Chapter 5

Modelling Intersections of Differential Risk and ART Coverage

5.1 Introduction

Early HIV treatment via antiretroviral therapy (ART) offers numerous individual-level health benefits [1–4], and can prevent transmission in serodiscordant partnerships [5–7]. As such, immediate initiation of ART has been recommended by WHO since 2016 [8]. Alongside expanding ART eligibility, interest has grown in the potential population-level prevention impacts of ART, motivating numerous modelling studies [9–12] and several large community-based trials [13–16] of ART scale-up as "treatment as prevention", especially within Sub-Saharan Africa. In general, the prevention impacts estimated via these trials have not met expectations from modelling, prompting questions about the potential influence of modelling assumptions on predictions [17].

Within these modelling studies, ART prevention impacts are usually quantified as incidence rate reduction or cumulative infections averted in scenarios with higher cascade attainment vs. scenarios with lower attainment [12]. Modelled populations are often stratified by risk, including key populations like FSW and their clients, to capture important epidemic dynamics related to risk heterogeneity [18–20]. However, these studies almost always assume that cascade attainment (i.e., proportions of PLHIV who are diagnosed, treated, and virally suppressed) or progression (i.e., rates of diagnosis, treatment initiation, and treatment failure/discontinuation) are equal across modelled risk groups. For example, among the modelling studies reviewed in Chapter **??**, key populations were usually assumed to have "average" cascade progression, or "above average" progression in some scenarios, but never "below average".

Yet, there is growing evidence of differential ART cascade across population strata, including age, gender, mobility, and risk [21, 22]. These differences can be driven by unique barriers to engagement in care faced by vulnerable populations, which intersect with drivers of HIV risk [23–25]. Moreover, the lowest cascades likely remain unmeasured [21, 26]. These intersections of risk and cascade heterogeneity could potentially undercut the prevention impacts of ART scale-up anticipated from model-based evidence [17]. Therefore, I sought to examine the following questions in an illustrative modelling analysis:

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

I examined these questions using the Eswatini model from Chapter **??**, focusing on differential risk related to sex work. Eswatini has recently achieved outstanding cascade gains, surpassing 95-95-95 (see § **??**) [27, 28]. As such, I used observed ART scale-up in Eswatini as a *base case* reflecting evidently attainable scale-up, and explored *counterfactual* scenarios in which scale-up was slower, and where specific risk groups could have been "left behind".

5.2 Methods

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

5.2.1 Model

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

5.2.2 Scenarios & Analyses

5.2.2.1 Objective 1: Influence of cascade differences between risk groups

For Objective 1, I defined the *base case* scenario to reflect observed cascade scale-up in Eswatini, reaching 95-95-95 by 2020 [28]. 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 [28]. In these counterfactual scenarios, I reduced cascade progression among specific risk groups in different combinations: FSW, clients, and/or the remaining population ("lower risk"). I reduced cascade progression by calibrating and applying a constant relative scaling factor "R" to group-specific rates of: diagnosis ($R_d \in [0, 1]$), treatment initiation ($R_t \in [0, 1]$), and treatment failure / discontinuation ($R_u \in [1, 20]$). When FSW and/or clients had reduced cascade, I calibrated their Rs so that these populations achieved approximately 60-40-80 by 2020. By contrast, I calibrated Rs for the lower risk population so that the Swati population *overall* achieved 80-80-90 in all 4 counterfactual scenarios, thus ensuring that a consistent proportion of the population overall experienced reduced viral

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

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

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

suppression. Table 5.1 summarizes these scenarios, while Figure A.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 assumed fixed rates of diagnosis, treatment initiation, and treatment failure / discontinuation thereafter.

I quantified ART prevention impacts via relative cumulative additional infections (CAI) and additional incidence rate (AIR) in the counterfactual scenarios (k) vs. the base case (0), over multiple time horizons up to 2030, starting from $t_0 = 2000$:

$$\text{CAI, AIR}\,(t) = \frac{\Omega_k(t) - \Omega_0(t)}{\Omega_0(t)}, \qquad \Omega(t) = \begin{cases} \int_{t_0}^{t} \Lambda(\tau)\, d\tau & \text{CAI} \\ \lambda(t) & \text{AIR} \end{cases} \tag{5.1}$$

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

5.2.2.2 Objective 2: Conditions under which cascade differences matter most

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

For this regression analysis, I obtained 10,000 samples. I explored a wider range of counterfactual scenarios vs. Objective 1 by randomly sampling the relative rates for diagnosis and treatment initiation $R_d, R_t \sim \text{Beta}\,(\alpha = 3.5, \beta = 1.9)$ and treatment failure $R_u \sim \text{Gamma}\,(\alpha = 3.4, \beta = 1.9)$ for each of: FSW, clients, and the remaining lower risk population (9 total values). These sampling distributions had 95% CI: (0.25, 0.95) and (1.5, 15), respectively, and were chosen to obtain cascades in 2020 spanning approximately 60-60-90 through 90-90-95 (Figure A.3). For each of $N_f = 1000$ model fits, I generated $N_k = 10$ counterfactual scenarios per fit via random relative rates "R" via Latin hypercube sampling, yielding $N_f N_k = 10{,}000$ total counterfactual samples for the regression.

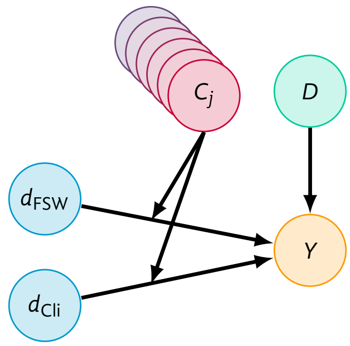

Figure 5.1: Directed acyclic graph (DAG) for inferring the epidemic conditions under which differential viral suppression across risk groups matters most

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

For each of these 10,000 samples, I defined relative CAI and AIR by 2030 vs. the base case, as in Objective 1. For each sample, I further defined U_{fki} for risk groups $i \in \{1: \text{FSW}, 2: \text{clients}, *: \text{overall}\}$ as the proportions virally unsuppressed among people living with HIV by 2020, reflecting a summary measure of ART cascade gaps. Using U_{fki}, I defined the main regression predictors as: $D_{fk} = U_{fk*} - U_{f0*} > 0$, reflecting differences in *population-overall* viral unsuppression in sample $k \in [1, 10]$ vs. the base case (denoted $k = 0$); and $d_{fki} = U_{fki} - U_{fk*} \lessgtr 0$, reflecting differences in *group-i-specific* viral unsuppression in sample k vs. the population overall in sample k — i.e., disproportionate unsuppression.

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

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

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

such that each outcome is modelled as a sum of the effects of: differential population-level unsuppression in the counterfactual vs. the base scenario (D); differential unsuppression among FSW and clients vs. the population overall within the counterfactual scenario (d_i); and effect modification of d_i by epidemic conditions (C_j). The model does not include an intercept because if $D = d_i = 0$, then we expect CAI = AIR = 0. I fitted this model for each outcome using generalized estimating equations [29] to control for repeated use of each model fit f. I standardized all model variables (D, d_i, C_j) via $\hat{x} = (x - \text{mean}(x))/\text{SD}(x)$ to avoid issues of different variable scales and collinearity in interaction terms. This standardization does not imply that regression coefficient magnitudes can be compared to indicate variable "importance", because the standardization applied to each variable is driven by the variance before standardization — in this case reflecting arbitrary ranges (D, d_i) or uncertainty in calibration (C_j).[1] Rather, effect sizes can be interpreted as: the expected change in outcome per standard deviation change in the variable.

5.3 Results

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

5.3.1 Objective 1: Influence of cascade differences between risk groups

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

5.3.2 Objective 2: Conditions under which cascade differences matter most

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

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

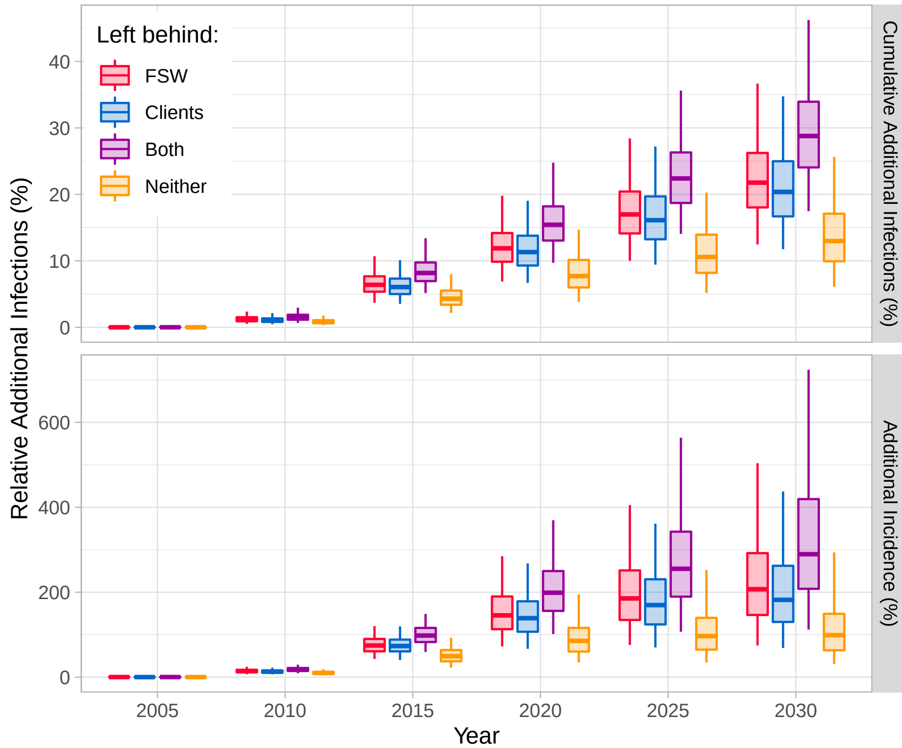

Figure 5.2: Relative additional infections under counterfactual scenarios vs. the base case

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

5.4 Discussion

I sought to explore how intersections of risk heterogeneity and differential ART coverage may influence model-estimated prevention impacts of ART. I 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. I also found that the transmission impact of leaving behind higher risk groups generally increased with: the size of the risk group, the size of their predominant partner group (i.e., clients for FSW and FSW for clients), and the rate of turnover among their predominant partner group.

Although my analysis only considered Eswatini, my findings are likely generalizeable to other epidemic contexts. In fact, HIV prevalence ratios between key populations and the population overall are relatively low in Eswatini versus elsewhere [30, 31]; thus, the transmission impact of cascade gaps among key populations in other contexts would likely be even greater than I found for Eswatini. Moreover, as HIV incidence declines in many settings, epidemics may become re-concentrated among key populations [32, 33], further magnifying the transmission impact of cascade disparities.

To my knowledge, this study is the first to explore the transmission impact of heterogeneity in ART coverage across risk groups, within consistent population-overall coverage. In my review of mathematical modelling of ART scale-up in Sub-Saharan Africa (Chapter **??**), I found that few studies have considered any cascade differences by risk group, but that such differences likely mediate ART prevention impacts [12].

Cascade gaps have been observed among men versus women [22, 34], younger versus older populations [22, 35], key populations versus the population overall [21], and within key populations themselves [36, 37]. Moreover, unmeasured cascades — such as among populations who have not been reached by programs and interventions — are likely lowest [21, 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 [1, 4], prevention in serodiscordant relationships [6], and contributing to population-level incidence declines [38]. 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 [17, 23–25]. Such populations can be reached effectively through tailored services to meet their unique needs [39], services which can be designed and refined with ongoing community engagement [40–42]. As I have shown, an equity-focused approach to ART scale-up can maximize prevention impacts, and accelerate the end of the HIV epidemic.

My analysis above has three major strengths. First, drawing on my conceptual framework for risk heterogeneity (Table **??**) and multiple sources of context-specific data [43–47], I captured several dimensions of risk heterogeneity, including: heterosexual anal sex, four types of sexual partnerships, sub-stratification of FSW and clients into higher and lower risk, and risk group turnover. Second, whereas most modelling studies of ART scale-up project hypothetical future scenarios which may not be achievable, my base case scenario reflects observed scale-up in Eswatini. Finally, my analytic approach to objective 2, in which epidemic conditions are conceptualized as potential effect modifiers, represents a unique methodological contribution to the HIV modelling literature.

My analysis above has three main limitations. First, I only considered heterosexual HIV transmission in Eswatini, and mainly explored risk heterogeneity related to sex work. However, my findings would likely generalize to other transmission networks and determinants of risk heterogeneity, including risk groups not always recognized as key populations, such as mobile populations and young women [48, 49]. Second, I did not consider transmitted drug resistance. Drug resistance is more likely to emerge in the context of barriers to viral suppression [50]; thus, cascade gaps among those at higher risk would likely accelerate emergence of transmitted drug resistance, and amplify impacts of such gaps. Third, even among the top 1% of model fits, substantial uncertainty remained in the values of inferred parameters, yielding wide confidence intervals in the outputs of interest (additional infections and incidence). In the absence of additional data, such intervals reflect true uncertainty in the magnitude of these outputs, though more advanced calibration techniques could potentially improve precision.

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

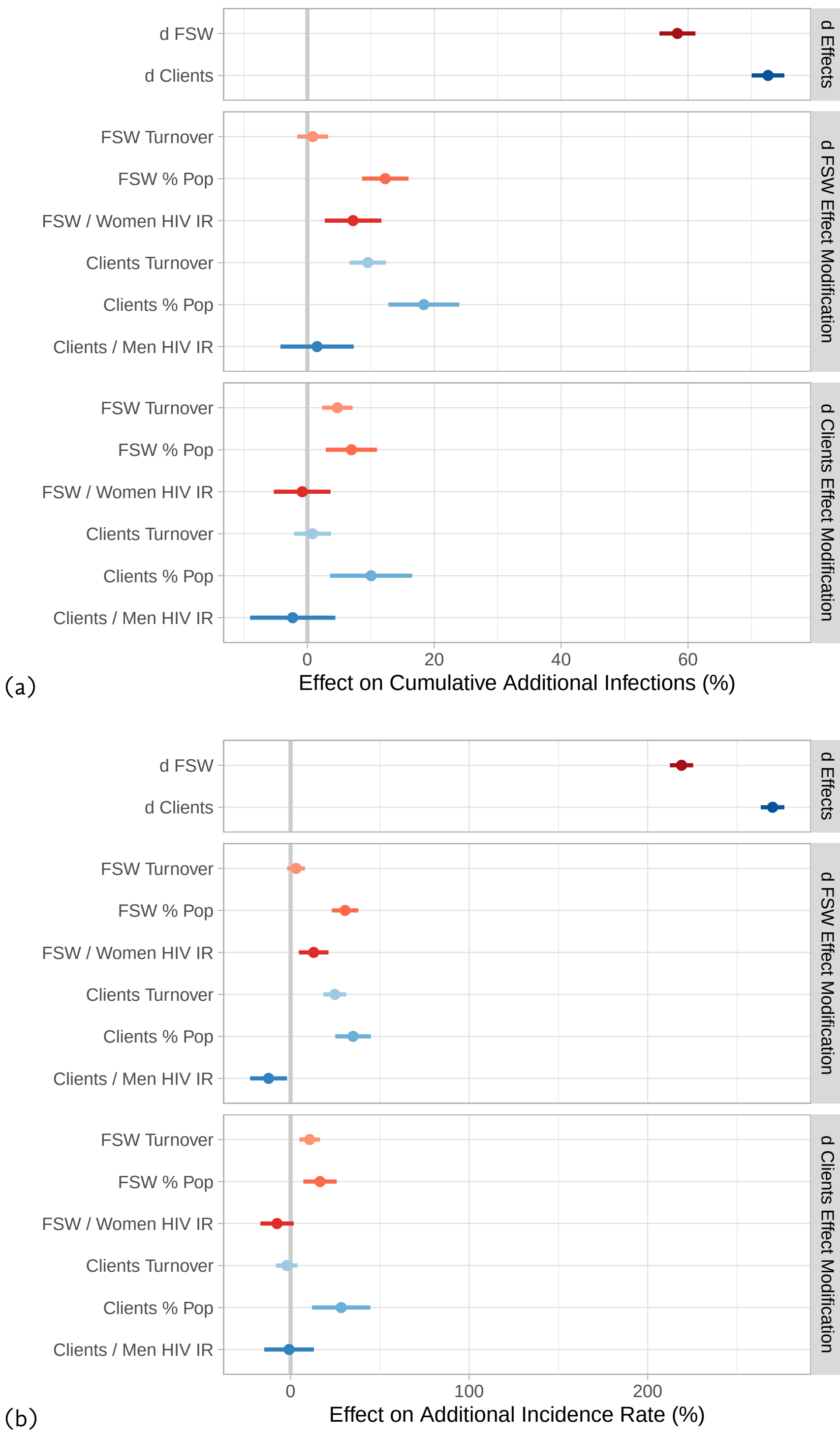

Figure 5.3

points and error bars: mean and 95% CI for each effect.

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Appendix A

Supplement to Chapter 5

A.1 Objective 1

A.1.1 Scenario Cascades

Figure A.1 illustrates ...

A.1.2 Distributions of Additional Infections

As in § **??**, Figure A.2 illustrates ...

A.2 Objective 2

Figure A.3 illustrates ...

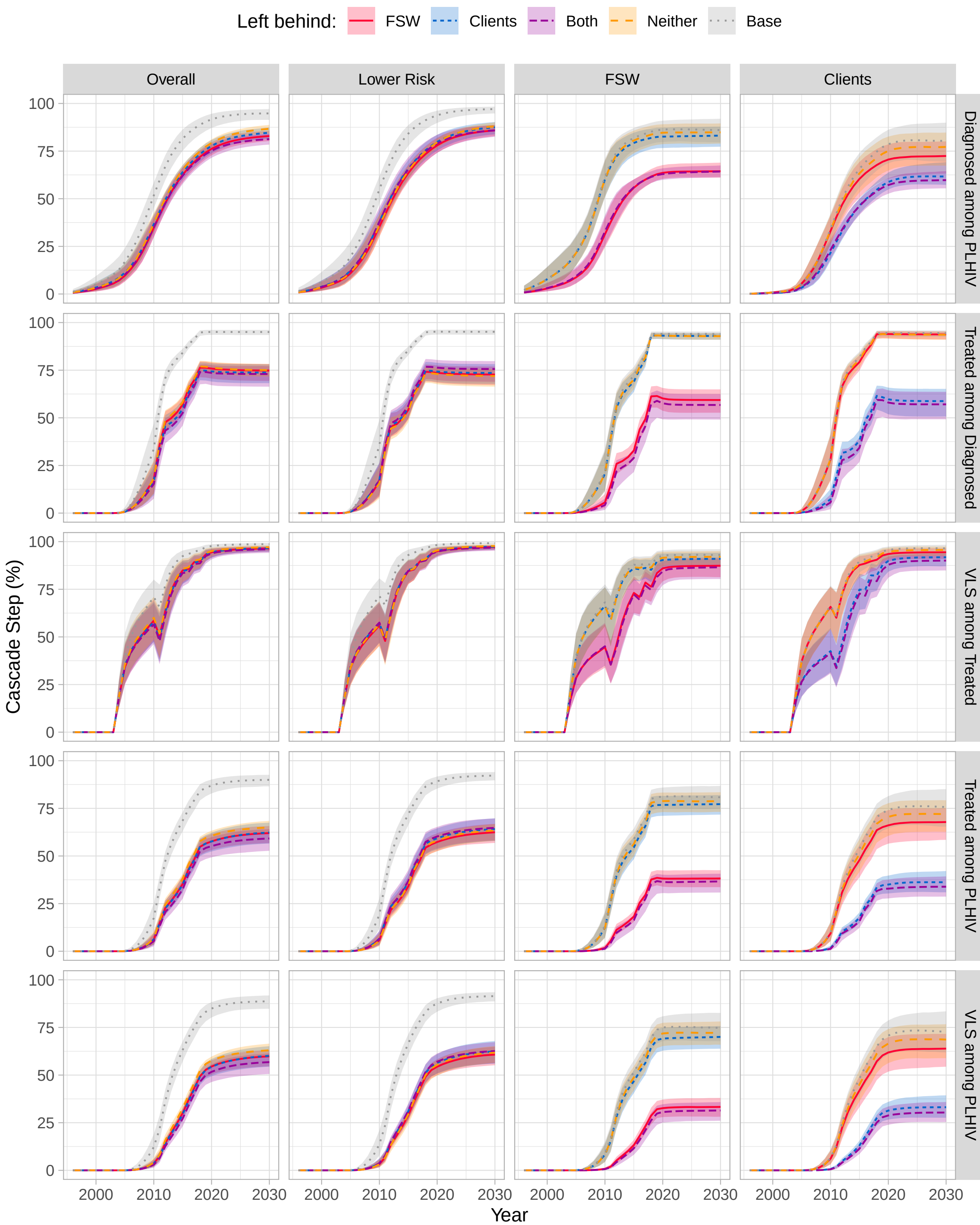

Figure A.1: Cascade attainment over time across scenarios

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.

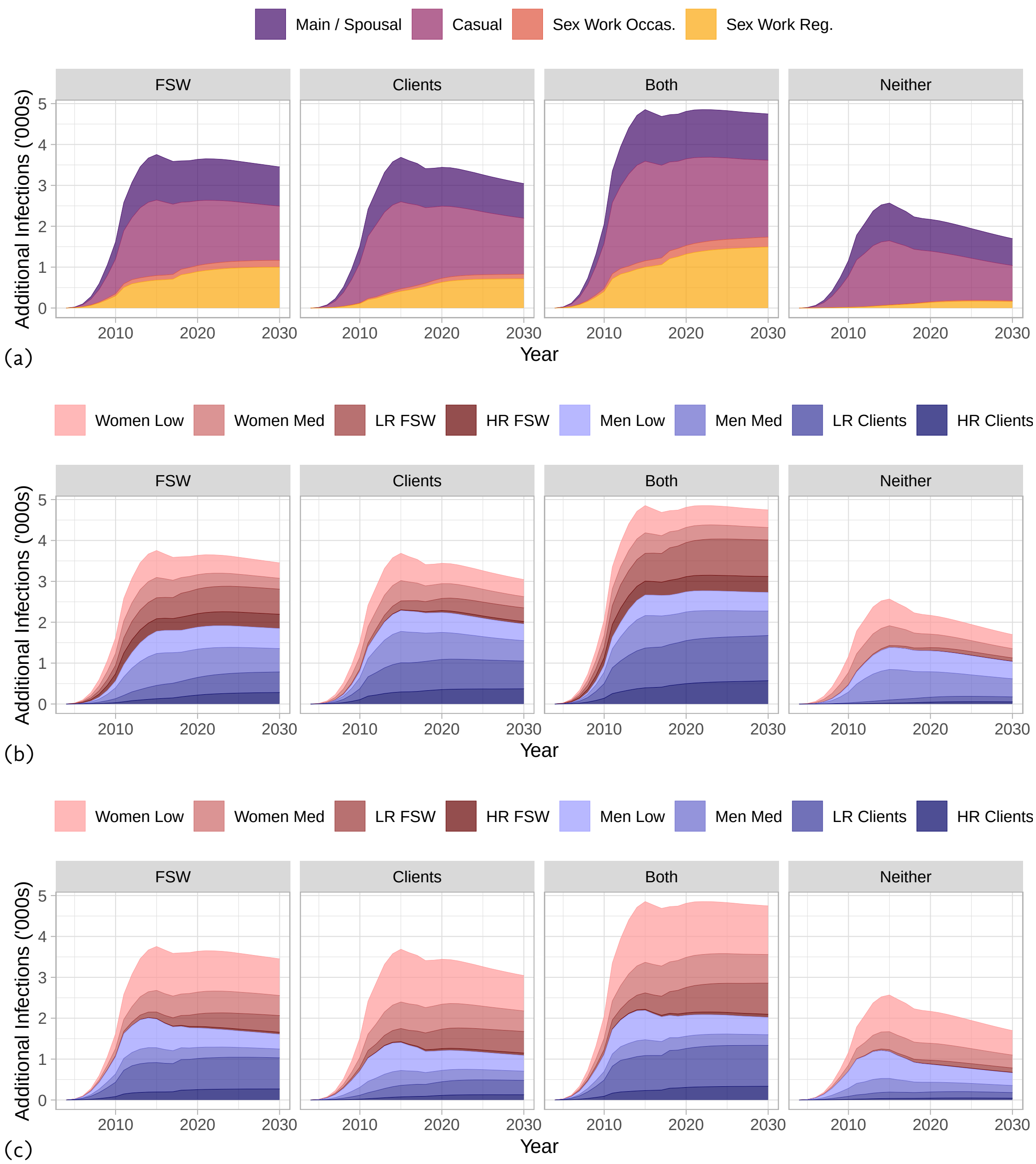

Figure A.2: Additional infections in each "who is left behind" counterfactual scenario vs. the base case, stratified by: (a) partnership type, (b) transmitting group, and (c) acquiring group

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.

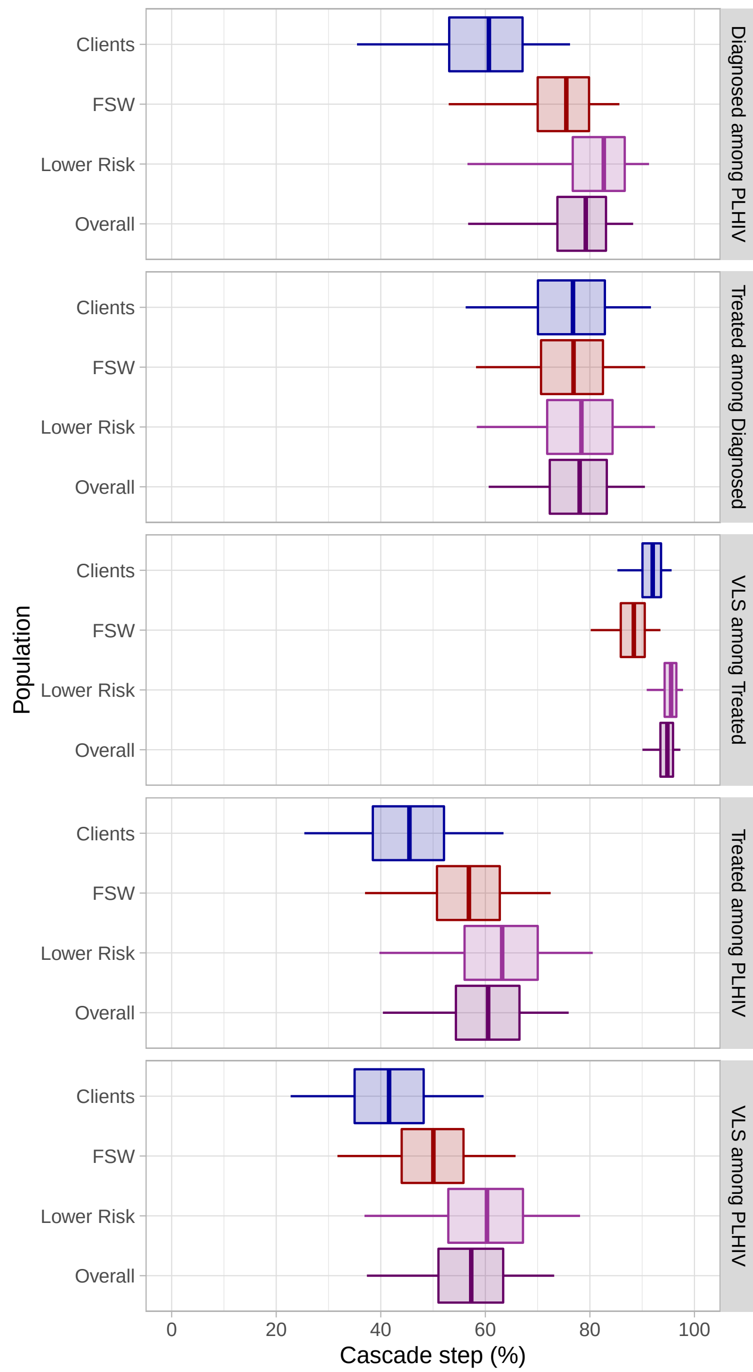

Figure A.3: Cascade attainment by 2020 across samples

Lower Risk: all women and men not involved in sex work; FSW: female sex workers; Clients: of FSW; whiskers, boxes, and midlines: 95% CI, 50% CI, median of model fits.