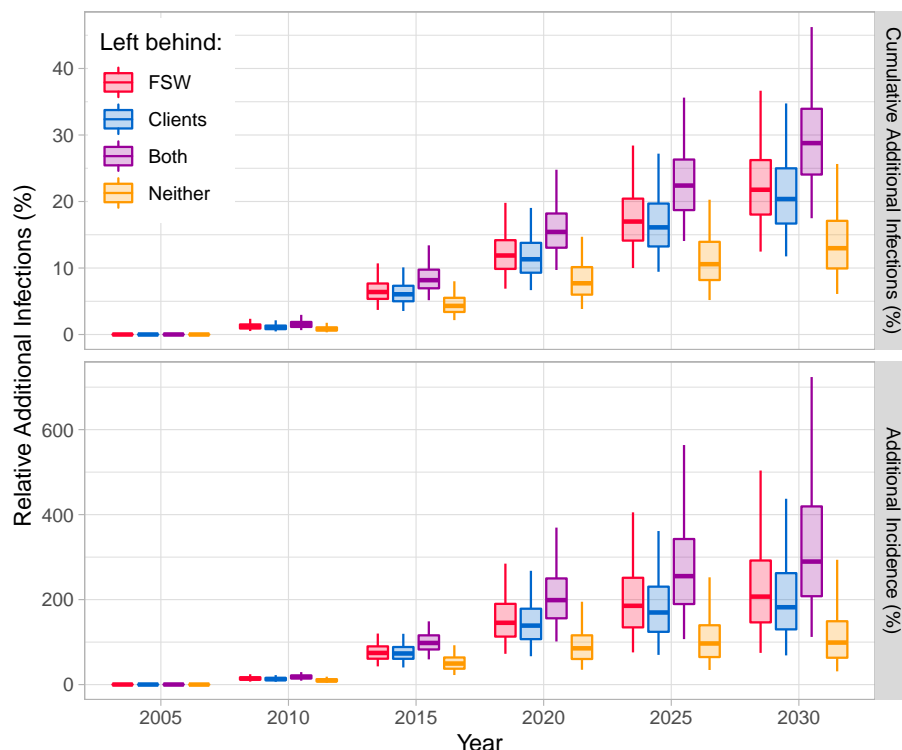


Figure 5.1: Relative additional infections under counterfactual scenarios vs. the base case

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.

[24, 25]. Moreover, unmeasured cascades — such as among populations who have not been reached by programs and interventions — are likely lowest [10, 26]. Consistent integration of these data going forward could improve the quality of model-based evidence for HIV resource prioritization.

Global ART scale-up undoubtedly has many benefits, including for individual-level health outcomes [27, 28], prevention in serodiscordant relationships [29], and contributing to population-level incidence declines [30]. 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 [12–15]. Such populations can be reached effectively through tailored services to meet their unique needs [31], services which can be designed and refined with ongoing community engagement [32–34]. As we have shown, an equity-focused approach to ART scale-up can maximize prevention impacts, and accelerate the end of the HIV epidemic.

Our study has two major strengths. First, drawing on our conceptual framework for risk heterogeneity [6, Table 1] and multiple sources of context-specific data [35–39], we 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, our base case scenario reflects observed scale-up in Eswatini.

Our study has three main limitations. First, we only considered heterosexual HIV transmission in Eswatini, and mainly explored risk heterogeneity related to sex work. However, our findings would likely generalize

to other transmission networks and determinants of risk heterogeneity, including risk groups not classically recognized as key populations, such as mobile populations and young women [40, 41]. Second, we did not consider transmitted drug resistance. Drug resistance is more likely to emerge in the context of barriers to viral suppression [42]; 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 our true uncertainty in the magnitude of these outputs, but not the trends across scenarios.

In summary, ... TODO

## References

- [1] UNAIDS. *90-90-90 An ambitious treatment target to help end the AIDS epidemic*. 2014. [http://www.unaids.org/sites/default/files/media\\_asset/90-90-90\\_en.pdf](http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf).
- [2] UNAIDS. *Fast-Track: Ending the AIDS epidemic by 2030*. Geneva, Switzerland, 2014.
- [3] Wim Delva et al. "HIV treatment as prevention: Principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001239. <https://doi.org/10.1371/journal.pmed.1001239>.
- [4] Jeffrey W. Eaton et al. "HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa". *PLOS Medicine* 9.7 (2012). Ed. by John Bartlett, e1001245. <https://doi.org/10.1371/journal.pmed.1001245>.
- [5] Jeffrey W Eaton et al. "Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: A combined analysis of 12 mathematical models". *The Lancet Global Health* 2.1 (2014), e23–e34. arXiv: NIHMS150003. <https://www.sciencedirect.com/science/article/pii/S2214109X13701724>.
- [6] Jesse Knight, Rupert Kaul, and Sharmistha Mishra. "Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review". *Epidemics* 40 (2022), p. 100608. <https://doi.org/10.1016/j.epidem.2022.100608>.
- [7] Hein Stigum, W. Falck, and P. Magnus. "The core group revisited: The effect of partner mixing and migration on the spread of gonorrhea, chlamydia, and HIV". *Mathematical Biosciences* 120.1 (1994), pp. 1–23. [https://doi.org/10.1016/0025-5564\(94\)90036-1](https://doi.org/10.1016/0025-5564(94)90036-1).
- [8] G. P. Garnett and R. M. Anderson. "Sexually transmitted diseases and sexual behavior: Insights from mathematical models". *Journal of Infectious Diseases* 174.S2 (1996), S150–S161. [https://doi.org/10.1093/infdis/174.Supplement\\_2.S150](https://doi.org/10.1093/infdis/174.Supplement_2.S150).
- [9] Charlotte Watts et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". *Sexually Transmitted Infections* 86.S3 (2010), pp. iii85–iii92. <https://doi.org/10.1136/sti.2010.044602>.
- [10] Avi Joseph Hakim et al. "Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response". *Journal of the International AIDS Society* 21 (2018), e25119. <http://doi.org/10.1002/jia2.25119>.
- [11] Dylan Green et al. *Evidence of sociodemographic heterogeneity across the HIV treatment cascade and progress towards 90-90-90 in sub-Saharan Africa – a systematic review and meta-analysis*. 2020. <https://doi.org/10.1002/jia2.25470>.
- [12] Rhoda K. Wanyenze et al. "“If you tell people that you had sex with a fellow man, it is hard to be helped and treated”: Barriers and opportunities for increasing access to HIV services among men who have sex with men in Uganda". *PLOS ONE* 11.1 (2016). <https://doi.org/10.1371/journal.pone.0147486>.
- [13] Sheree Schwartz et al. "Engagement in the HIV care cascade and barriers to antiretroviral therapy uptake among female sex workers in Port Elizabeth, South Africa: Findings from a respondent-driven sampling study". *Sexually Transmitted Infections* 93.4 (2017), pp. 290–296. <https://sti.bmj.com/content/93/4/290>.
- [14] Megan Schmidt-Sane. "Male partners of female sex workers: The intersectional risk environment of HIV/AIDS in a Kampala informal settlement". *Social Science and Medicine* 298 (2022), p. 114873.
- [15] Stefan Baral et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment". *The Lancet HIV* 6 (2019), e632–638. [http://doi.org/10.1016/s2352-3018\(19\)30226-7](http://doi.org/10.1016/s2352-3018(19)30226-7).
- [16] Fiona Walsh et al. "Getting to 90–90–90: Experiences from the MaxART Early Access to ART for All (EAAA) Trial in Eswatini". *Current HIV/AIDS Reports* 17.4 (2020), pp. 324–332. <https://europepmc.org/article/med/32474844>.
- [17] UNAIDS. *AIDSinfo*. 2023. <http://aidsinfo.unaids.org>.
- [18] Stefan Baral et al. "Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis". *The Lancet Infectious Diseases* 12.7 (2012), pp. 538–549. [https://doi.org/10.1016/S1473-3099\(12\)70066-1](https://doi.org/10.1016/S1473-3099(12)70066-1).
- [19] P. H. Septime Hessou et al. "Comparison of the prevalence rates of HIV infection between men who have sex with men (MSM) and men in the general population in sub-Saharan Africa: A systematic review and meta-analysis". *BMC Public Health* 19.1 (2019), pp. 1–10. <https://doi.org/10.1186/s12889-019-8000-x>.

- [20] Tim Brown and Wiwat Peerapatanapokin. "Evolving HIV epidemics: The urgent need to refocus on populations with risk". *Current Opinion in HIV and AIDS* 14.5 (2019), pp. 337–353. <https://doi.org/10.1097/COH.0000000000000571>.
- [21] Geoff P Garnett. "Reductions in HIV incidence are likely to increase the importance of key population programmes for HIV control in sub-Saharan Africa". *Journal of the International AIDS Society* 24.S3 (2021), e25727. <https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25727> <https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25727> <https://onlinelibrary.wiley.com/doi/10.1002/jia2.25727>.
- [22] Caitlin Quinn et al. "Who are the missing men? Characterising men who never tested for HIV from population-based surveys in six sub-Saharan African countries". *Journal of the International AIDS Society* 22.10 (2019), e25398. <https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25398> <https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25398> <https://onlinelibrary.wiley.com/doi/10.1002/jia2.25398>.
- [23] Refeletswe Lebelonyane et al. "To achieve 95-95-95 targets we must reach men and youth: High level of knowledge of HIV status, ART coverage, and viral suppression in the Botswana Combination Prevention Project through universal test and treat approach." *PLOS ONE* 16.8 (2021), e0255227. <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0255227> <http://www.ncbi.nlm.nih.gov/pubmed/34375343>.
- [24] Yunia Mayanja et al. "'Test and Treat' Among Women at High Risk for HIV-infection in Kampala, Uganda: Antiretroviral Therapy Initiation and Associated Factors". *AIDS and Behavior* 22.3 (2018), pp. 1053–1061. <https://doi.org/10.1007/s10461-017-1973-5>.
- [25] Maya Jaffer et al. "The HIV Cascade of Care and Service Utilisation at Sex Work Programmes Among Female Sex Workers in South Africa". *AIDS and Behavior* 26.9 (2022), pp. 2907–2919. <https://link.springer.com/article/10.1007/s10461-022-03616-6>.
- [26] Makini A. S. Boothe et al. "Low engagement in HIV services and progress through the treatment cascade among key populations living with HIV in Mozambique: alarming gaps in knowledge of status". *BMC Public Health* 21.1 (2021), pp. 1–8. <https://link.springer.com/articles/10.1186/s12889-020-10039-2> <https://link.springer.com/article/10.1186/s12889-020-10039-2>.
- [27] Delphine Gabillard et al. "Mortality, AIDS-morbidity, and loss to follow-up by current CD4 cell count among HIV-1-infected adults receiving antiretroviral therapy in Africa and Asia: Data from the ANRS 12222 collaboration". *Journal of Acquired Immune Deficiency Syndromes* 62.5 (2013), pp. 555–561. <https://doi.org/10.1097/QAI.0b013e3182821821>.
- [28] Jens D Lundgren et al. "Initiation of antiretroviral therapy in early asymptomatic HIV infection." *New England Journal of Medicine* 373.9 (2015), pp. 795–807. <https://doi.org/10.1056/NEJMoa1506816>.
- [29] Myron S. Cohen et al. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission". *New England Journal of Medicine* 375.9 (2016), pp. 830–839. <https://doi.org/10.1056/nejmoa1600693>.
- [30] Diane Havlir et al. *What do the Universal Test and Treat trials tell us about the path to HIV epidemic control?* 2020. <https://doi.org/10.1002/jia2.25455>.
- [31] Peter Ehrenkranz, Anna Grimsrud, and Miriam Rabkin. *Differentiated service delivery: Navigating the path to scale*. 2019. <https://doi.org/10.1097/COH.0000000000000509>.
- [32] Chido D. Chikwari, Stefanie Dringus, and Rashida A. Ferrand. "Barriers to, and emerging strategies for, HIV testing among adolescents in sub-Saharan Africa". *Current Opinion in HIV and AIDS* 13.3 (2018), pp. 257–264.
- [33] Charmaine Khudzie Mlambo et al. "Experiences from a community advisory Board in the Implementation of early access to ART for all in Eswatini: A qualitative study". *BMC Medical Ethics* 20.1 (2019), pp. 1–11. <https://bmcmethics.biomedcentral.com/articles/10.1186/s12910-019-0384-8>.
- [34] Carly A. Comins et al. "Opportunities and considerations for the design of decentralized delivery of antiretroviral therapy for female sex workers living with HIV in South Africa". *BMC Health Services Research* 22:1 22.1 (2022), pp. 1–10. <https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-08506-0>.
- [35] Central Statistical Office Swaziland. *Swaziland Demographic and Health Survey 2006-07*. Mbabane, Swaziland, 2008. <https://dhsprogram.com/>.
- [36] Swaziland Ministry of Health. *Swaziland HIV Incidence Measurement Survey: First Findings Report*. Mbabane, Swaziland, 2012. <http://shims.icap.columbia.edu/>.
- [37] Jessica Justman et al. "Swaziland HIV Incidence Measurement Survey (SHIMS): a prospective national cohort study". *The Lancet HIV* 4.2 (2016), e83–e92. [https://doi.org/10.1016/S2352-3018\(16\)30190-4](https://doi.org/10.1016/S2352-3018(16)30190-4).

- [38] Stefan Baral et al. "Reconceptualizing the HIV epidemiology and prevention needs of female sex workers (FSW) in Swaziland". *PLOS ONE* 9.12 (2014), e115465. <http://doi.org/10.1371/journal.pone.0115465>.
- [39] PEPFAR. *Characterizing the HIV Prevention and Treatment Needs among Key Populations, including Men who Have Sex with Men and Female Sex Workers in Swaziland: From Evidence to Action*. Mbabane, Swaziland, 2015.
- [40] Frank Tanser et al. "HIV treatment cascade in migrants and mobile populations". *Current Opinion in HIV and AIDS* 10.6 (2015), pp. 430–438. <http://doi.org/10.1097/COH.000000000000192>.
- [41] Eve Cheuk et al. "Transitions: Novel Study Methods to Understand Early HIV Risk Among Adolescent Girls and Young Women in Mombasa, Kenya, and Dnipro, Ukraine". *Frontiers in Reproductive Health* 2 (2020), p. 10. <https://doi.org/10.3389/frph.2020.00007>.
- [42] Quang D. Pham et al. "Global burden of transmitted HIV drug resistance and HIV-exposure categories: A systematic review and meta-analysis". *AIDS* 28.18 (2014), pp. 2751–2762. <https://doi.org/10.1097/QAD.000000000000494>.

## Chapter 6

# Conclusion

TODO



## Appendix A

# Supporting Mathematics

### A.1 Distributions

#### A.1.1 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  $\theta$ . 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  $\theta$ , given a set of quantiles (e.g.,  $q = \{q_{2.5}, q_{97.5}\}$  for the 95% CI). For each estimation, I minimized<sup>1</sup> the the following error function:

$$J(\theta) = \sum_i |q_i - Q(p_i | \theta)|^\omega \quad (\text{A.1})$$

where  $\omega$  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 A.1.

#### A.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:

$$p(n) = \binom{N}{n} \rho^n (1 - \rho)^{N-n} \quad (\text{A.2})$$

However, Eq. (A.2) is only defined for discrete values of  $n$ . It is more convenient to have a continuous distribution for  $\rho$ , 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

<sup>1</sup> Using [docs.scipy.org/doc/scipy/reference/optimize.minimize-lbfgsb.html](https://docs.scipy.org/doc/scipy/reference/optimize.minimize-lbfgsb.html)

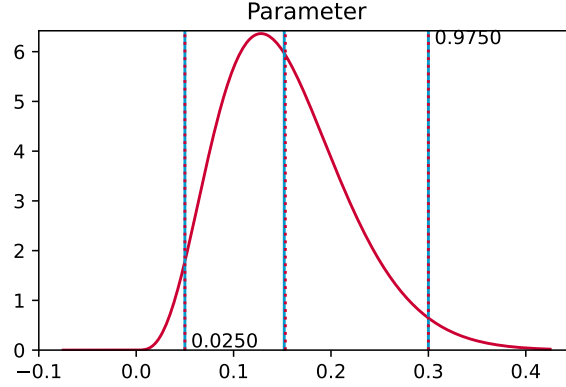


Figure A.1: Example distribution fitting validation plot

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  $f(x | \theta)$ .

approximation of the binomial distribution (BAB):

$$p(\rho) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} \rho^{\alpha-1} (1 - \rho)^{\beta-1} \quad (\text{A.3})$$

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 A.2 illustrates the approximation for  $N = \{10, 20, 40\}$  and  $\rho = \{0.01, 0.1, 0.5\}$ .

### A.1.3 Joint Sampling with Relational Constraints

Figure A.3 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.

## A.2 Durations

### A.2.1 Exponential Duration Assumption in Compartmental Models

Let  $\lambda$  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.

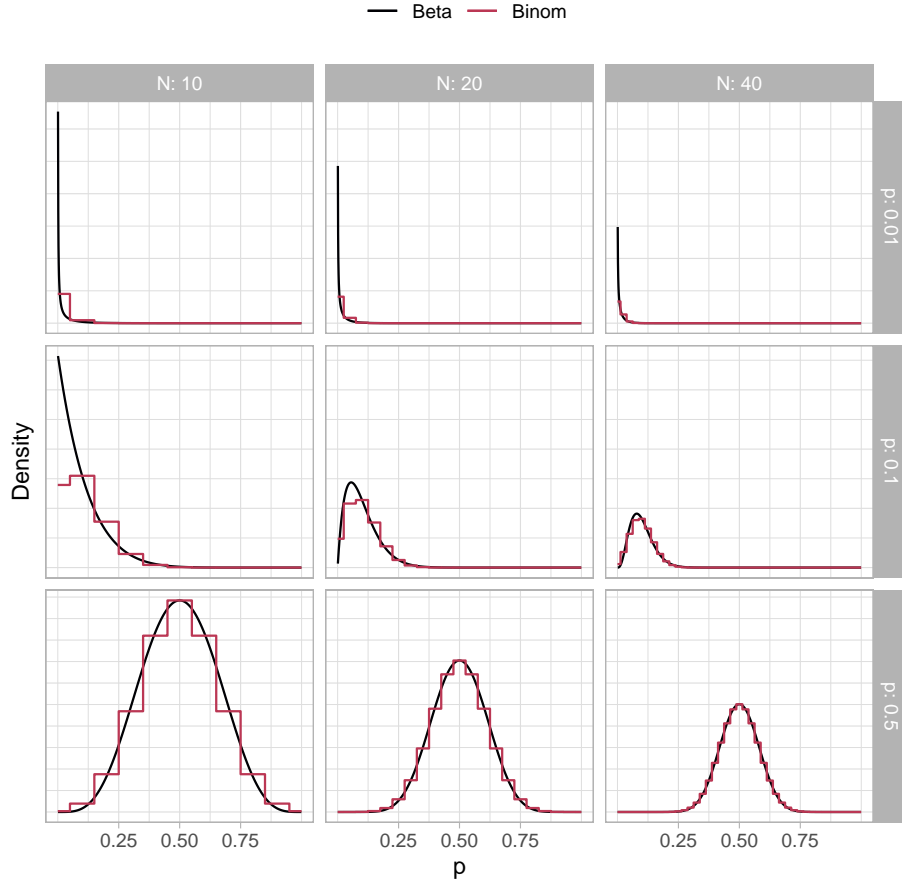


Figure A.2: Beta approximation of the binomial distribution (BAB)

**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  $\tau$  (median duration), the exit rate  $\lambda$  is given by  $\log(2)/\tau$ .

**Collapsing Compartments in Series.** Let compartments A and B be in series, with exit rates  $\lambda_A$  and  $\lambda_B$  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  $\lambda_A$  and  $\lambda_B$  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  $\delta_{AB} = 1/(\lambda_A + \lambda_B)$ .

### A.2.2 Estimating Duration in Sex Work from Cross Sectional Data

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,

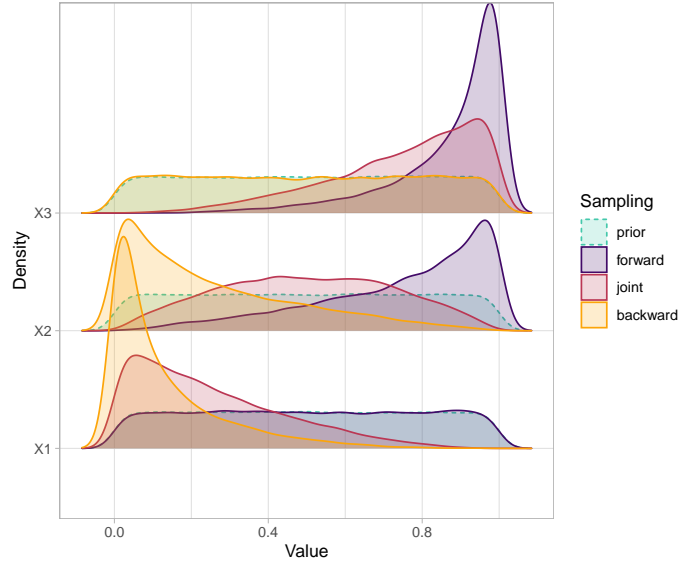


Figure A.3: Illustration of different sampling biases when enforcing  $X_1 < X_2 < X_3$

because respondents will continue selling sex after the survey [1].<sup>2</sup>

Figure A.4 illustrates a steady-state population with 7 women selling sex at any given time. The steady-state assumption implies that a women leaving sex work after  $\delta$  years will be immediately replaced by a women entering sex work whose eventual duration will also be  $\delta$  years. Let  $\delta$  be this true duration, and  $\delta_s$  be the duration reported in the survey. If we assume that the survey reaches women at a random time point during the duration  $\delta$ , then  $\delta_s \sim \text{Unif}(0, \delta)$ , and the mean reported duration is  $E(\delta_s) = \frac{1}{2}E(\delta)$ . Thus,  $E(\delta) = 2E(\delta_s)$  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 [2]. Thus, we would expect that  $f = E(\delta)/E(\delta_s) \in (1, 2)$ , which we can use to compute the mean exit rate as described in § A.2.1.

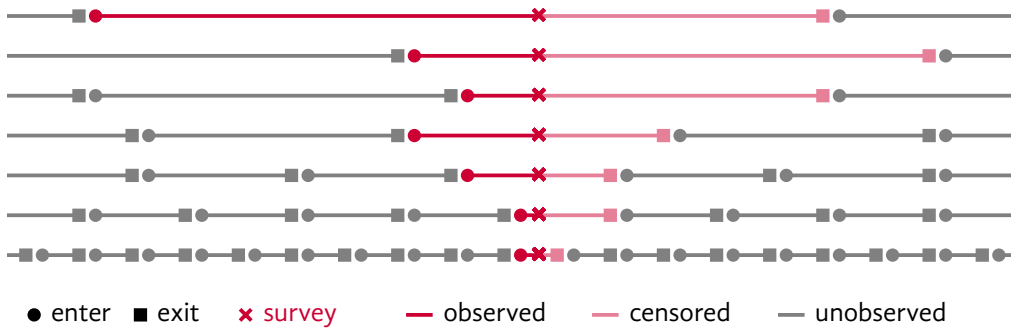


Figure A.4: Illustrative steady-state population of 7 FSW, with varying true durations in sex work  $\delta$ , vs. the observed durations in sex work  $\delta_s$  via cross-sectional survey.

<sup>2</sup> An 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](https://stats.stackexchange.com/questions/298828).

Another observation we can make from Figure A.4 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.

### A.2.3 Quantifying Partnerships

Similar to § A.2.2, sexual partnerships are often quantified using cross-sectional surveys. In this case, respondents are typically asked to report the numbers of unique partners during a standardized recall period  $\gamma$  — e.g., “How many different people have you had sex with during the past year?” Such data can then be used to inform modelled rates of partnership change  $Q$  and/or numbers of concurrent partnerships  $K$ .

If partnership duration is long and the recall period is short — including  $\gamma \approx 0$  for “Are you currently in a long-term sexual partnership?” — the reported partnerships mostly reflect *ongoing* partnerships, and thus  $C \approx K$ . 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  $C/\gamma \approx Q$ . However, if partnership duration and recall period are similar in length, the reported partnerships reflect a mixture of tail-ends, complete, and ongoing partnerships, and thus  $C$  overestimates  $K$ , but  $C/\gamma$  also overestimates  $Q$ . In summary:

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

I developed an approach to estimate  $Q$  and  $K$  from  $C$  and  $\gamma$ . The approach draws on a similar assumption as in § A.2.2: 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  $\delta$  overall, as illustrated in Figure A.5. As such, we can define  $Q$  and  $K$  as:

$$Q = \frac{C}{\gamma + \delta} \quad (\text{A.4})$$

$$K = \frac{C\delta}{\gamma + \delta} = Q\delta \quad (\text{A.5})$$

As an example, Figure A.5 illustrates a recall period of  $\gamma = 6$  years, for which  $C = 9$  partnerships are reported, having durations of  $\delta = 3$  years. Thus, we can compute  $Q = 9/(6 + 3) = 1$  and  $K = 1(3) = 3$ , which can be verified by careful examination of Figure A.5.

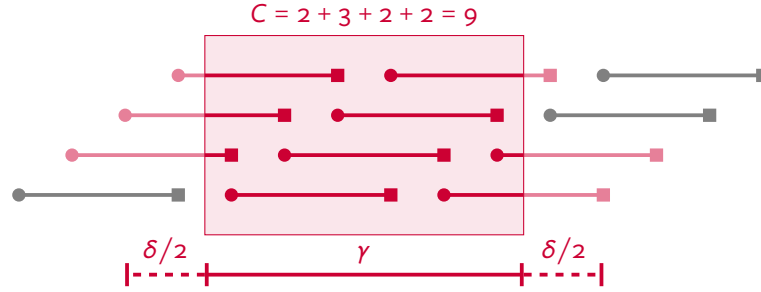


Figure A.5: Illustration of conceptual framework for quantifying partnerships from the number reported during a given recall period

Circle: partnership start; line: ongoing partnership; square: partnership end; red: reported partnership; grey: partnership not reported;  $\gamma$ /red: recall period;  $\delta$ : partnership duration;  $C$ : number of reported partnerships for  $\gamma$ .

## A.3 Miscellaneous

### A.3.1 Proof that $B_{\text{WPH}} \geq B_{\text{BPH}}$

In § 4.1.1, I claimed that the per-partnership probability of transmission  $B$  is larger for within- vs. between-partnership heterogeneity —  $B_{\text{WPH}} \geq B_{\text{BPH}}$ , from Eqs. (4.5) and (4.6), respectively — given the same set of transmission modifiers  $R_f, \alpha_f$ . Here is a proof of that claim:

$$B_{\text{WPH}} \geq B_{\text{BPH}} \\ 1 - \prod_f (1 - \beta_f)^{A\alpha_f} \geq 1 - \sum_f \alpha_f (1 - \beta_f)^A \quad (\text{A.6})$$

Let  $x_f = (1 - \beta_f)^A$ ; then

$$\prod_f x_f^{\alpha_f} \leq \sum_f \alpha_f x_f \quad (\text{A.7})$$

Since  $\sum_f \alpha_f = 1$  and  $\alpha_f \in [0, 1]$  are effectively weights, Eq. (A.7) is the weighted arithmetic mean–geometric mean (AM–GM) inequality [3]. In fact, Aldaz [3] further shows that the gap between  $B_{\text{WPH}}$  and  $B_{\text{BPH}}$  increases with the  $\alpha_f$ -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 [4] we can also show that the approach in [5] (and others) to aggregate heterogeneity by HIV infection stage first produces an intermediate per-partnership probability  $B'$ :<sup>3</sup>

$$B_{\text{WPH}} \geq B' \geq B_{\text{BPH}}, \quad B' = 1 - \left(1 - \sum_f \alpha_f \beta_f\right)^A \quad (\text{A.8})$$

<sup>3</sup> [math.stackexchange.com/questions/4660409](https://math.stackexchange.com/questions/4660409)

## References

- [1] Erika Fazito et al. "Analysis of duration of risk behaviour for key populations: a literature review." *Sexually transmitted infections* 88.S2 (2012), pp. i24–i32. <https://doi.org/10.1136/sextrans-2012-050647>.
- [2] Eve Cheuk et al. "Transitions: Novel Study Methods to Understand Early HIV Risk Among Adolescent Girls and Young Women in Mombasa, Kenya, and Dnipro, Ukraine". *Frontiers in Reproductive Health* 2 (2020), p. 10. <https://doi.org/10.3389/frph.2020.00007>.
- [3] J. M. Aldaz. "Self-improvement of the inequality between arithmetic and geometric means". *Journal of Mathematical Inequalities* 2 (2009), pp. 213–216. <https://doi.org/10.7153/jmi-03-21>.
- [4] J. L.W.V. Jensen. "Sur les fonctions convexes et les inégalités entre les valeurs moyennes". *Acta Mathematica* 30.1 (1906), pp. 175–193. <https://doi.org/10.1007/BF02418571>.
- [5] Cliff C. Kerr et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376. <https://doi.org/10.1097/QAI.0000000000000605>.

## Appendix B

# Supplement to Chapter 2

These materials are copied verbatim from the appendix of [95].

### B.1 Search Strategy

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

#### B.1.1 Search Terms

Our search strategy and step-wise results are as follows (Table B.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 B.1: Systematic review search terms and hits

Term	Hits	
M1	238,076	model, theoretical/
M2	334,921	model, biological/
M3	302,802	computer simulation/
M4	196,814	patient-specific modeling/
M5	67,459	monte carlo method/
M6	32,801	exp stochastic processes/
M7	455,312	(model* ADJ3 (math* OR transmission OR dynamic* OR epidemi* OR compartmental OR deterministic OR individual OR agent OR network OR infectious disease* OR markov OR dynamic* OR simulat*)).mp
M8	1,369,153	OR/ M1-M7
H1	290,863	exp HIV/
H2	651,624	exp HIV infections/
H3	753,274	(HIV OR HIV1* OR HIV2* OR HIV-1* OR HIV-2*).mp
H4	369,182	hiv infect*.mp

continued ...



## B.1 SEARCH STRATEGY

148

... 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

### B.1.2 Inclusion/Exclusion Criteria

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

Include	Exclude
<b>Publication Type</b>	
<ul style="list-style-type: none"> <li>English language</li> <li>published before 2020</li> <li>peer-reviewed journal article</li> </ul>	<ul style="list-style-type: none"> <li>non-English language</li> <li>published in or after 2020</li> <li>non-peer-reviewed article</li> <li>review article<sup>1</sup></li> <li>textbook, grey literature</li> <li>opinions, comments, correspondence</li> <li>conference abstracts and proceedings</li> <li>model comparison study</li> </ul>
<b>Mathematical Modelling of HIV Transmission</b>	
<ul style="list-style-type: none"> <li>sexual HIV transmission model</li> <li>non-linear HIV transmission model<sup>2</sup></li> <li>population-level dynamics</li> <li>compartmental model<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>no sexual HIV transmission modelled</li> <li>HIV transmission model is linear</li> <li>only within-host/cellular/protein modelling</li> <li>individual-based model</li> </ul>
<b>Context &amp; Objectives</b>	
<ul style="list-style-type: none"> <li>any region in Sub-Saharan Africa (SSA)<sup>4</sup></li> <li>assess prevention impact of ART scale-up for all<sup>5</sup></li> </ul>	<ul style="list-style-type: none"> <li>only regions outside SSA modelled</li> <li>only theoretical context modelled</li> <li>only individual-level benefits of ART modelled</li> <li>only prevention benefits of other interventions</li> <li>no base-case scenario reflecting status quo<sup>*</sup></li> <li>only ART-combination interventions<sup>*</sup></li> <li>only ART intervention targeted to some risk groups<sup>*</sup></li> <li>only ART prevention impacts reported for some risk groups<sup>*</sup></li> <li>ART prevention impacts not reported<sup>5*</sup></li> </ul>

<sup>1</sup> Review articles were included if they also presented new HIV transmission modelling results fitting our criteria. <sup>2</sup> 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  $t$ . <sup>3</sup> We defined a *compartmental model* as one where the system variables represent the numbers of individuals in each state, rather than unique individuals. <sup>4</sup> SSA was defined based on the countries in the UN regions of East, South, Central, and West Africa, plus South Sudan (see Table B.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. <sup>5</sup> 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. <sup>\*</sup> Used to define Dataset B only.

### B.1.3 Included Studies

#### B.1.3.1 Dataset B

- [1] 2005 Salomon et al.
- [2] 2006 Abbas, Anderson, and Mellors
- [3] 2009 Granich et al.
- [4] 2009 Hallett et al.
- [5] 2010 Bacaer, Pretorius, and Auvert
- [6] 2010 Pretorius et al.
- [7] 2011 Metzger, Lloyd-Smith, and Weinberger
- [8] 2012 Yusuf and Benyah
- [9] 2012 Andrews et al.
- [10] 2012 Granich et al.
- [11] 2012 Wagner and Blower
- [12] 2013 Abbas et al.
- [13] 2013 Long and Stavert
- [14] 2013 Cremin et al.
- [15] 2013 Alsallaq et al.
- [16] 2014 Nichols et al.
- [17] 2014 Nichols et al.
- [18] 2014 Alistar, Grant, and Bendavid
- [19] 2014 Eaton and Hallett
- [20] 2015 Ying et al.
- [21] 2015 Low et al.
- [22] 2015 Khademi, Anand, and Potts
- [23] 2015 Gilbert et al.
- [24] 2015 Heaton et al.
- [25] 2016 Rahman, Vaidya, and Zou
- [26] 2016 Gilbert et al.
- [27] 2016 Blaizot et al.
- [28] 2016 Ying et al.
- [29] 2016 Barnighausen, Bloom, and Humair
- [30] 2016 Heffernan et al.
- [31] 2017 Maheu-Giroux et al.
- [32] 2017 Maheu-Giroux et al.
- [33] 2017 Volz et al.
- [34] 2017 Blaizot et al.
- [35] 2018 Mukandavire et al.
- [36] 2018 Guillon
- [37] 2018 Akudibillah, Pandey, and Medlock
- [38] 2018 Stuart et al.
- [39] 2018 Montigny et al.
- [40] 2019 Hauser et al.

#### B.1.3.2 Dataset A less B

- [41] 2006 Johnson and Dorrington
- [42] 2006 Baggaley, Garnett, and Ferguson
- [43] 2006 Wilson, Kahn, and Blower
- [44] 2008 Bacaer et al.
- [45] 2009 Chigidi and Lungu
- [46] 2010 Williams et al.
- [47] 2011 Nyabadza and Mukandavire
- [48] 2012 Barnighausen, Bloom, and Humair
- [49] 2013 Wagner, Coburn, and Blower
- [50] 2013 Decker et al.
- [51] 2013 Wirtz et al.
- [52] 2014 Shafer et al.
- [53] 2014 Hove-Musekwa et al.
- [54] 2014 Braithwaite et al.
- [55] 2014 Nichols et al.
- [56] 2014 Abu-Raddad and Awad
- [57] 2014 Anderson et al.
- [58] 2014 Alistar et al.
- [59] 2014 Cori et al.
- [60] 2014 Stover et al.
- [61] 2014 Wirtz et al.
- [62] 2015 Korenromp et al.
- [63] 2015 Knight et al.
- [64] 2015 Kerr et al.
- [65] 2015 Fraser et al.
- [66] 2015 Kassa and Ouhinou
- [67] 2015 Bekker et al.
- [68] 2015 Shannon et al.
- [69] 2015 Blaizot et al.
- [70] 2016 Smith et al.
- [71] 2016 Atun et al.
- [72] 2016 Shattock et al.
- [73] 2016 McGillen et al.
- [74] 2016 Johnson et al.
- [75] 2016 Sharma et al.
- [76] 2017 Akudibillah, Pandey, and Medlock
- [77] 2017 Alsallaq et al.
- [78] 2017 Anderson et al.
- [79] 2017 Chiu et al.
- [80] 2017 Johnson et al.
- [81] 2017 Stuart et al.
- [82] 2017 McGillen et al.
- [83] 2017 Cremin et al.
- [84] 2018 Ross et al.
- [85] 2018 Anderson et al.
- [86] 2018 Anderson et al.
- [87] 2018 Omondi, Mbogo, and Luboobi
- [88] 2018 Woods et al.

- [89] 2018 Stevens et al.
- [90] 2019 Stopard et al.
- [91] 2019 Beacroft and Hallett
- [92] 2019 Reidy et al.
- [93] 2019 Omondi, Mbogo, and Luboobi
- [94] 2019 Maheu-Giroux et al.

## B.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.<sup>1</sup>

**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.

### B.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 B.1 for related search terms. If a study modelled multiple countries at a national scale or smaller, the counter for each country was incremented.

### B.2.2 Risk Heterogeneity

#### B.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

<sup>1</sup> WebPlotDigitizer: [apps.automeris.io/wpd/](https://apps.automeris.io/wpd/)

having  $>50 \times$  the partners of the lowest sexually active female activity group [96–98]. 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 [97]. 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.

### B.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.

### B.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.

### B.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.

## B.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.

## B.2.4 Antiretroviral Therapy

### B.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.

### B.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.

### B.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.

## B.2.5 ART Prevention Impact

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

### B.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  $t_0$ .

### B.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%.



## B.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](https://github.com/mishra-lab/sr-heterogeneity-hiv-models)

### B.3.1 Map

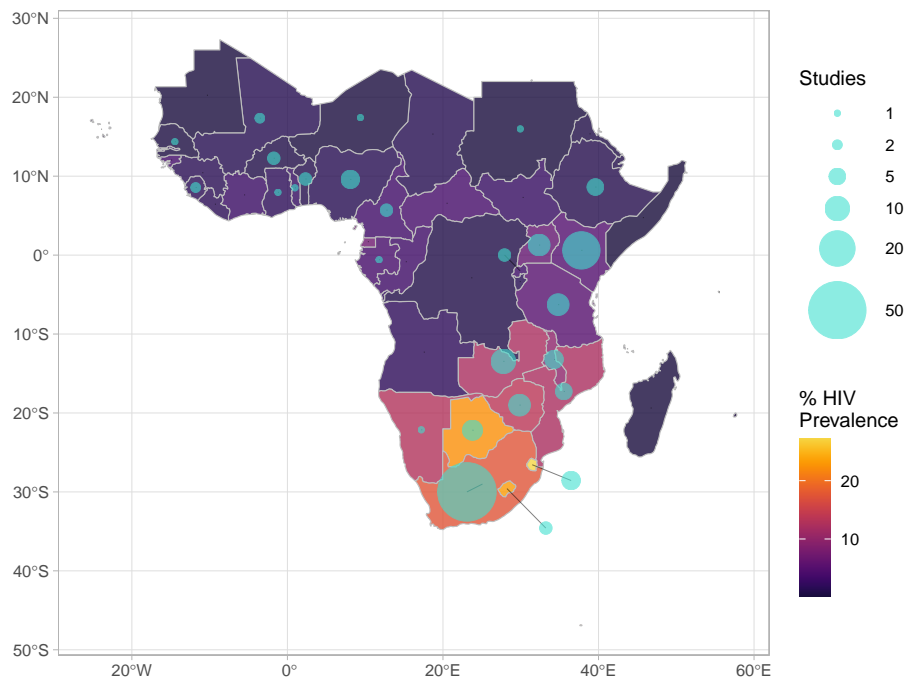
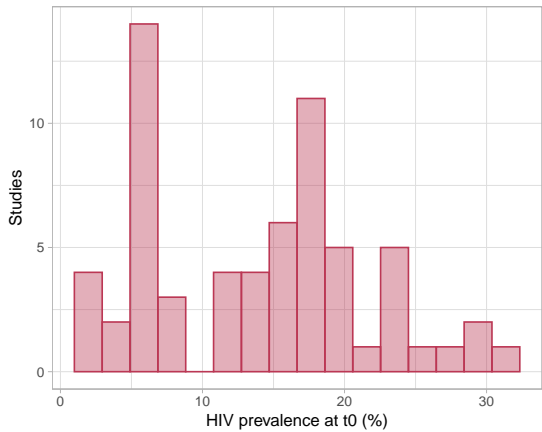


Figure B.1: Map showing number of studies (of 94 total) applying HIV transmission modelling in each country vs the number of people living with HIV (PLHIV, millions)

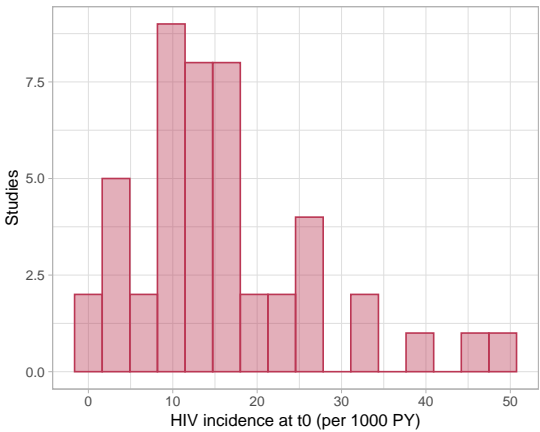
### B.3.2 Risk Heterogeneity

#### B.3.2.1 Distributions

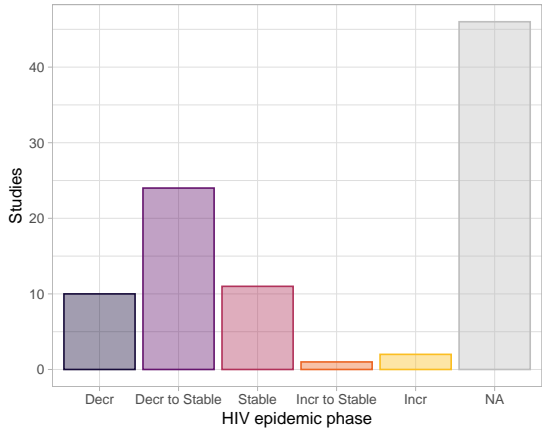
The following figures illustrate the distributions (number of studies) of various parameter values and modelling assumptions related to factors of heterogeneity and intervention contexts.



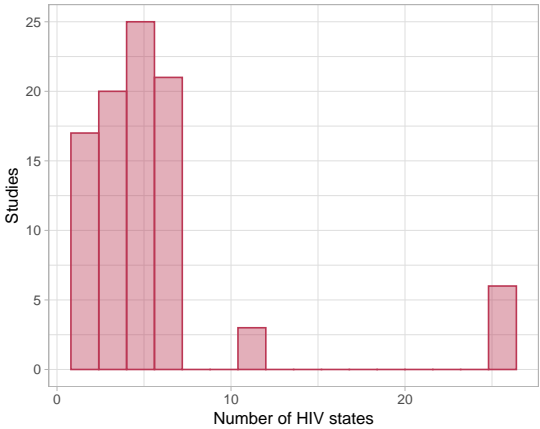
(a) HIV prevalence at  $t_0$  (%)



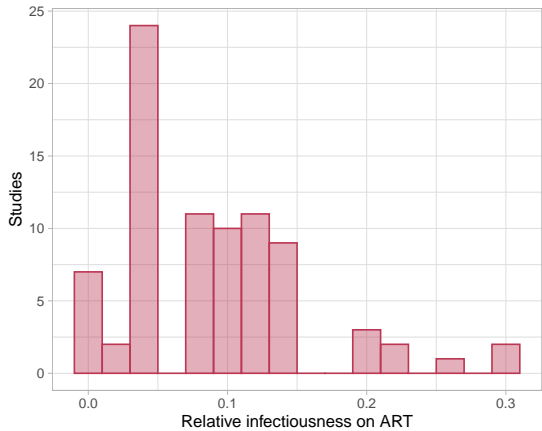
(b) HIV incidence at  $t_0$  (per 1000 PY)



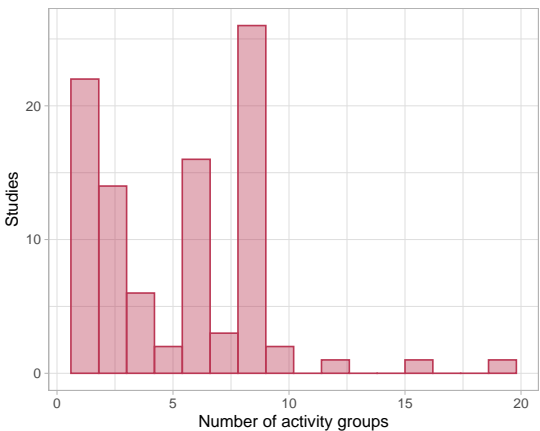
(c) HIV epidemic phase



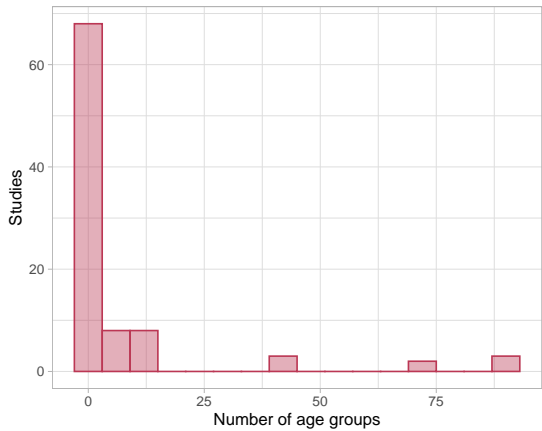
(d) Number of HIV states



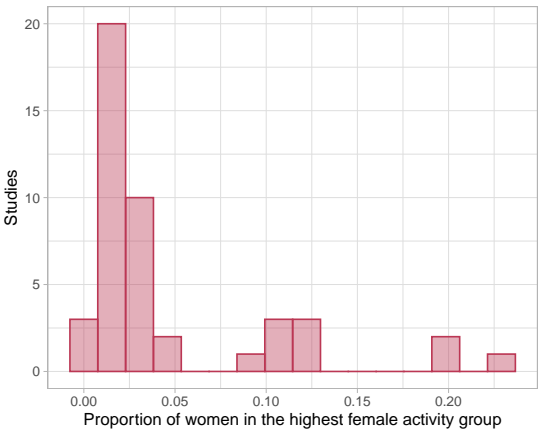
(e) Relative infectiousness on ART



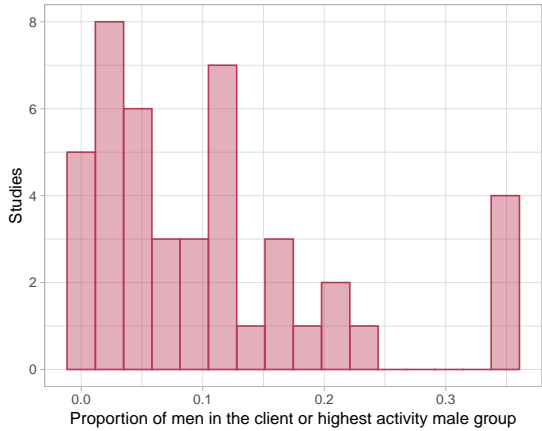
(f) Number of activity groups



(g) Number of age groups



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

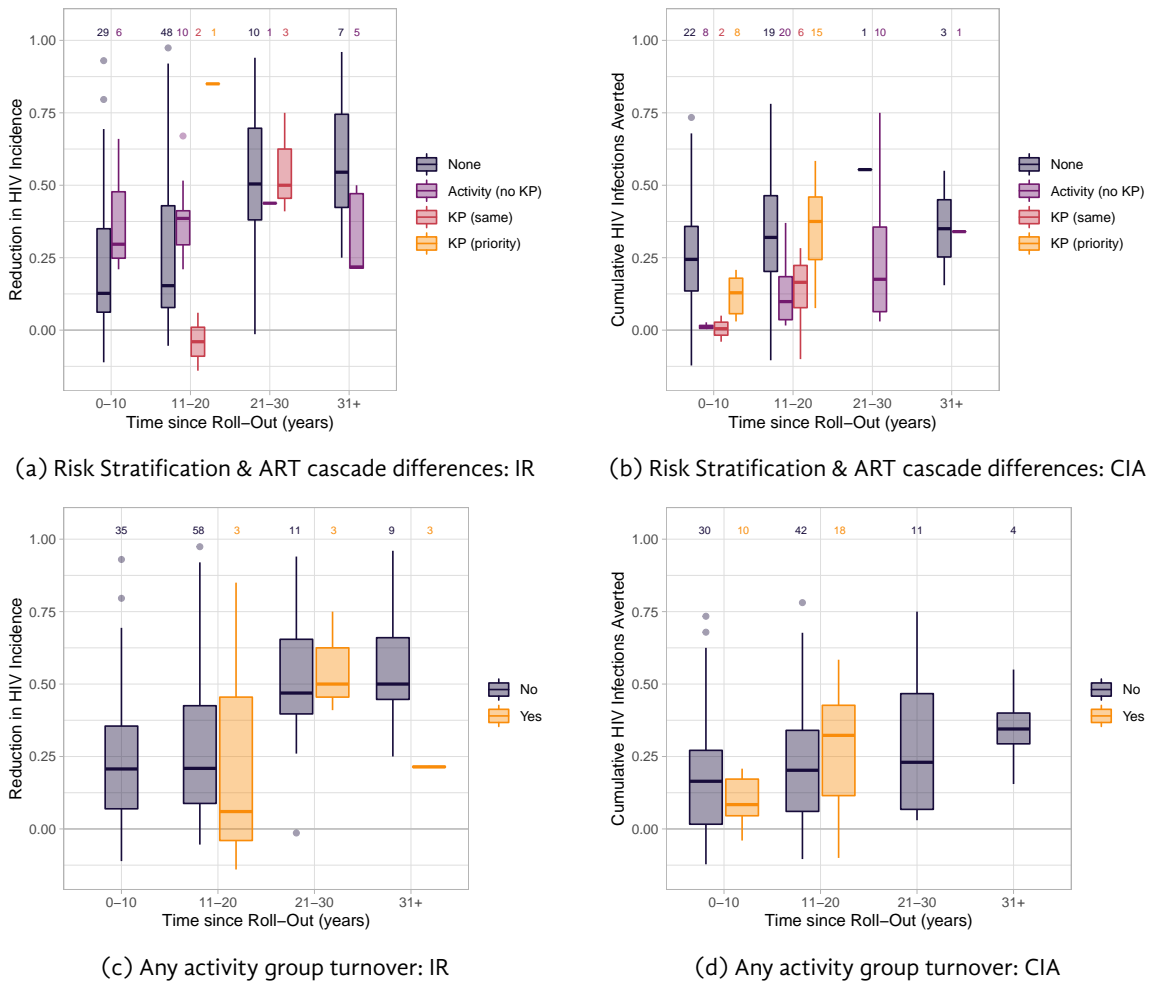


(i) Proportion of men in the client or highest activity male group

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

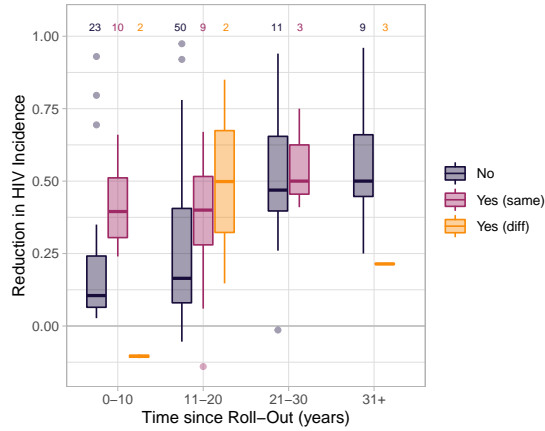
B.3.3 ART Prevention Impact

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: 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.

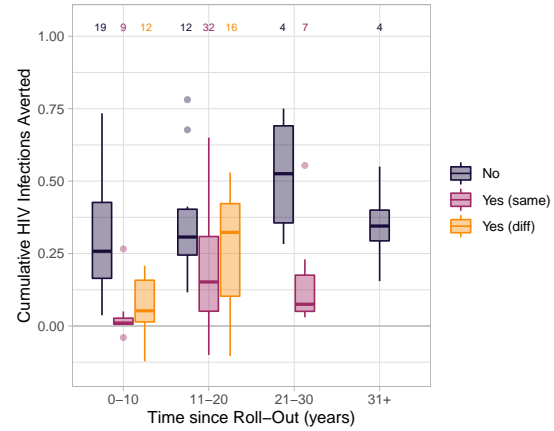


## B.3 SUPPLEMENTAL RESULTS

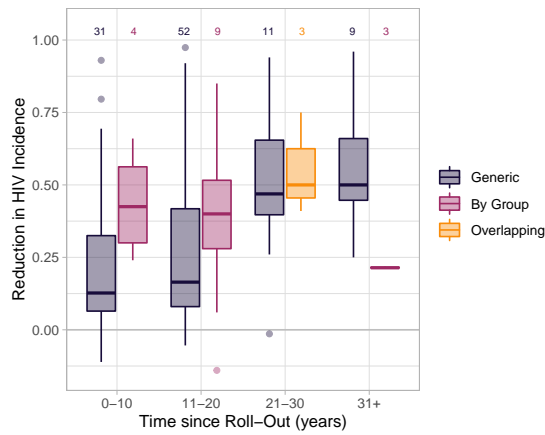
160



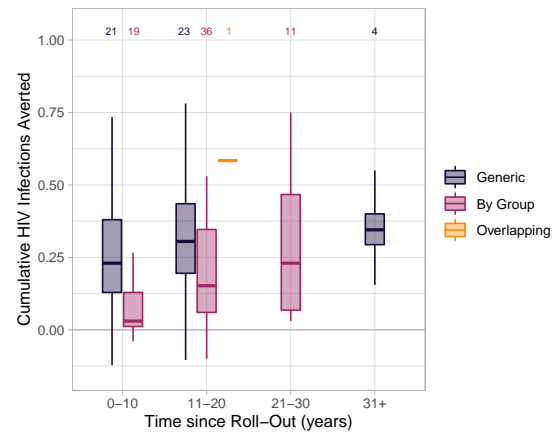
(e) Sex stratification &amp; any ART cascade differences: IR



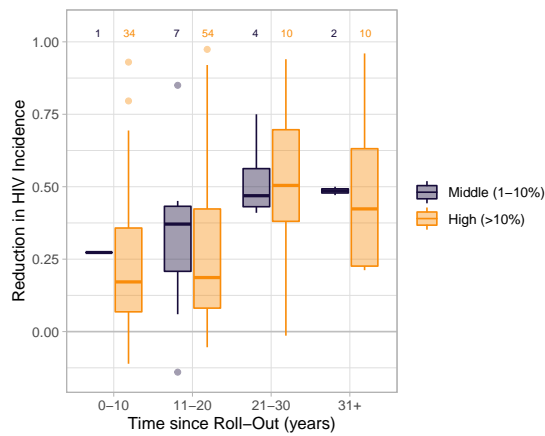
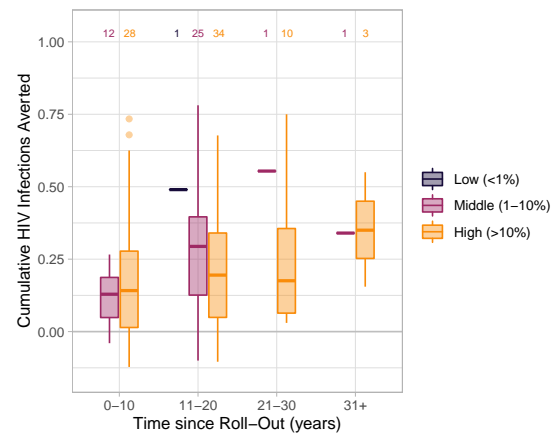
(f) Sex stratification &amp; any ART cascade differences: CIA

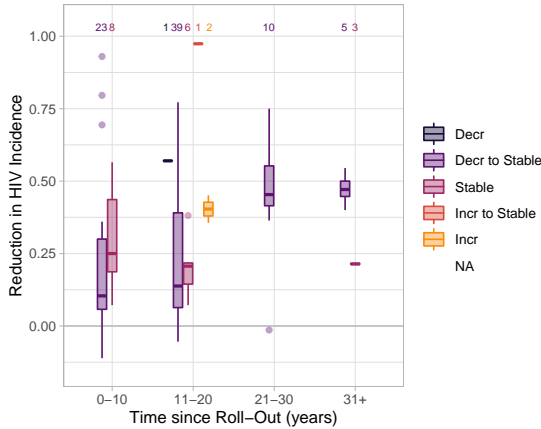


(g) Type of partnership definition: IR

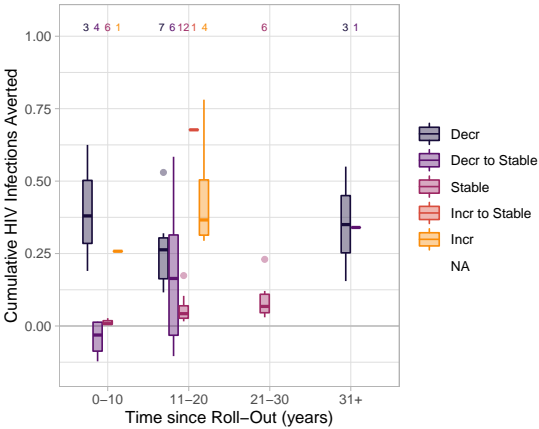


(h) Type of partnership definition: CIA

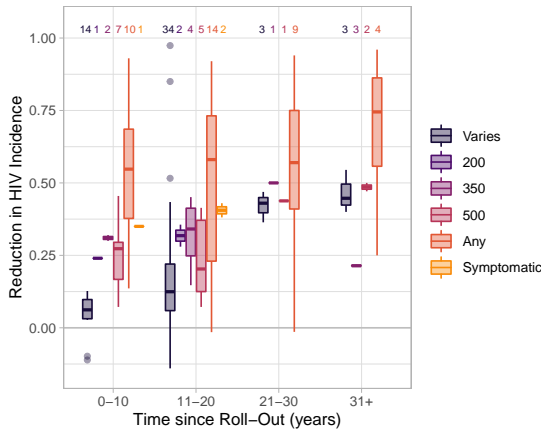
(i) HIV prevalence at  $t_0$  (%): IR(j) HIV prevalence at  $t_0$  (%): CIA



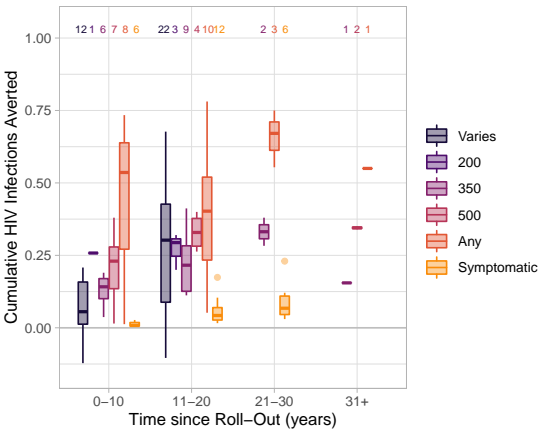
(k) HIV epidemic phase: IR



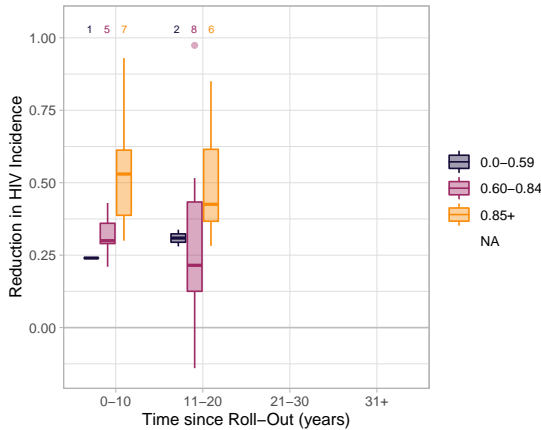
(l) HIV epidemic phase: CIA



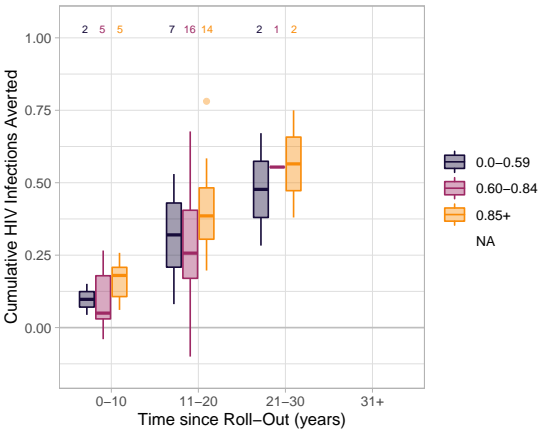
(m) CD4 initiation criteria: IR



(n) CD4 initiation criteria: CIA



(o) ART intervention coverage target: IR



(p) ART intervention coverage target: CIA

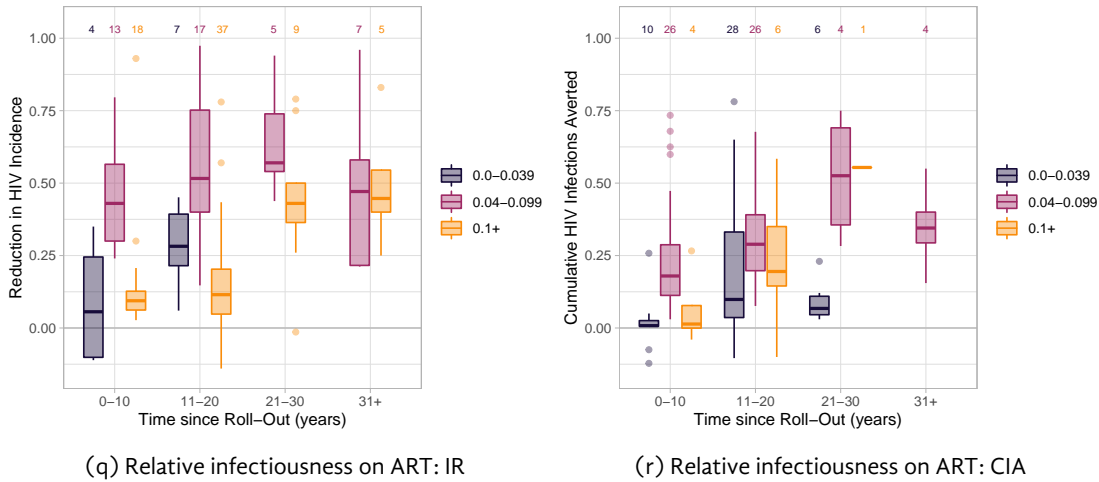


Figure B.3: Projected ART prevention impacts: incidence reduction (IR) and cumulative infections averted (CIA), stratified by factors of heterogeneity and intervention contexts

## B.4 PRISMA-ScR Checklist

Page/section numbers refer to [95].

### 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 #
<b>TITLE</b>			
Title	1	Identify the report as a scoping review.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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



**St. Michael's**  
Inspired Care.  
Inspiring Science.



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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

JB1 = 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 (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169:467–473. doi: 10.7326/M18-0850.



**St. Michael's**  
Inspired Care.  
Inspiring Science.

## References

- [1] Joshua A. Salomon et al. "Integrating HIV prevention and treatment: From slogans to impact". *PLOS Medicine* 2.1 (2005), pp. 0050–0056. <https://doi.org/10.1371/journal.pmed.0020016>.
- [2] Ume L Abbas, Roy M Anderson, and John W Mellors. "Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings." *Journal of Acquired Immune Deficiency Syndromes* 41.5 (2006), pp. 632–641. <https://doi.org/10.1097/01.qai.0000194234.31078.bf>.
- [3] Reuben M Granich et al. "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model". *The Lancet* 373.9657 (2009), pp. 48–57. [https://doi.org/10.1016/S0140-6736\(08\)61697-9](https://doi.org/10.1016/S0140-6736(08)61697-9).
- [4] Timothy B Hallett et al. "The role of testing and counselling for HIV prevention and care in the era of scaling-up antiretroviral therapy". *Epidemics* 1.2 (2009), pp. 77–82. <https://doi.org/10.1016/j.epidem.2009.02.001>.
- [5] Nicolas Bacaer, Carel Pretorius, and Bertran Auvert. "An Age-Structured Model for the Potential Impact of Generalized Access to Antiretrovirals on the South African HIV Epidemic". *Bulletin of Mathematical Biology* 72.8 (2010), pp. 2180–2198. <https://doi.org/10.1007/s11538-010-9535-2>.
- [6] Carel Pretorius et al. "Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa". *PLOS ONE* 5.11 (2010), e13646. <http://doi.org/10.1371/journal.pone.0013646>.
- [7] Vincent T Metzger, James O Lloyd-Smith, and Leor S Weinberger. "Autonomous targeting of infectious superspreaders using engineered transmissible therapies". *PLOS Computational Biology* 7.3 (2011), e1002015. <https://doi.org/10.1371/journal.pcbi.1002015>.
- [8] Tunde T Yusuf and Francis Benyah. "Optimal strategy for controlling the spread of HIV/AIDS disease: A case study of South Africa". *Journal of Biological Dynamics* 6.2 (2012), pp. 475–494. <https://doi.org/10.1080/17513758.2011.628700>.
- [9] Jason R Andrews et al. "Projecting the benefits of antiretroviral therapy for HIV prevention: the impact of population mobility and linkage to care." *The Journal of Infectious Diseases* 206.4 (2012), pp. 543–551. <https://doi.org/10.1093/infdis/jis401>.
- [10] Reuben Granich et al. "Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011–2050". *PLOS ONE* 7.2 (2012), e30216. <https://doi.org/10.1371/journal.pone.0030216>.
- [11] Wagner G Wagner and Sally Blower. "Universal Access to HIV Treatment versus Universal 'Test and Treat': Transmission, Drug Resistance & Treatment Costs". *PLOS ONE* 7.9 (2012), e41212. <https://doi.org/10.1371/journal.pone.0041212>.
- [12] Ume L Abbas et al. "Antiretroviral therapy and pre-exposure prophylaxis: Combined impact on HIV transmission and drug resistance in South Africa". *The Journal of Infectious Diseases* 208.2 (2013), pp. 224–234. <https://doi.org/10.1093/infdis/jit150>.
- [13] Elisa F. Long and Robert R. Stavert. "Portfolios of biomedical HIV interventions in South Africa: A cost-effectiveness analysis". *Journal of General Internal Medicine* 28.10 (2013), pp. 1294–1301. <https://pubmed.ncbi.nlm.nih.gov/24011111/>. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3785647/>.
- [14] Ide Cremin et al. "The new role of antiretrovirals in combination HIV prevention: A mathematical modelling analysis". *AIDS* 27.3 (2013), pp. 447–458. <https://doi.org/10.1097/QAD.0b013e32835ca2dd>.
- [15] Ramzi A Alsallaq et al. "Understanding the Potential Impact of a Combination HIV Prevention Intervention in a Hyper-Endemic Community". *PLOS ONE* 8.1 (2013), e54575. <https://doi.org/10.1371/journal.pone.0054575>.
- [16] Brooke E Nichols et al. "Cost-effectiveness of PrEP in HIV/AIDS control in Zambia: A stochastic league approach". *Journal of Acquired Immune Deficiency Syndromes* 66.2 (2014), pp. 221–228. <https://doi.org/10.1097/QAI.000000000000145>.
- [17] Brooke E Nichols et al. "Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: A modeling study". *AIDS* 28.1 (2014), pp. 73–83. <https://doi.org/10.1097/01.aids.0000433239.01611.52>.
- [18] Sabrina S Alistar, Philip M Grant, and Eran Bendavid. "Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa". *BMC Medicine* 12.1 (2014), p. 46. <https://doi.org/10.1186/1741-7015-12-46>.
- [19] Jeffrey W. Eaton and Timothy B. Hallett. "Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence". *Proceedings of the National Academy of Sciences* 111.45 (2014), pp. 16202–16207. <https://doi.org/10.1073/pnas.1323007111>.

- [20] Roger Ying et al. "Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda". *Journal of the International AIDS Society* 18.S3 (2015), p. 20013. <http://doi.org/10.7448/IAS.18.4.20013>.
- [21] Andrea Low et al. "Potential impact of existing interventions and of antiretroviral use in female sex workers on transmission of HIV in Burkina Faso: A modeling study". *Journal of Acquired Immune Deficiency Syndromes* 68 (2015), S180–S188. <https://doi.org/10.1097/QAI.0000000000000441>.
- [22] Amin Khademi, Sunanth Anand, and David Potts. "Measuring the potential impact of combination HIV prevention in sub-Saharan Africa". *Medicine* 94.37 (2015), e1453. <http://doi.org/10.1097/MD.0000000000001453>.
- [23] Jennifer A Gilbert et al. "Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa". *PLOS ONE* 10.5 (2015), e0126267. <https://doi.org/10.1371/journal.pone.0126267>.
- [24] Laura M Heaton et al. "Estimating the impact of the US President's Emergency Plan for AIDS Relief on HIV treatment and prevention programmes in Africa". *Sexually Transmitted Infections* 91.8 (2015), pp. 615–620. <https://doi.org/10.1136/sextrans-2014-051991>.
- [25] S M Ashrafur Rahman, Naveen K Vaidya, and Xingfou Zou. "Impact of early treatment programs on HIV epidemics: An immunity-based mathematical model". *Mathematical Biosciences* 280 (2016), pp. 38–49. <http://doi.org/10.1016/j.mbs.2016.07.009>.
- [26] Jennifer A Gilbert et al. "Cost-effectiveness of community-based TB/HIV screening and linkage to care in rural South Africa". *PLOS ONE* 11.12 (2016), e0165614. <https://doi.org/10.1371/journal.pone.0165614>.
- [27] Stephanie Blaizot et al. "Potential impact of multiple interventions on HIV incidence in a hyperendemic region in Western Kenya: A modelling study". *BMC Infectious Diseases* 16.1 (2016), p. 189. <https://doi.org/10.1186/s12879-016-1520-4>.
- [28] Roger Ying et al. "Home testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modelling analysis". *The Lancet HIV* 3.6 (2016), e275–e282. [http://doi.org/10.1016/S2352-3018\(16\)30009-1](http://doi.org/10.1016/S2352-3018(16)30009-1).
- [29] Till Barnighausen, David E Bloom, and Salal Humair. "Human resources for treating HIV/AIDS: Are the preventive effects of antiretroviral treatment a game changer?" *PLOS ONE* 11.10 (2016), e0163960. <https://doi.org/10.1371/journal.pone.0163960>.
- [30] Alastair Heffernan et al. "Impact and cost-effectiveness of point-of-care CD4 testing on the HIV epidemic in South Africa". *PLOS ONE* 11.7 (2016), e0158303. <https://doi.org/10.1371/journal.pone.0158303>.
- [31] Mathieu Maheu-Giroux et al. "Changing Dynamics of HIV Transmission in Côte d'Ivoire: Modeling Who Acquired and Transmitted Infections and Estimating the Impact of Past HIV Interventions (1976–2015)". *Journal of Acquired Immune Deficiency Syndromes* 75.5 (2017), pp. 517–527. <https://doi.org/10.1097/QAI.0000000000001434>.
- [32] Mathieu Maheu-Giroux et al. "Population-level impact of an accelerated HIV response plan to reach the UNAIDS 90–90–90 target in Côte d'Ivoire: Insights from mathematical modeling". *PLOS Medicine* 14.6 (2017). Ed. by Nicola Low, e1002321. <https://doi.org/10.1371/journal.pmed.1002321>.
- [33] Erik M Volz et al. "Phylogenetic analysis to inform prevention efforts in mixed HIV epidemics". *Virus Evolution* 3.2 (2017), vex014. <http://doi.org/10.1093/ve/vex014>.
- [34] Stephanie Blaizot et al. "Combined interventions to reduce HIV incidence in KwaZulu-Natal: a modelling study". *BMC Infectious Diseases* 17.1 (2017), p. 522. <https://doi.org/10.1186/s12879-017-2612-5>.
- [35] Christinah Mukandavire et al. "Estimating the contribution of key populations towards the spread of HIV in Dakar, Senegal". *Journal of the International AIDS Society* 21 (2018), e25126. <https://doi.org/10.1002/jia2.25126>.
- [36] Marlene Guillon. "Success factors for universal access to antiretroviral treatments in South Africa". *The International Journal of Health Planning and Management* 33.4 (2018), e1160–e1178. <https://doi.org/10.1002/hpm.2602>.
- [37] Gordon Akudibillah, Abhishek Pandey, and Jan Medlock. "Optimal control for HIV treatment". *Mathematical Biosciences and Engineering* 16.1 (2018), pp. 373–396. <https://doi.org/10.3934/mbe.2019018>.
- [38] Robyn M. Stuart et al. *How should HIV resources be allocated? Lessons learnt from applying optima HIV in 23 countries*. 2018. <https://doi.org/10.1002/jia2.25097>.
- [39] Simon de Montigny et al. "Assessing the utility of the tipping point ratio to monitor HIV treatment programmes in the era of universal access to ART". *Infectious Disease Modelling* 3 (2018), pp. 85–96. <https://doi.org/10.1016/j.idm.2018.03.005>.

- [40] Anthony Hauser et al. "Bridging the gap between hiv epidemiology and antiretroviral resistance evolution: Modelling the spread of resistance in south africa". *PLOS Computational Biology* 15.6 (2019), e1007083. <https://doi.org/10.1371/journal.pcbi.1007083>.
- [41] Leigh F. Johnson and Rob E. Dorrington. "Modelling the demographic impact of HIV/AIDS in South Africa and the likely impact of interventions". *Demographic Research* 14.22 (2006), pp. 541–574. <https://doi.org/10.4054/DemRes.2006.14.22>.
- [42] Rebecca F Baggeley, Geoff P Garnett, and Niel M Ferguson. "Modelling the Impact of Antiretroviral Use in Resource-Poor Settings". *PLOS Medicine* 3.4 (2006), pp. 493–504. <https://doi.org/10.1371/journal.pmed.0030124>.
- [43] David P. Wilson, James Kahn, and Sally M. Blower. "Predicting the epidemiological impact of antiretroviral allocation strategies in KwaZulu-Natal: The effect of the urban-rural divide". *Proceedings of the National Academy of Sciences of the United States of America* 103.38 (2006), pp. 14228–14233. <https://doi.org/10.1073/pnas.0509689103>.
- [44] Nicolas Bacaer et al. "Modeling the joint epidemics of TB and HIV in a South African township". *Journal of Mathematical Biology* 57.4 (2008), pp. 557–593. <https://doi.org/10.1007/s00285-008-0177-z>.
- [45] Esther Chigidi and Edward M Lungu. "Hiv model incorporating differential progression for treatment-naïve and treatment-experienced infectives". *Mathematical Biosciences and Engineering* 6.3 (2009), pp. 427–450. <https://doi.org/10.3934/mbe.2009.6.427>.
- [46] Brian G Williams et al. "Antiretroviral therapy for tuberculosis control in nine African countries". *Proceedings of the National Academy of Sciences of the United States of America* 107.45 (2010), pp. 19485–19489. <https://doi.org/10.1073/pnas.1005660107>.
- [47] Farai Nyabadza and Zindoga Mukandavire. "Modelling HIV/AIDS in the presence of an HIV testing and screening campaign". *Journal of Theoretical Biology* 280.1 (2011), pp. 167–179. <https://doi.org/10.1016/j.jtbi.2011.04.021>.
- [48] T. Barnighausen, D. E. Bloom, and S. Humair. "Economics of antiretroviral treatment vs. circumcision for HIV prevention". *Proceedings of the National Academy of Sciences* 109.52 (2012), pp. 21271–21276. <https://doi.org/10.1073/pnas.1209017110>.
- [49] Bradley G Wagner, Brian J Coburn, and Sally Blower. "Increasing survival time decreases the cost-effectiveness of using "test & treat" to eliminate HIV epidemics". *Mathematical Biosciences and Engineering* 10.5-6 (2013), pp. 1673–1686. <https://doi.org/10.3934/mbe.2013.10.1673>.
- [50] Michele R Decker et al. "Estimating the impact of reducing violence against female sex workers on HIV epidemics in Kenya and Ukraine: a policy modeling exercise." *American Journal of Reproductive Immunology* 69.S1 (2013), pp. 122–132. <https://doi.org/10.1111/aji.12063>.
- [51] Andrea L Wirtz et al. "Modelling the impact of HIV prevention and treatment for men who have sex with men on HIV epidemic trajectories in low- and middle-income countries". *International Journal of STD and AIDS* 24.1 (2013), pp. 18–30. <https://doi.org/10.1177/0956462412472291>.
- [52] Leigh Anne Shafer et al. "The dual impact of antiretroviral therapy and sexual behaviour changes on HIV epidemiologic trends in Uganda: A modelling study". *Sexually Transmitted Infections* 90.5 (2014), pp. 423–429. <https://doi.org/10.1136/sextrans-2013-051219>.
- [53] Senelani D Hove-Musekwa et al. "Cost-Effectiveness Analysis of Hospitalization and Home-Based Care Strategies for People Living with HIV/AIDS: The Case of Zimbabwe." *International Scholarly Research Notices* 2014 (2014), p. 836439. <https://doi.org/10.1155/2014/836439>.
- [54] Ronald Scott Braithwaite et al. "How do different eligibility guidelines for antiretroviral therapy affect the cost-effectiveness of routine viral load testing in sub-Saharan Africa". *AIDS* 28.S1 (2014), S73–S83. <https://doi.org/10.1097/QAD.000000000000110>.
- [55] Brooke E Nichols et al. "Increasing the use of second-line therapy is a cost-effective approach to prevent the spread of drug-resistant HIV: a mathematical modelling study". *Journal of the International AIDS Society* 17 (2014), p. 19164. <https://doi.org/10.7448/IAS.17.1.19164>.
- [56] Laith J Abu-Raddad and Susanne F Awad. "How does population viral load vary with the evolution of a large HIV epidemic in sub-Saharan Africa?" *AIDS* 28.6 (2014), pp. 927–929. <https://doi.org/10.1097/QAD.0000000000000211>.
- [57] Sarah Jane Anderson et al. "Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study". *The Lancet* 384.9939 (2014), pp. 249–256. [https://doi.org/10.1016/S0140-6736\(14\)61053-9](https://doi.org/10.1016/S0140-6736(14)61053-9).

- [58] Sabina S Alistar et al. "HIV epidemic control-a model for optimal allocation of prevention and treatment resources". *Health Care Management Science* 17.2 (2014), pp. 162–181. <https://doi.org/10.1007/s10729-013-9240-4>.
- [59] Anne Cori et al. "HPTN 071 (PopART): A cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: Mathematical model". *PLOS ONE* 9.1 (2014), e84511. <https://doi.org/10.1371/journal.pone.0084511>.
- [60] John Stover et al. "How Can We Get Close to Zero? The Potential Contribution of Biomedical Prevention and the Investment Framework towards an Effective Response to HIV". *PLOS ONE* 9.11 (2014), e111956. <https://doi.org/10.1371/journal.pone.0111956>.
- [61] Andrea L Wirtz et al. "Epidemic impacts of a community empowerment intervention for HIV prevention among female sex workers in generalized and concentrated epidemics". *PLOS ONE* 9.2 (2014), e88047. <https://doi.org/10.1371/journal.pone.0088047>.
- [62] Eline L Korenromp et al. "Impact and cost of the HIV/AIDS national strategic plan for Mozambique, 2015-2019-projections with the spectrum/goals model". *PLOS ONE* 10.11 (2015), e0142908. <https://doi.org/10.1371/journal.pone.0142908>.
- [63] Gwenan M Knight et al. "Tuberculosis Prevention in South Africa". *PLOS ONE* 10.4 (2015), e0122514. <https://doi.org/10.1371/journal.pone.0122514>.
- [64] Cliff C. Kerr et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376. <https://doi.org/10.1097/QAI.0000000000000605>.
- [65] Nicole Fraser et al. "Reorienting the HIV response in Niger toward sex work interventions: From better evidence to targeted and expanded practice". *Journal of Acquired Immune Deficiency Syndromes* 68.S2 (2015), S213–S220. <https://doi.org/10.1097/QAI.0000000000000456>.
- [66] Semu Mitiku Kassa and Aziz Ouhinou. "The impact of self-protective measures in the optimal interventions for controlling infectious diseases of human population". *Journal of Mathematical Biology* 70.1-2 (2015), pp. 213–236. <https://doi.org/10.1007/s00285-014-0761-3>.
- [67] Linda-Gail Bekker et al. "Combination HIV prevention for female sex workers: What is the evidence?" *The Lancet* 385.9962 (2015), pp. 72–87. [https://doi.org/10.1016/S0140-6736\(14\)60974-0](https://doi.org/10.1016/S0140-6736(14)60974-0).
- [68] Kate Shannon et al. "Global epidemiology of HIV among female sex workers: Influence of structural determinants". *The Lancet* 385.9962 (2015), pp. 55–71. [https://doi.org/10.1016/S0140-6736\(14\)60931-4](https://doi.org/10.1016/S0140-6736(14)60931-4).
- [69] Stephanie Blaizot et al. "Estimation and short-term prediction of the course of the HIV epidemic using demographic and health survey methodology-like data". *PLOS ONE* 10.6 (2015), e0130387. <https://doi.org/10.1371/journal.pone.0130387>.
- [70] Jennifer A Smith et al. "Maximising HIV prevention by balancing the opportunities of today with the promises of tomorrow: a modelling study". *The Lancet HIV* 3.7 (2016), e289–e296. [https://doi.org/10.1016/S2352-3018\(16\)30036-4](https://doi.org/10.1016/S2352-3018(16)30036-4).
- [71] Rifat Atun et al. "Long-term financing needs for HIV control in sub-Saharan Africa in 2015-2050: a modelling study." *BMJ Open* 6.3 (2016), e009656. <https://doi.org/10.1136/bmjopen-2015-009656>.
- [72] Andrew J Shattock et al. "In the interests of time: Improving HIV allocative efficiency modelling via optimal time-varying allocations". *Journal of the International AIDS Society* 19.1 (2016), p. 20627. <https://doi.org/10.7448/IAS.19.1.20627>.
- [73] Jessica B McGillen et al. "Optimum resource allocation to reduce HIV incidence across sub-Saharan Africa: a mathematical modelling study". *The Lancet HIV* 3.9 (2016), e441–e448. [https://doi.org/10.1016/S2352-3018\(16\)30051-0](https://doi.org/10.1016/S2352-3018(16)30051-0).
- [74] Leigh F. Johnson et al. "Prospects for HIV control in South Africa: a model-based analysis". *Global Health Action* 9.1 (2016). <https://doi.org/10.3402/gha.v9.30314>.
- [75] Monisha Sharma et al. "Modeling the cost-effectiveness of homebased HIV testing and education (HOPE) for pregnant women and their male partners in Nyanza Province, Kenya". *AIDS Research and Human Retroviruses* 32.S1 (2016), p. 300. <https://doi.org/10.1097/QAI.0000000000001057>.
- [76] Gordon Akudibillah, Abhishek Pandey, and Jan Medlock. "Maximizing the benefits of ART and PrEP in resource-limited settings". *Epidemiology and Infection* 145.5 (2017), pp. 942–956. <https://doi.org/10.1017/S0950268816002958>.
- [77] Ramzi A Alsallaq et al. "The potential impact and cost of focusing HIV prevention on young women and men: A modeling analysis in western Kenya". *PLOS ONE* 12.4 (2017), e0175447. <https://doi.org/10.1371/journal.pone.0175447>.

- [78] Sarah-Jane Anderson et al. "HIV prevention where it is needed most: Comparison of strategies for the geographical allocation of interventions: Comparison". *Journal of the International AIDS Society* 20.4 (2017), e25020. <https://doi.org/10.1002/jia2.25020>.
- [79] Calvin Chiu et al. "Designing an optimal HIV programme for South Africa: Does the optimal package change when diminishing returns are considered?" *BMC Public Health* 17.1 (2017), p. 143. <https://doi.org/10.1186/s12889-017-4023-3>.
- [80] Leigh F Johnson et al. "Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study". *PLOS Medicine* 14.12 (2017), e1002468. <https://doi.org/10.1371/journal.pmed.1002468>.
- [81] Robyn M Stuart et al. "Getting it right when budgets are tight: Using optimal expansion pathways to prioritize responses to concentrated and mixed HIV epidemics". *PLOS ONE* 12.10 (2017), e0185077. <https://doi.org/10.1371/journal.pone.0185077>.
- [82] Jessica B McGillen et al. "Consequences of a changing US strategy in the global HIV investment landscape". *AIDS* 31.18 (2017), F19–F23. <https://doi.org/10.1097/QAD.0000000000001669>.
- [83] Ide Cremin et al. "PrEP for key populations in combination HIV prevention in Nairobi: a mathematical modelling study". *The Lancet HIV* 4.5 (2017), e214–e222. [https://doi.org/10.1016/S2352-3018\(17\)30021-8](https://doi.org/10.1016/S2352-3018(17)30021-8).
- [84] Jennifer M Ross et al. "Modeling HIV disease progression and transmission at population-level: The potential impact of modifying disease progression in HIV treatment programs." *Epidemics* 23 (2018), pp. 34–41. <https://doi.org/10.1016/j.epidem.2017.12.001>.
- [85] Sarah-Jane Anderson et al. "Frontloading HIV financing maximizes the achievable impact of hiv prevention". *Journal of the International AIDS Society* 21.3 (2018), e25087. <https://doi.org/10.1002/jia2.25087>.
- [86] Sarah-Jane Anderson et al. "The importance of local epidemic conditions in monitoring progress towards HIV epidemic control in Kenya: a modelling study". *Journal of the International AIDS Society* 21.11 (2018), e25203. <https://doi.org/10.1002/jia2.25203>.
- [87] Evans Otieno Omondi, Rachel Waema Mbogo, and Livingstone S Luboobi. "Mathematical analysis of sex-structured population model of HIV infection in Kenya". *Letters in Biomathematics* 5.1 (2018), pp. 174–194. <https://doi.org/10.1080/23737867.2018.1506712>.
- [88] Beth Woods et al. "Appraising the value of evidence generation activities: an HIV modelling study." *BMJ Global Health* 3.6 (2018), e000488. <https://doi.org/10.1136/bmjgh-2017-000488>.
- [89] Elizabeth R Stevens et al. "Cost-effectiveness of a combination strategy to enhance the HIV care continuum in Swaziland: Link4health". *PLOS ONE* 13.9 (2018), e0204245. <https://doi.org/10.1371/journal.pone.0204245>.
- [90] Isaac J Stopard et al. "The influence of constraints on the efficient allocation of resources for HIV prevention". *AIDS* 33.7 (2019), pp. 1241–1246. <https://doi.org/10.1097/QAD.0000000000002158>.
- [91] Leo Beacroft and Timothy B Hallett. "The potential impact of a "curative intervention" for HIV: a modelling study." *Global Health Research and Policy* 4 (2019), p. 2. <https://doi.org/10.1186/s41256-019-0107-1>.
- [92] Meghan Reidy et al. "Evaluating the potential impact and cost-effectiveness of dapivirine vaginal ring pre-exposure prophylaxis for HIV prevention". *PLOS ONE* 14.6 (2019), e0218710. <https://doi.org/10.1371/journal.pone.0218710>.
- [93] Evans Otieno Omondi, Rachel Waema Mbogo, and Livingstone S Luboobi. "A mathematical modelling study of HIV infection in two heterosexual age groups in Kenya". *Infectious Disease Modelling* 4 (2019), pp. 83–98. <https://doi.org/10.1016/j.idm.2019.04.003>.
- [94] Mathieu Maheu-Giroux et al. "Cost-Effectiveness of Accelerated HIV Response Scenarios in Cote d'Ivoire". *Journal of Acquired Immune Deficiency Syndromes* 80.5 (2019), pp. 503–512. <https://doi.org/10.1097/QAI.0000000000001956>.
- [95] Jesse Knight, Rupert Kaul, and Sharmistha Mishra. "Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review". *Epidemics* 40 (2022), p. 100608. <https://doi.org/10.1016/j.epidem.2022.100608>.
- [96] Judith Vandepitte et al. "Estimates of the number of female sex workers in different regions of the world". *Sexually Transmitted Infections* 82.S3 (2006). <https://doi.org/10.1136/sti.2006.020081>.
- [97] M. Carael et al. "Clients of sex workers in different regions of the world: Hard to count". *Sexually Transmitted Infections* 82.S3 (2006), pp. iii26–iii33. <https://doi.org/10.1136/sti.2006.021196>.

- [98] Fiona Scorgie et al. "Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review". *AIDS and Behavior* 16.4 (2012), pp. 920–933. <https://doi.org/10.1007/s10461-011-9985-z>.

# Appendix C

## Supplement to Chapter 3

### C.1 Female Sex Worker Data

TODO ...Figure C.1. Figure C.2.

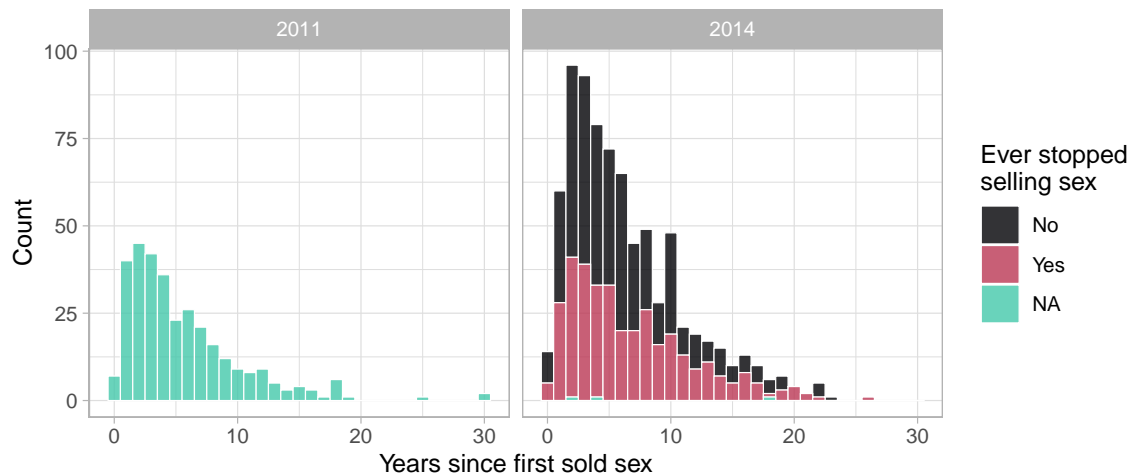


Figure C.1: Years since first sold sex among FSW in Eswatini (unadjusted)

Data sources: 2011 [1], 2014 [2]



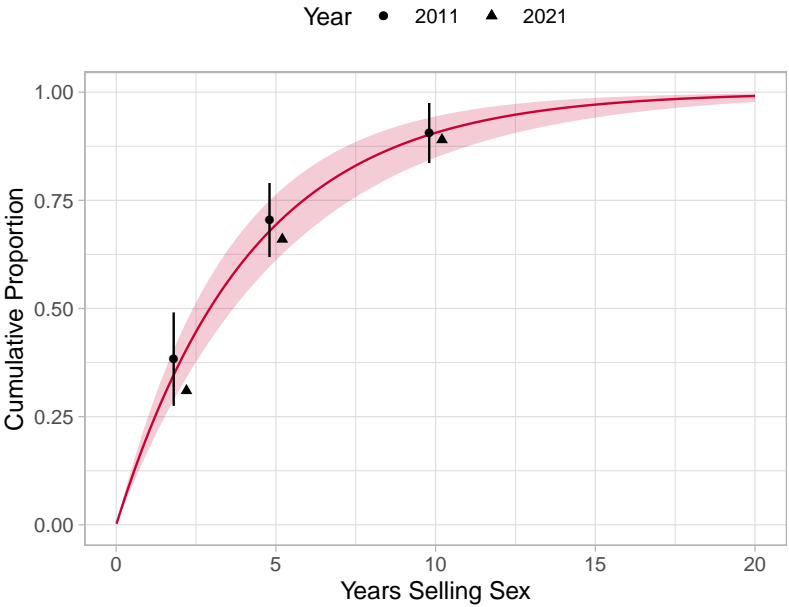


Figure C.2: Cumulative distribution of years selling sex among FSW in Eswatini (RDS-adjusted)

The line and shaded region illustrate the median and 95% CI of sampled exponential distributions, respectively; calibration data from [1] (2011) and [3] (2011).

C.2 Non-Sex Work: Adjusted Partner Numbers

Figure C.3 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.

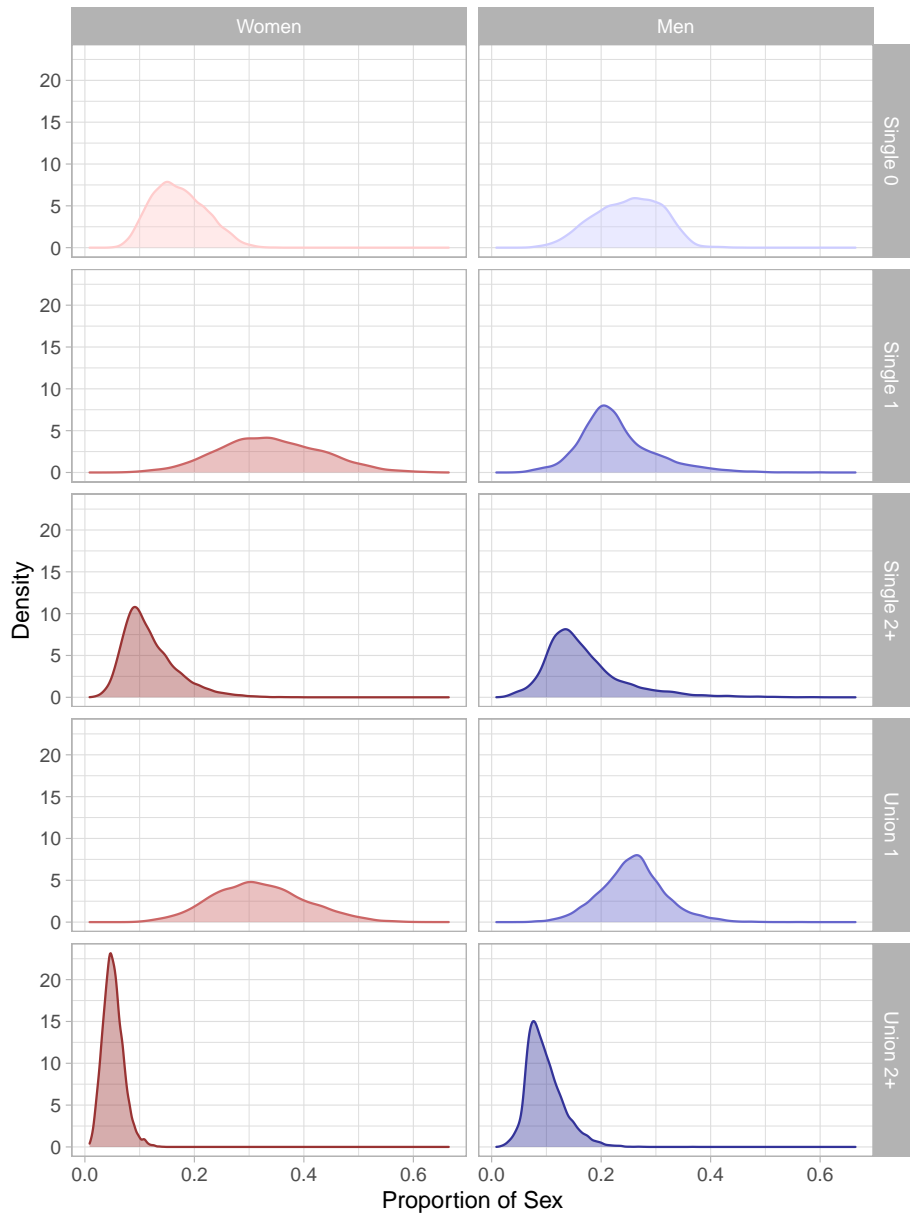


Figure C.3: Density distributions for adjusted proportions of women and men aged 15–49, stratified by union status and numbers of partners in the past 12 months

## C.3 Model Calibration

Table C.1 gives the short names (used in code and results figures) and definitions of the calibrated model parameters ( $N = 73$ ). The precise 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](https://github.com/mishra-lab/hiv-fsw-art/blob/master/code/model/params.py)

Table C.1: Definitions of calibrated parameters

*	Parameter	Definition
	t0_hiv	year of HIV introduction to Eswatini
	PX_w_fsw	proportion of women who are FSW
	PX_w_h	proportion of women who have 2+ partners in p12m
	PX_m_m	proportion of men who have 2+ partners in p12m
	dur_fsw_l	duration in sex work among lower risk FSW
	dur_fsw_h	duration in sex work among higher risk FSW
	dur_cli	duration buying sex among clients
	turn_xm_xl	turnover rate from medium to lowest activity (women and men)
	Pturn_fsw_m:l	proportion of FSW who transition to medium activity
	Pturn_cli_m:l	proportion of clients who transition to medium activity
	growth_2050	rate of Eswatini population growth in 2050
	C12m_msp_xl	number of main/spousal partners in p12m among lowest activity
	C12m_cas_xl	number of casual partners in p12m among lowest activity
	C12m_cas_wm	number of casual partners in p12m among medium activity women
	RC_cas_cli:wm	relative number of casual partners among clients vs medium activity women
	C1m_swo_fsw_l	number of occasional sex work partners in p1m among lower risk FSW
	C1m_swr_fsw_l	number of regular sex work partners in p1m among lower risk FSW
	RC_swo_fsw_h:l	relative number of occasional sex work partners among higher vs lower risk FSW
	RC_swr_fsw_h:l	relative number of regular sex work partners among higher vs lower risk FSW
	KF_swx_cli	rate of visiting FSW (sex acts) among clients overall
	RKF_swx_cli_h:l	relative rate of visiting (sex acts) among higher vs lower risk clients
	F_msp	rate of sex acts in main/spousal partnerships
	RF_cas:msp	relative rate of sex acts in casual vs main/spousal partnerships
	dur_msp	duration of main/spousal partnerships
	dur_cas	duration of casual partnerships
	dur_swr	duration of regular sex work partnerships
a	F_swr	rate of sex acts in regular sex work partnerships
	PF_ai	proportion of sex acts which are anal in all partnerships
	pref_msp_xl	log-odds of main/spousal partnership formation among lowest activity
	pref_mcx_swx	log-odds of non-sex work partnership formation among FSW and clients
	Rbeta_condom	relative per-act probability of HIV transmission with a condom
	RPF_condom_a:v	relative condom use in anal vs vaginal sex
	RPF_condom_1996	relative condom use in all partnerships in 1996 vs 2002 or 2006
b	PF_condom_msp_2006	condom use in main/spousal partnerships in 2006
b	PF_condom_msp_2016	condom use in main/spousal partnerships in 2006
b	PF_condom_cas_2006	condom use in casual partnerships in 2006
b	PF_condom_cas_2016	condom use in casual partnerships in 2016
b	PF_condom_swo_2002	condom use in occasional sex work partnerships in 2002
b	PF_condom_swo_2011	condom use in occasional sex work partnerships in 2011
b	PF_condom_swo_2014	condom use in occasional sex work partnerships in 2014
b	PF_condom_swr_2002	condom use in regular sex work partnerships in 2002

continued ...

... continued

*	Parameter	Definition
b	PF_condom_swr_2011	condom use in regular sex work partnerships in 2011
b	PF_condom_swr_2014	condom use in regular sex work partnerships in 2014
	PF_circum_2050	prevalence of circumcision by 2050
	beta_0	per-act probability of HIV transmission $\beta$ for CD4 > 350 (reference)
c	Rbeta_acute	relative $\beta$ during acute infection
	Rbeta_350	relative $\beta$ for 200 < CD4 < 350
	Rbeta_200	relative $\beta$ for CD4 < 350
	Rbeta_vi_rec	relative $\beta$ for receptive vaginal sex
	aRbeta_gud_sus	additional relative $\beta$ for GUD among susceptible partner
	aRbeta_gud_inf	additional relative $\beta$ for GUD among infectious partner
c	dur_acute	duration of acute infection
d	P_gud_fsw_l	prevalence of GUD among lower risk FSW
d	RP_gud_fsw_h:l	relative prevalence of GUD among higher vs lower risk FSW
	RP_gud_2050	relative prevalence of GUD overall in 2050 vs 2020
	iP_gud_h:l	prevalence interpolator for GUD among medium activity vs DHS and FSW
	Rbeta_uvls	relative $\beta$ on ART but before VLS
	Rdx_global	relative rate of diagnosis overall
	dx_w_2002	rate of diagnosis among women in 2002
	dx_w_2006	rate of diagnosis among women in 2006
	Rdx_m:w_2006	relative rate of diagnosis among men vs women in 2006
	dx_wq_2011	rate of diagnosis among non-FSW women in 2011
	Rdx_m:wq_2011	relative rate of diagnosis among men vs non-FSW women in 2011
	aRdx_fsw:wq_2011	additional relative rate of diagnosis among FSW vs non-FSW women in 2011
	aRdx_wq_16:11	additional relative rate of diagnosis among non-FSW women in 2016 vs 2011
	aRdx_fsw:wq_2016	additional relative rate of diagnosis among FSW vs non-FSW women in 2016
	tx_2010	rate of ART initiation among diagnosed and eligible in 2010
	tx_2012	rate of ART initiation among diagnosed and eligible in 2012
	Rtx_fsw:wq	relative rate of ART initiation among FSW vs non-FSW women
	ivx	duration on ART before achieving VLS initially
	Runvx_m:wq	relative rate of viral unsuppression among men vs non-FSW women
	Runvx_fsw:wq	relative rate of viral unsuppression among FSW vs non-FSW women
	revx_2010	rate of viral re-suppression in 2010

\* relational sampling constraints (see § C.3.1); FSW: female sex worker; p12m: past 12 months;  $\beta$ : 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.,  $P_0 = 0.2, P_1 = 0.4, iP_x = 0.5 \rightarrow P_x = 0.3$ ; all rates in per-year; all durations in years; all parameters reflect stratum averages.

### C.3.1 Relational Sampling Constraints

Several relational constraints were imposed on calibrated parameter values during sampling. Incorporating constraints within Latin hypercube sampling is challenging [4]. 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 § A.1.3, this sampling strategy effectively changes the prior distribution to reflect both the original prior and the specified constraints.

- a.  $K_{\text{sw}_0\text{fsw}_l} * RC_{\text{sw}_0\text{fsw}_h:l} * F_{\text{sw}_0} + K_{\text{swr}_\text{fsw}_l} * RC_{\text{swr}_\text{fsw}_h:l} * F_{\text{swr}} < 2*365$   
 where:  $K_{\text{swx}_\text{fsw}_l} = C1m_{\text{swx}_\text{fsw}_l} * dur_{\text{swx}} / (dur_{\text{swx}} + 1/12)$
- b. Let “c\_” denote PF\_condom\_:
- $c_{\text{msp}_2006} < c_{\text{msp}_2016}$
  - $c_{\text{cas}_2006} < c_{\text{cas}_2016}$
  - $c_{\text{sw}_02002} < c_{\text{sw}_02011} < c_{\text{sw}_02014}$
  - $c_{\text{swr}_2002} < c_{\text{swr}_2011} < c_{\text{swr}_2014}$
  - $c_{\text{msp}_2006} < c_{\text{cas}_2006}$
  - $c_{\text{msp}_2016} < c_{\text{cas}_2016}$
  - $c_{\text{swr}_2002} < c_{\text{sw}_02002}$
  - $c_{\text{swr}_2011} < c_{\text{sw}_02011}$
  - $c_{\text{swr}_2014} < c_{\text{sw}_02014}$
- c.  $1 \leq (Rbeta_{\text{acute}} * dur_{\text{acute}}) \leq 63$
- d.  $P_{\text{gud}_\text{fsw}_l} > .07$   
 $(P_{\text{gud}_\text{fsw}_l} * RP_{\text{gud}_\text{fsw}_h:l}) < 1$

### C.3.2 Results

This section provides additional results to supplement § 3.4.2.

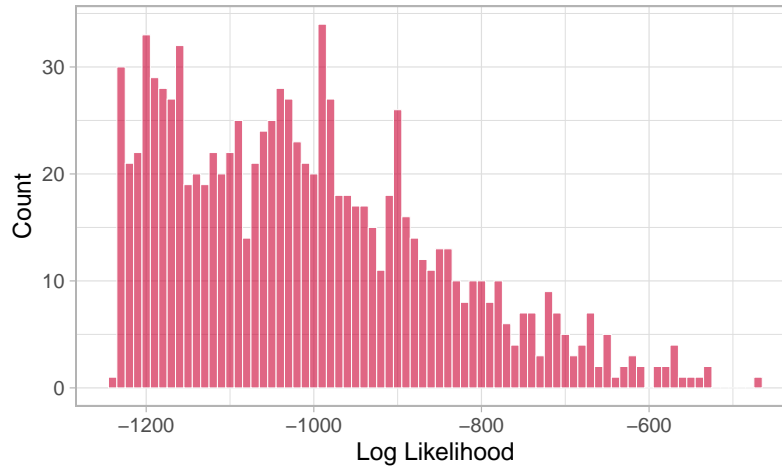


Figure C.4: Distribution of log-likelihoods among model fits

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

Figures C.5 and C.6 illustrate the modelled ratios of HIV prevalence and incidence, respectively, between selected risk groups, and associated calibration targets. Figure C.8 similarly illustrates the total Eswatini population size aged 15–49, and Figure C.9 illustrates condom use within each partnership type.

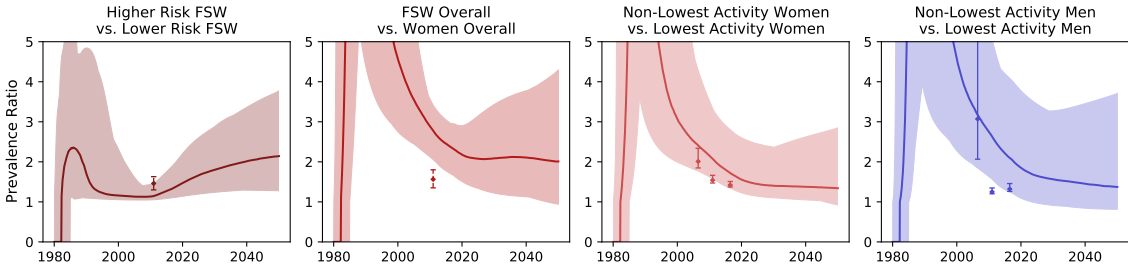


Figure C.5: Modelled HIV prevalence ratios between selected risk groups and associated calibration targets

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.

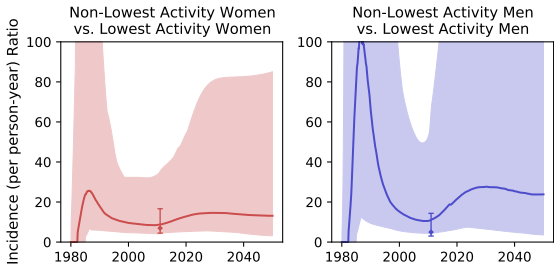


Figure C.6: Modelled HIV incidence ratios between selected risk groups and associated calibration targets

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 C.7: HIV prevalence data from antenatal care clinics in Eswatini

Figure C.8: 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.

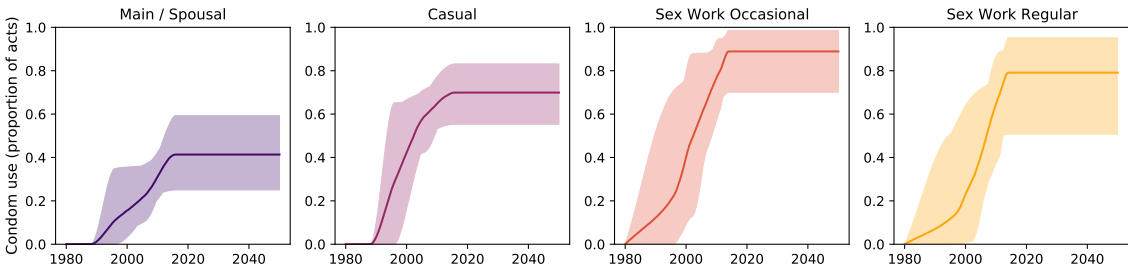


Figure C.9: Modelled condom use within different partnership types

1000 model fits (top 1% by likelihood among 100,000 sampled parameter sets); ribbon and curve: range and median of model fits.

## References

- [1] Stefan Baral et al. “Reconceptualizing the HIV epidemiology and prevention needs of female sex workers (FSW) in Swaziland”. *PLOS ONE* 9.12 (2014), e115465. <http://doi.org/10.1371/journal.pone.0115465>.
- [2] PEPFAR. *Characterizing the HIV Prevention and Treatment Needs among Key Populations, including Men who Have Sex with Men and Female Sex Workers in Swaziland: From Evidence to Action*. Mbabane, Swaziland, 2015.
- [3] Eswatini Ministry of Health. *2020–2021 Integrated Biological-Behavioral Surveillance Survey among Female Sex Workers and Men Who Have sex with Men in Eswatini*. Mbabane, Eswatini, 2022.
- [4] Matthieu Petelet et al. “Latin hypercube sampling with inequality constraints”. *AStA Advances in Statistical Analysis* 94.4 (2010), pp. 325–339. arXiv: [0909.0329](https://arxiv.org/abs/0909.0329). <https://link.springer.com/article/10.1007/s10182-010-0144-z>.

## Appendix D

# Supplement to Chapter 4

TODO



## Appendix E

# Supplement to Chapter 5

### E.1 Supplementary Results

#### E.1.1 Scenario Cascades

Figure E.1 illustrates ...

#### E.1.2 Distributions of Additional Infections

As in § 3.4.3, Figure E.2 illustrates ...

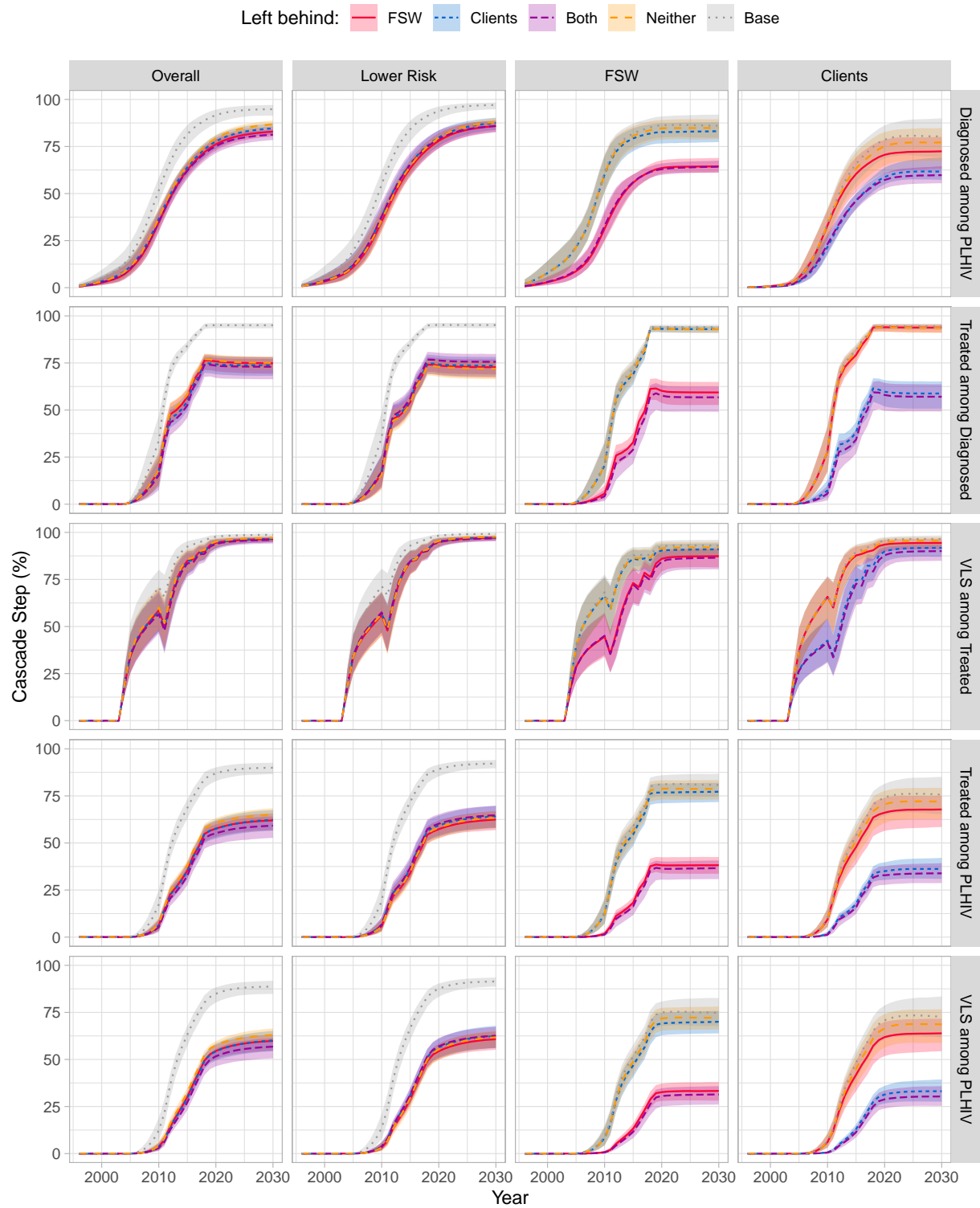


Figure E.1: Cascade attainment over time across scenarios

Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW; 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.

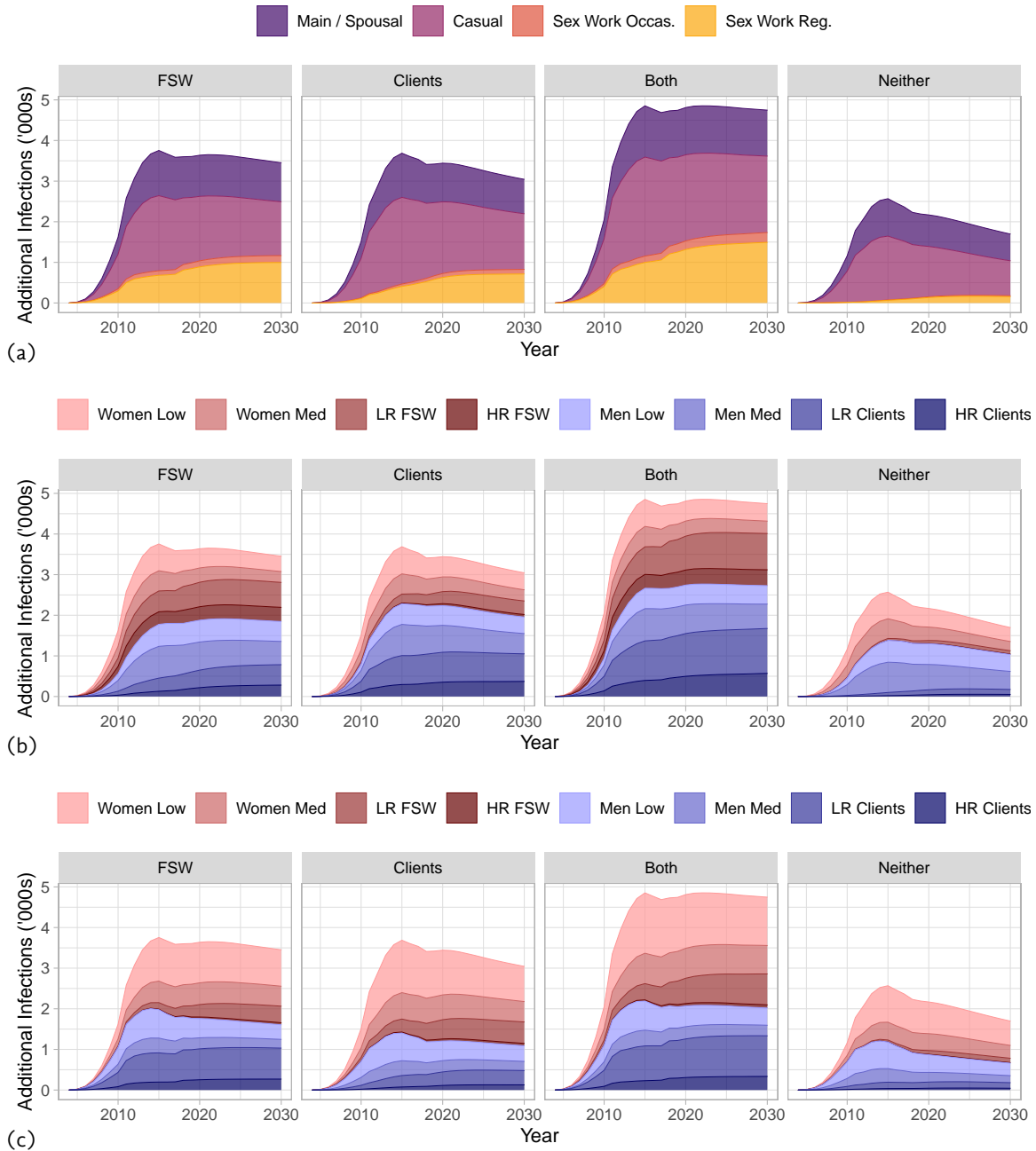


Figure E.2: Additional infections in each “who is left behind” counterfactual scenario vs. the base case, stratified by: (a) partnership type, (b) transmitting group, and (c) acquiring group

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.