Title: Intersections of risk and intervention heterogeneity: a modelling study on the prevention impacts of antiretroviral therapy in eSwatini

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Abstract

1 Introduction

…

We sought to answer the following questions (objectives):

1. How are projections of ART prevention benefits influenced by differences in ART cascade between risk groups?

2. Under which epidemic conditions do such differences have largest influence?

2 Methods

We constructed a deterministic compartmental model of heterosexual HIV transmission, stratified by sex, sexual activity, HIV natural history, and ART cascade of care. The model includes 8 risk groups, including higher and lower risk female sex workers (FSW), and higher and lower risk clients of FSW, and 4 partnership types, including regular and occasional sex work (Figure A.1). We calibrated the model to reflect the HIV epidemic and ART scale-up in eSwatini (base case). We then explored counterfactual scenarios in which ART cascade was reduced among various combinations of risk groups, and quantified ART prevention impacts by comparing base case and counterfactual scenarios.

2.1 Model Parameterization & Calibration

Complete model details are given in Appendix A, and all code is available online.[1]

HIV: Our model of HIV natural history included acute infection and stages defined by CD4-count. We modelled relative rates of infectiousness by stage as an approximation of viral load [1–3], as well as rates of HIV-attributable mortality [4–6].

Risk heterogeneity: We captured risk heterogeneity through risk group-level factors, including group size, average duration in group, STI symptom prevalence, and numbers / types of partnerships per year; and partnership-level factors, including assortative mixing, partnership duration, frequency of vaginal / anal sex, and levels of condom use. Table 1 summarizes key parameter values and sampling distributions related to risk heterogeneity. Only condom use varied (increased) over time (Figure A.6). To parameterize higher versus lower risk FSW, we conducted exploratory analysis of survey data from Swazi FSW in 2011 [7] and 2014 [8] (Appendix **??**). We parameterized the remaining risk groups using reported data from national studies in 2006 [9], 2011 [10], and 2016 [11]. We modelled expansion of voluntary medical male circumcision [11], but did not model other interventions (e.g. ongoing pre-exposure prophylaxis scale-up [12]) nor non-heterosexual HIV transmission.

ART cascade: We modelled rates of HIV diagnosis among people living with HIV as monotonically increasing over time, with a base rate defined for low/medium activity women, and fixed relative rates for low/medium activity men (< 1), clients (< 1), and FSW (> 1). We modelled ART initiation similarly except: the relative rate for ART initiation among FSW was < 1, and we defined an additional relative rate by CD4 count (≤ 1) to reflect historical ART eligibility criteria. We modelled viral suppression using a fixed rate for all groups, corresponding to an average of 4 months on ART. We modelled treatment failure / discontinuation with a single monotonically decreasing rate applied to all risk groups in the base case, reflecting improving treatment success / retention over time. Individuals with treatment failure / discontinuation could re-initiate ART at a fixed rate, reflecting re-engagement in care or detection of treatment failure and initiation of alternative regimens. We modelled rapid CD4 recovery during the first 4 months of ART, followed by slower recovery while virally suppressed [13–15]. We modelled reduced HIV-attributable mortality among individuals on ART, in addition to mortality benefits of CD4 recovery.

Calibration: We calibrated the model to reflect available data from eSwatini on HIV prevalence, HIV incidence, and ART cascade of care, stratified by risk groups (Appendix A.3) [7–11]. To reflect uncertainty in model inputs, we sampled 100,000 sets of parameter values from specified prior distributions (e.g. Table 1). Parameters were sampled using Latin hypercube sampling [16] to obtain

[1] github.com/mishra-lab/hiv-fsw-art

Table 1: Model parameters related to risk heterogeneity

		Prior			
Parameter	Stratification	Mean	(95% CI)	Distrib.	Ref.
Population size (% of total)	FSW of women overall	2.8	(0.6, 6.5)	Beta	
	Clients of men overall	30	(6.0, 70)	—	See XX
	HR FSW of FSW overall	20	—	—	Assumed
	HR clients of clients overall	20	—	—	Assumed
Duration in group (mean years)	HR FSW	3.6	(1.9, 5.8)	Gamma	See XX
	LR FSW	10	(9.0, 11)	Gamma	See XX
	All clients	10	(6.0, 15)	Gamma	
Relative infectiousness	Acute infection	5.3	(1.0, 13)	Gamma	
	Any GUD p12m	2.9	(1.0, 5.7)	Gamma	
Relative susceptibility	Receptive vaginal sex	1.45	(1.0, 2.0)	Gamma	
	Receptive anal sex	10	—	—	
	Any GUD p12m: women	5.3	(1.5, 12)	Gamma	
	Any GUD p12m: men	7.7	(2.0, 18)	Gamma	
Any GUD p12m prevalence (%)	HR FSW	16	(7, 28)	Beta	
	LR FSW	47	(19, 89)	—	
	HR clients	12	(7, 22)	—	
	Everybody else	7	—	—	
Sex acts per partnership-year	Main/spousal	78	(27, 156)	Gamma	
	Casual	30	(4.4, 82)	—	See XX
	Occasional sex work	12	—	—	Assumed
	Regular sex work	31	(18, 48)	Gamma	
Partnership anal sex (% of acts)	Main/spousal & casual	5.9	(0.6, 17)	Beta	
	Occasional & regular sex work	9.7	(0.6, 29)	Beta	
Condom use in 2020 (% of acts protected)	Main/spousal	42	(31, 54)	Beta	See XX
	Casual	69	(65, 74)	Beta	See XX
	Occasional sex work	88	(78, 97)	Beta	See XX
	Regular sex work	79	(64, 90)	Beta	See XX
	Anal vs vaginal sex	77	(50, 95)	Beta	
Partnerships per year	LR FSW, occasional sex work	49	(30, 72)	Gamma	
	HR FSW, occasional sex work	98	(58, 153)	—	
	LR FSW, regular sex work	101	(73, 133)	Gamma	
	HR FSW, regular sex work	151	(107, 205)	—	
Sex work visits per year	LR clients	26	(11, 50)	Gamma	
	HR clients	89	(34, 174)	Gamma	

Notation — FSW: female sex workers; Clients: of FSW; HR: higher risk; LR: lower risk; p12m: past 12 months.

good coverage of parameter space, except parameters with relational constraints (e.g. condom use in casual partnerships must be higher than in main/spousal partnerships), which were sampled randomly. We computed the likelihood of each parameter set by comparing model projections to calibration targets, each target having an uncertainty distribution (Appendix A.3). We then selected the top 1% (1000) of parameter sets by likelihood ("model fits") for all subsequent analyses.

2.2 Scenarios & Analysis

2.2.1 Objective 1: Influence of differences in cascade between risk groups

For Objective 1, we used calibrated model fits as the *base case* scenario, reflecting observed ART cascade scale-up in eSwatini [9–11], following WHO guidelines and reaching approximately 95-95-95 overall by 2020 [17]. We also assumed that FSW specifically achieved 95-95-95 by 2020, reflecting trends in available data [7, 8], although the true FSW cascade in 2020 may have been lower.

Next, we defined 4 *counterfactual* scenarios in which the overall population reached 60-80-80 by 2020, via reduced cascade progression among specific risk groups: FSW, clients, and/or the remaining population ("lower risk") (Table 2). We reduced cascade progression by applying a 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 ($R_f \in [1, 25]$). When FSW and/or clients had reduced cascade, we calibrated their Rs so that they achieved approximately 40-60-80 by 2020. By contrast, we calibrated Rs for the lower risk population so that the population *overall* achieved 60-80-80 in all counterfactual scenarios, thus ensuring that a consistent proportion of the overall population experienced reduced cascade. When cascade rates among FSW and/or clients were unchanged from the base case, the cascade they achieved by 2020 could be lower than 95-95-95 due 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.

We quantified ART prevention impacts via cumulative additional infections (CAI) and additional incidence (AI) in the counterfactual scenarios versus the base case. Differences (CAI and AI) were defined relative to the base case, and computed over multiple time horizons up to 2040. For each scenario, we computed ART prevention impacts for each model fit, and reported median (95% CI) values across model fits, reflecting uncertainty.

Table 2: 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	LR
Base Case	95-95-95	—	95-95-95	—	—	—
Leave Behind: FSW	40-60-80	—	60-80-80	✓	✗	✓
Leave Behind: Clients	—	40-60-80	60-80-80	✗	✓	✓
Leave Behind: FSW & Clients	40-60-80	40-60-80	60-80-80	✓	✓	✓
Leave Behind: Neither	—	—	60-80-80	✗	✗	✓

[a] Cascade: % diagnosed among HIV+; % on ART among diagnosed; % virally suppressed among on ART; [b] Rates of: diagnosis; ART initiation; treatment failure.

2.2.2 Objective 2: Conditions under which cascade differences matter most

For Objective 2, we aimed to estimate the effects of lower ART cascades among certain risk groups on relative CAI and AI, and potential effect modification by epidemic conditions. For this analysis, we explored a wider range of counterfactual scenarios by randomly sampling $R_d, R_t \sim \text{Beta}(\alpha = 1.8, \beta = 1.2)$, and $R_f \sim \text{Gamma}(\alpha = 1.33, \beta = 3)$ for each of: FSW, clients, and the remaining lower risk population (9 total values). Sampling distributions were chosen to obtain cascades in 2020 spanning approximately 25-50-75 through 95-95-95. We sampled 10 sets of R for each model fit using Latin hypercube sampling. For each R sample and model fit (10,000 total parameter sets), we computed: the relative CAI and AI versus the base case, as in Objective 1; the proportion virally suppressed (*VS*) among people living with HIV in all 3 groups by 2020, as a summary measure of ART cascade; and the absolute difference in *VS* versus the base case scenari, *dVS*.

Next, we defined the following key measures of epidemic conditions (*EC*) related to sex work: FSW and client population sizes (% population overall); average duration selling sex (FSW) and buying sex (clients); HIV prevalence ratios in 2000 among FSW vs lower risk women, and among clients vs lower risk men. For these measures, we combined higher and lower risk FSW, and likewise higher and lower risk clients. We used HIV prevalence ratios to reflect summary measures of risk heterogeneity under pre-ART conditions. By contrast, including all modelled risk factors for HIV acquisition and transmission (Table 1) in the analysis could lead to overfitting and improper inference due to effect mediation. Finally, we fit a general linear model of the form:

$$CAI = \sum_i \beta_i \, dVS_i + \sum_{ij\ (i \neq j)} \beta_{ij} \, dVS_i \, dVS_j + \sum_i \sum_k \beta_{ik} \, dVS_i \, EC_k \tag{1}$$

and determined the significance of effects (β_i), interactions (β_{ij}), and effect modification by epidemic conditions (β_{ik}). We used a generalized estimating equation to control for repeated use of each model fit. We used standardized variables (*dVS* and *EC*) $\hat{x}_k = (x_k - \mu_{x_k})/\sigma_{x_k}$ to assess the relative influence of each variable. We did not include an intercept because we know that if $dVS_1 = dVS_2 = dVS_3 = 0$, then the counterfactual is equal to the base case scenario, and thus $CAI = AI = 0$.

3 Results

Early epidemic emergence was driven by regular sex work partnerships (Figures B.1 and B.3). However, main/spousal partnerships contributed the majority of infections by 2000, including 64% (median) of new infections in 2020 in the base case. By 2020, clients of FSW had transmitted the most infections (Figure B.2a) and lower risk women had acquired the most infections (Figure B.2b). Overall HIV prevalence in 2020 was median (95% confidence interval): 25.3 (19.7, 31.5)% (Figure A.2), and overall incidence was 8 (4, 15) per 1000 person-years (Figure A.3). The prevalence ratio among FSW versus lower risk women was 1.74 (1.13, 2.43), and among clients of FSW versus lower risk men it was 1.30 (1.05, 1.79) (Figure A.4). Due to turnover and higher HIV incidence among FSW, achieving similar rates of diagnosis among FSW versus other women (Figure A.5a) required 2.53 (1.04, 4.88) times the rate of testing. Sex work contributed a growing proportion of infections over 2020–2040: from 21% to 26% (Figure B.1).

3.1 Influence of differences in cascade between risk groups

Figure 1 illustrates cumulative additional infections in each counterfactual scenario (60-80-80 overall by 2020) versus the base case (95-95-95 overall by 2020); Figure B.5 illustrates additional incidence. Leaving behind FSW and clients resulted the most additional infections: 66.7 (39.2, 111.1)% more than the base case by 2040. By contrast, leaving behind neither FSW nor clients resulted in the fewest additional infections: 48.1 (23.0, 91.3)% more than the base case by 2040 — a 27.5 (8.3, 51.4)% reduction. Leaving behind either FSW or clients resulted in a similar number of additional infections: 56.1 (29.9, 98.0)% and 54.2 (30.5, 95.1)%, respectively. However, who acquired these additional infections differed (Figure B.6c), 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 main/spousal partnerships in all scenarios (Figure B.6a).

3.2 Conditions under which cascade differences matter most

Figure 2 illustrates the standardized effects of reduced viral suppression (*dVS*) among FSW, clients, and the remaining population ("lower risk") on cumulative additional infections versus the base case by 2040, as well as effect modification by epidemic conditions. Trends were consistent across multiple time horizons (Figure B.8) and for additional incidence by 2040 (Figure B.9). Reduced cascade among the lower risk population had a larger independent effect than reduced cascade among FSW or clients, likely due to larger group size and the highly generalized epidemic context. Interaction between all pairs of *dVS* terms were significant, suggesting that reduced cascade across multiple sub-populations synergistically contributes to additional infections, perhaps reflecting residual transmission networks unreached by ART scale-up.

Reduced cascade among FSW was associated with more additional infections when the FSW population size was larger, and when the duration in sex work was shorter (marginal significance). Reduced cascade among clients was associated with more additional infections when the HIV prevalence ratio among FSW vs lower risk women was larger, and when the client population size was larger (marginal significance). Reduced cascade among lower risk men and women was associated with more additional infections when the HIV prevalence ratio among FSW vs lower risk women was larger, and when the client population size was smaller.

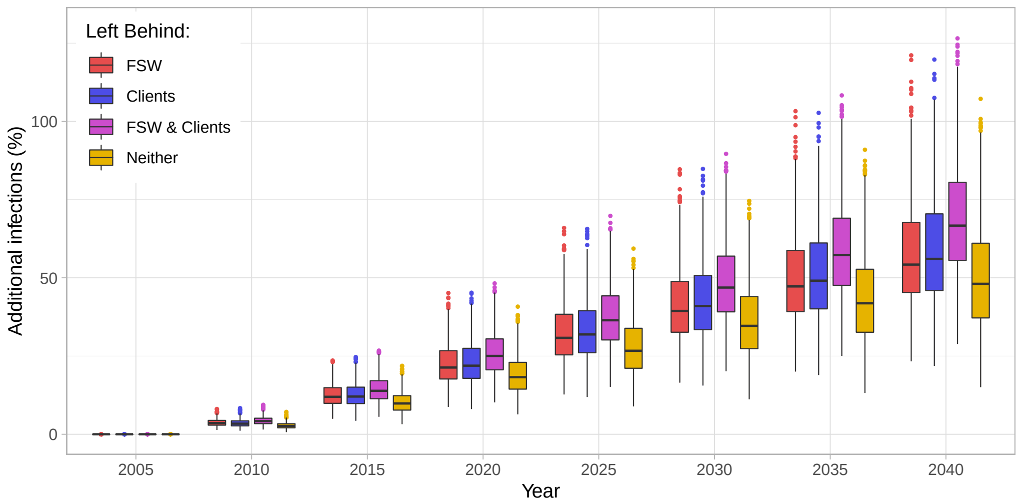

Figure 1: Cumulative additional HIV infections (%) in counterfactual scenarios (60-80-80 overall by 2020) vs the base case scenario (95-95-95 by 2020). Scenarios explore reduced cascades (40-60-80 by 2020) among FSW, clients of FSW, both, or neither as part of reduced cascade overall.

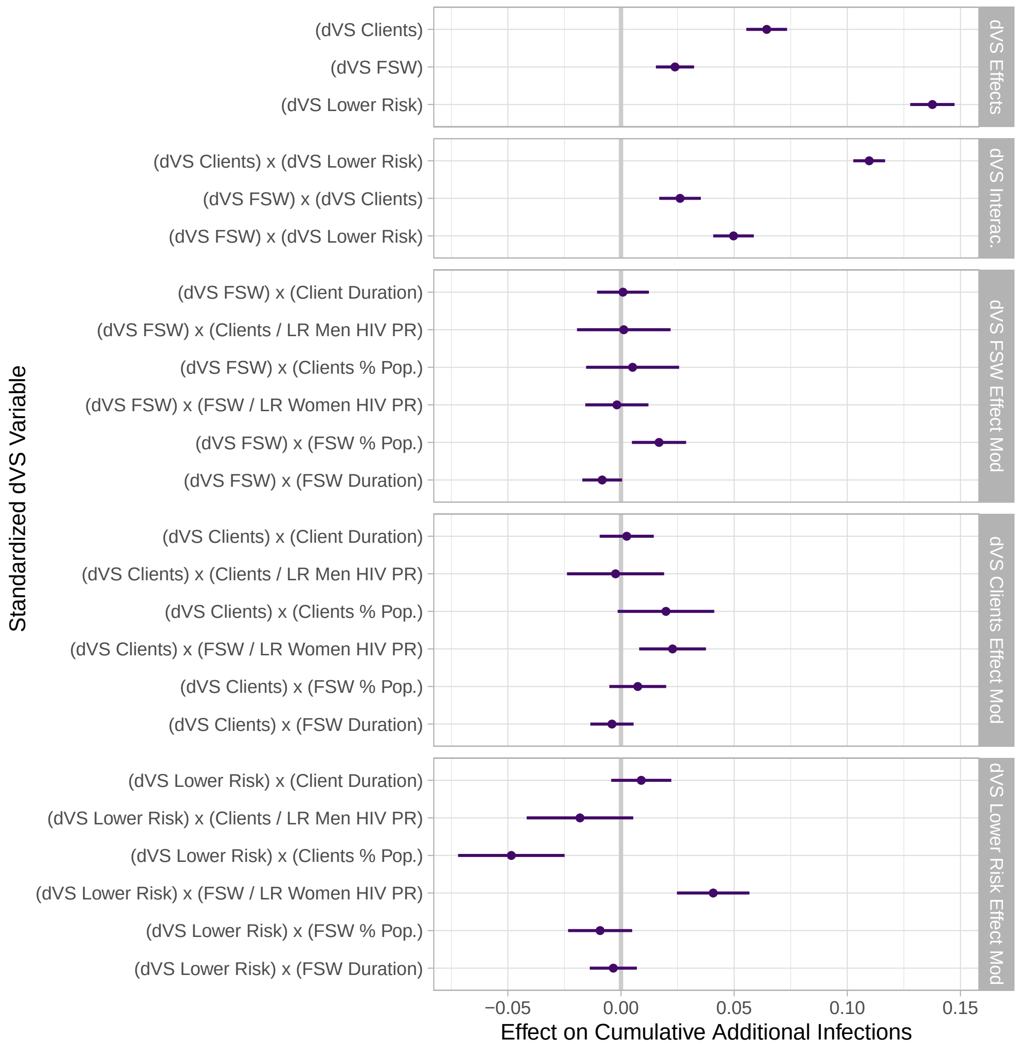

Figure 2: Standardized effects of reduced viral suppression (dVS) among different populations on cumulative additional infections by 2040, plus effect modification by epidemic conditions

Points and lines show the mean and 95% confidence interval for β terms from Eq. (1). *dVS*: absolute difference in viral suppression in each counterfactual scenario versus the base case; FSW: female sex workers; Clients: of FSW; LR: lower risk; Duration: average time spent in the risk group; % Pop: relative population size; HIV PR: HIV prevalence ratio. All model variables were standardized like $\hat{x}_k = (x_k - \mu_{x_k})/\sigma_{x_k}$ to reflect the relative influence of variables.

4 Discussion

…larger HIV prevalence ratio among FSW versus other women magnified the effects of lower cascade among any group (FSW, clients, or everybody else) on cumulative additional infections.

…such differences could be even greater in the context of concentrated or mixed epidemics, as compared to the highly generalized eSwatini HIV epidemic explored.

…prevalence among FSW may actually decline faster than among women overall, due to short duration in sex work; thus the prevalence ratio among FSW versus women overall may decline.

…

Multiple factors contributed to differential acquisition and transmission risk among men vs women:
…

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APPENDIX

Title: Intersections of risk and intervention heterogeneity: a modelling study on the prevention impacts of antiretroviral therapy in eSwatini

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A Model

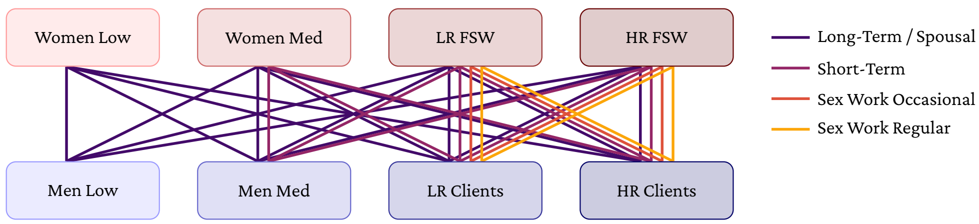
A.1 Structure & Notation

Table A.1 summarizes the modelled population stratifications, including 2 sex × 4 activity × (5 HIV × 5 cascade + 1 susceptible) = 208 total possible states. Figure A.1 summarizes the model structure and state transitions with respect to (a) risk groups and partnership types; (b) HIV status; and (c) ART cascade.

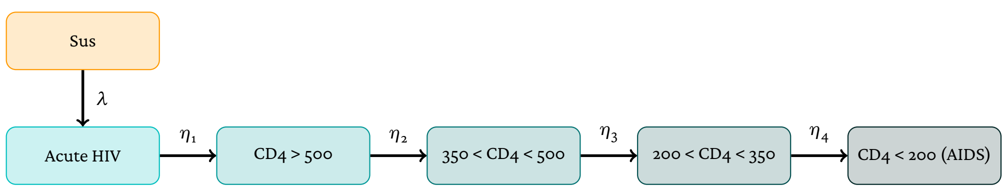
Table A.1: Modelled stratifications: population (top) and partnership-level dimensions (bottom)

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

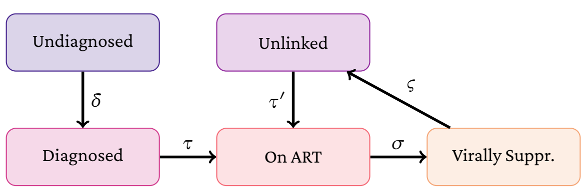
A.2 Parameterization



(a) Risk groups and partnership types



(b) HIV states



(c) ART cascade states

Figure A.1: Model structure and transitions

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

A.3 Calibration

Figures A.2 and A.3 illustrate HIV prevalence and incidence in the base case scenario, and the associated calibration targets. Figure A.4 similarly shows prevalence ratios between selected risk groups.

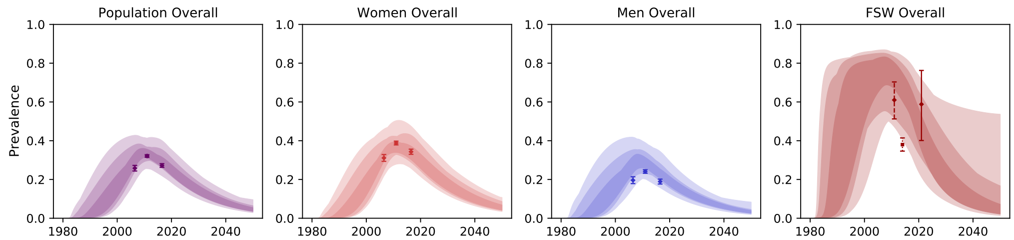


Figure A.2: HIV prevalence in the base case scenario and associated calibration targets

Three ribbons illustrate range of 100%, top 20%, and top 4% of model fits by likelihood for all base case calibration targets; points and error bars illustrate the mean and 95% CI for each calibration target.

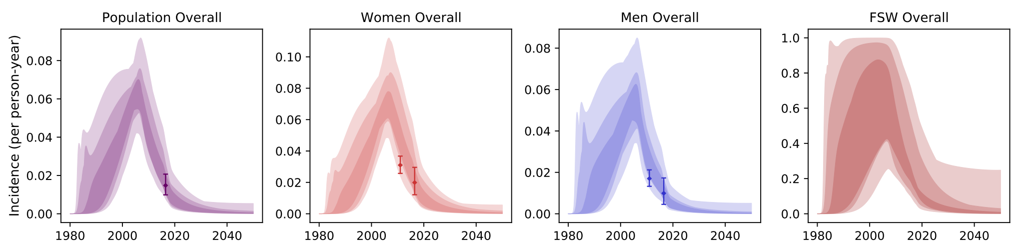


Figure A.3: HIV incidence in the base case scenario and associated calibration targets

Three ribbons illustrate range of 100%, top 20%, and top 4% of model fits by likelihood for all base case calibration targets; points and error bars illustrate the mean and 95% CI for each calibration target.

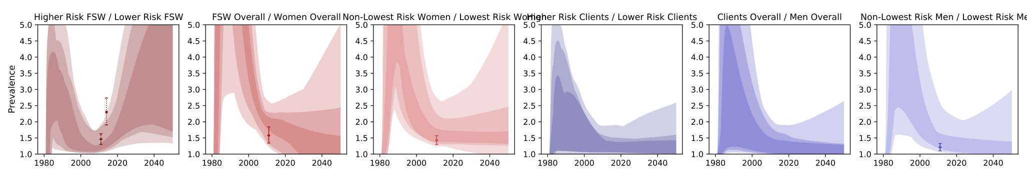
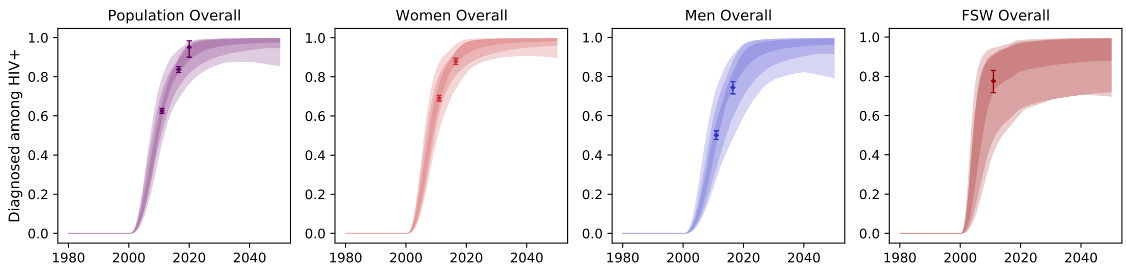
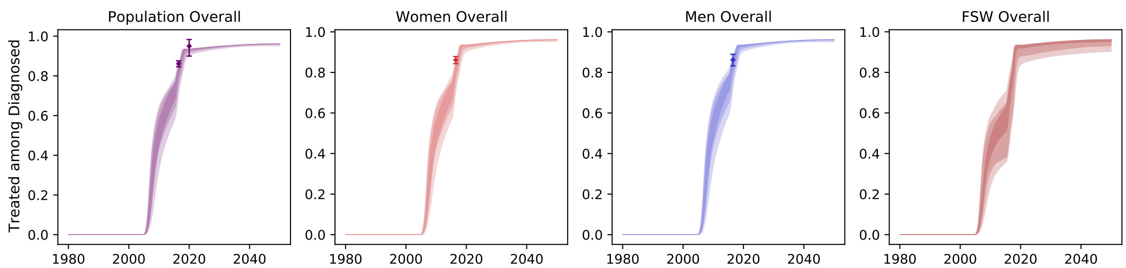


Figure A.4: HIV prevalence ratios in the base case scenario and associated calibration targets

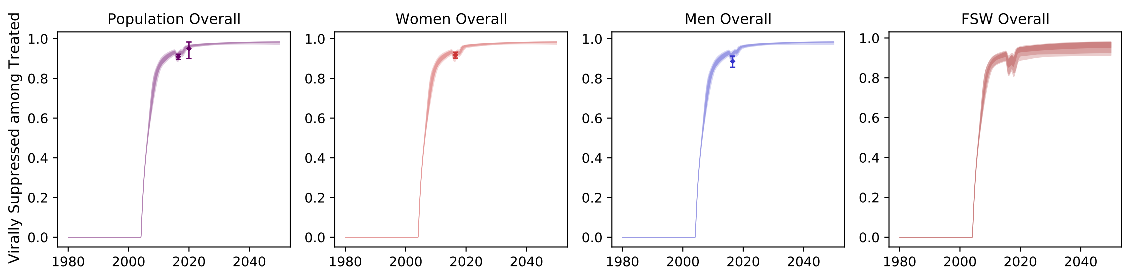
Three ribbons illustrate range of 100%, top 20%, and top 4% of model fits by likelihood for all base case calibration targets; points and error bars illustrate the mean and 95% CI for each calibration target.



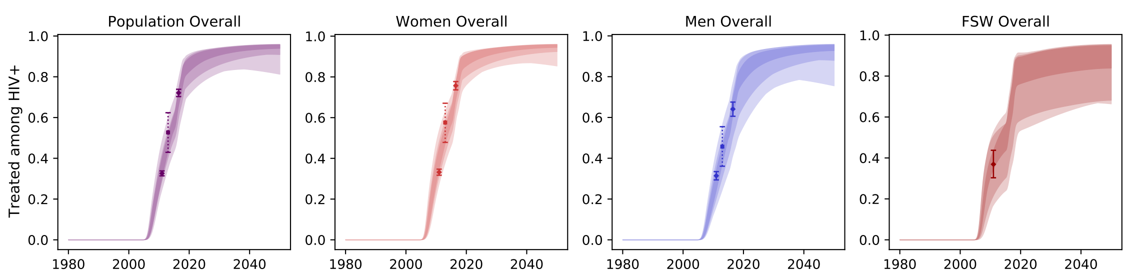
(a) % Diagnosed among HIV+



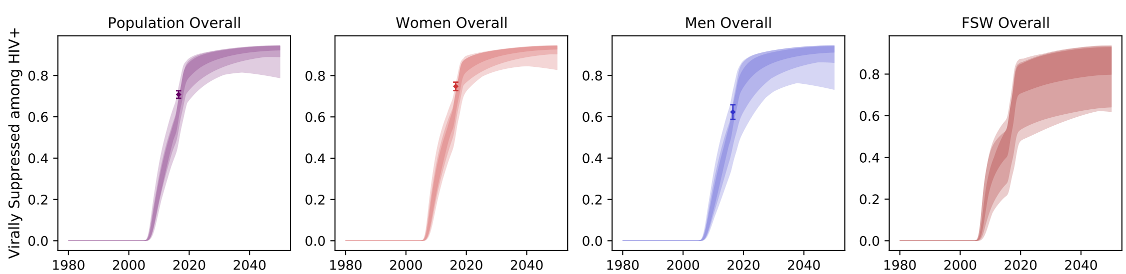
(b) % On ART among diagnosed



(c) % Virally suppressed among on ART



(d) % On ART among HIV+



(e) % Virally suppressed HIV+

Figure A.5: ART cascade in the base case scenario and associated calibration targets

Three ribbons illustrate range of 100%, top 20%, and top 4% of model fits by likelihood for all base case calibration targets; points and error bars illustrate the mean and 95% CI for each calibration target.

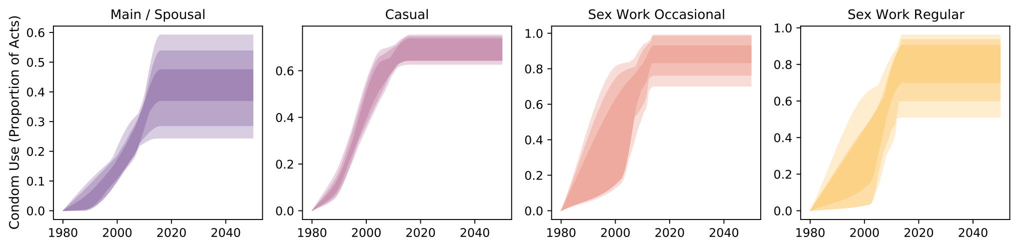


Figure A.6: Condom use by partnership type in the base case scenario and associated calibration targets

Three ribbons illustrate range of 100%, top 20%, and top 4% of model fits by likelihood for all base case calibration targets

B Supplemental Results

B.1 Base Case

B.1.1 Distribution of Infections

The following figures explore the numbers and proportions of infections transmitted between risk groups, stratified by partnership type throughout the epidemic. For each stratification (from, to, partnership type, and year), we use the median numbers of infections across all model fits. Figure B.1 illustrates infections transmitted via the modelled partnership types over time in the base case, while Figure B.2 illustrates the risk groups transmitting (a) and acquiring (b) infections. Figure B.3 illustrates the distribution of infections stratified by all three factors every 10 years using an alluvial diagram. Figure B.4 illustrates the ratio of infections transmitted from vs acquired among individuals in each risk group, which could be interpreted as a measure related to the group-specific reproductive number.

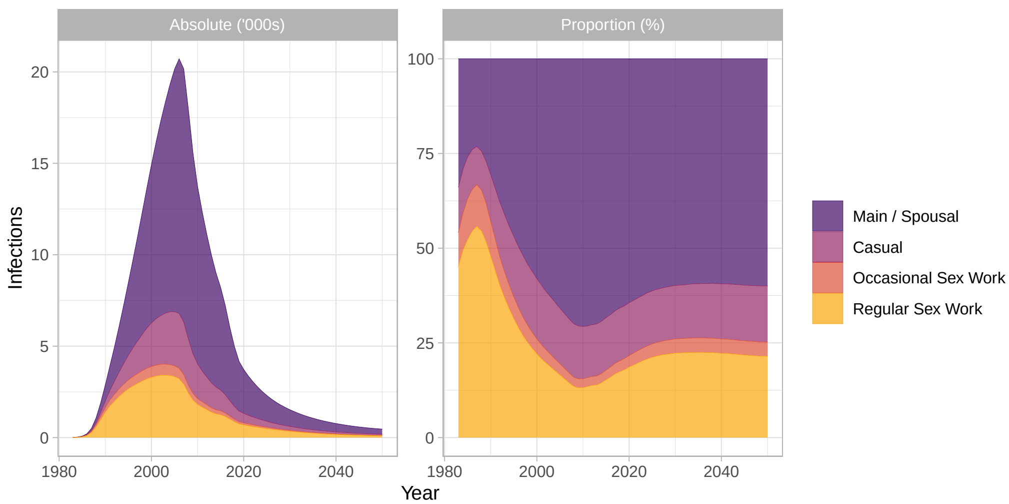
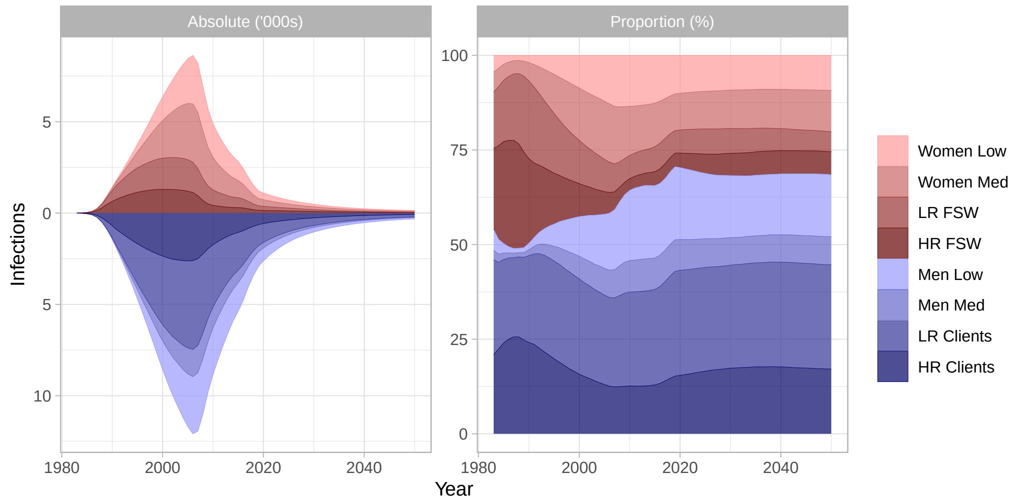
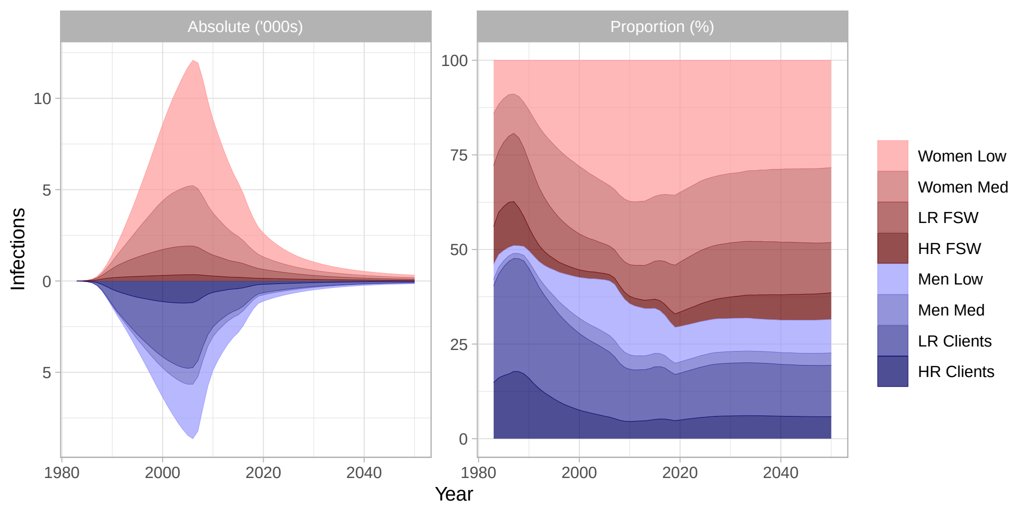


Figure B.1: Absolute numbers and proportions of infections transmitted via different modelled partnership types in the base case scenario

Median numbers of infections across all model fits are shown.



(a) Transmitted from



(b) Acquired among

Figure B.2: Absolute numbers and proportions of infections (a) transmitted from and (b) acquired among modelled risk groups in the base case scenario

Notation — Low/LR: lower risk; Med: medium risk; HR: higher risk; FSW: female sex workers; Clients: of FSW. Median numbers of infections across all model fits are shown.

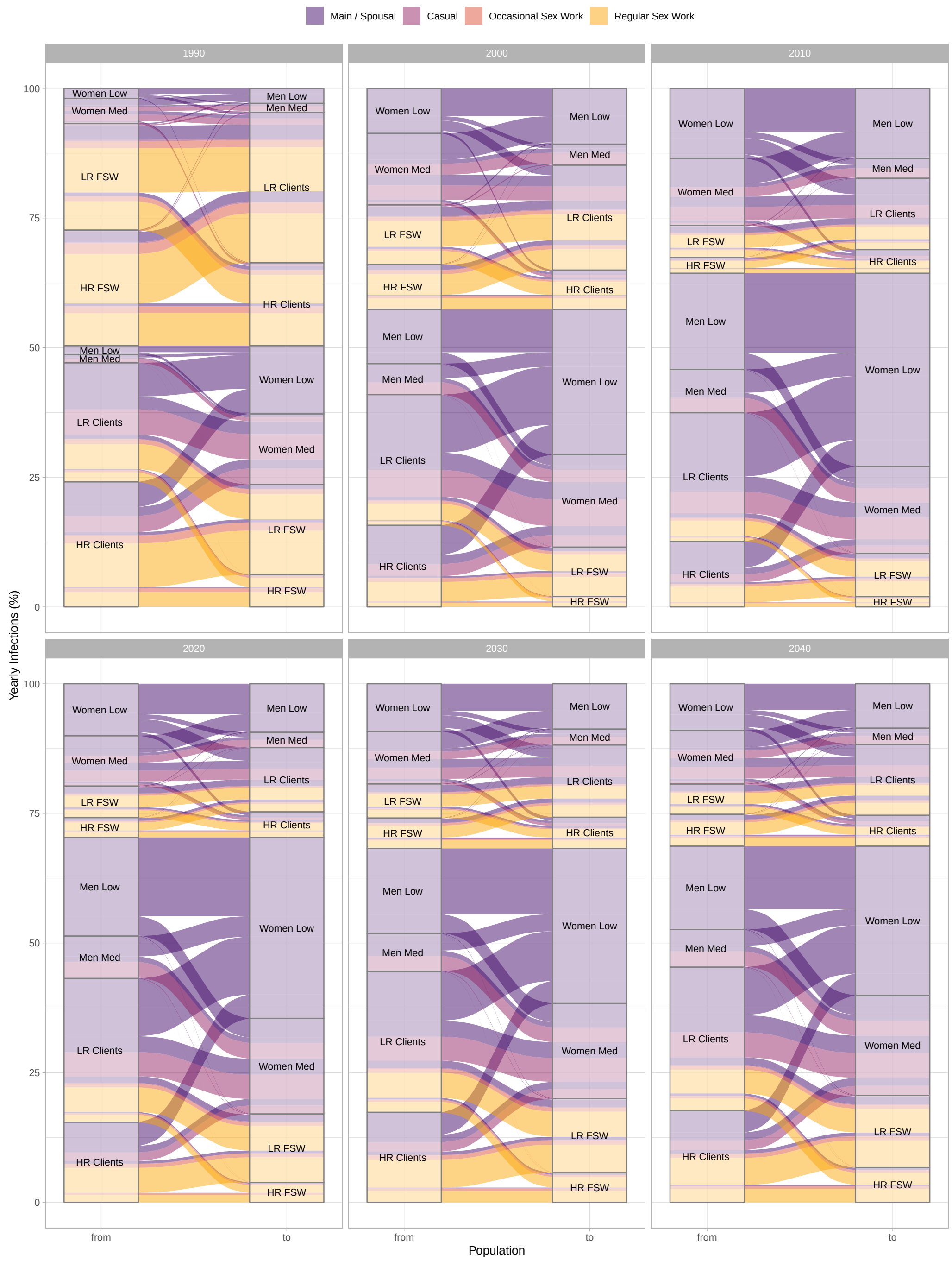


Figure B.3: Alluvial diagram showing proportions of all yearly infections (flows) transmitted from (left) to (right) modelled risk groups, stratified by partnership type (color) and year (facets), in the base case scenario

Median numbers of infections across all model fits are shown. An animated version of this figure is available online at `github.com/mishra-lab/hiv-fsw-art`

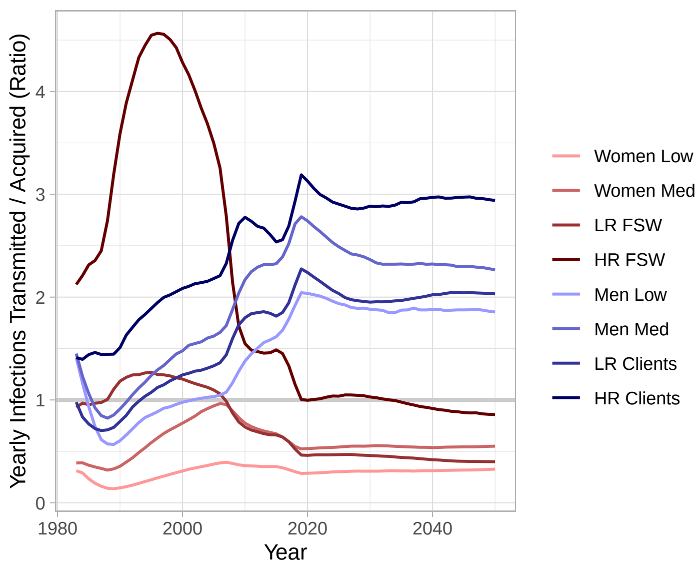


Figure B.4: Ratio of yearly infections transmitted from vs acquired among modelled risk groups in the base case scenario

Median numbers of infections across all model fits are shown.

B.2 Objective 1

B.2.1 Additional Incidence

Figure B.5 illustrates …

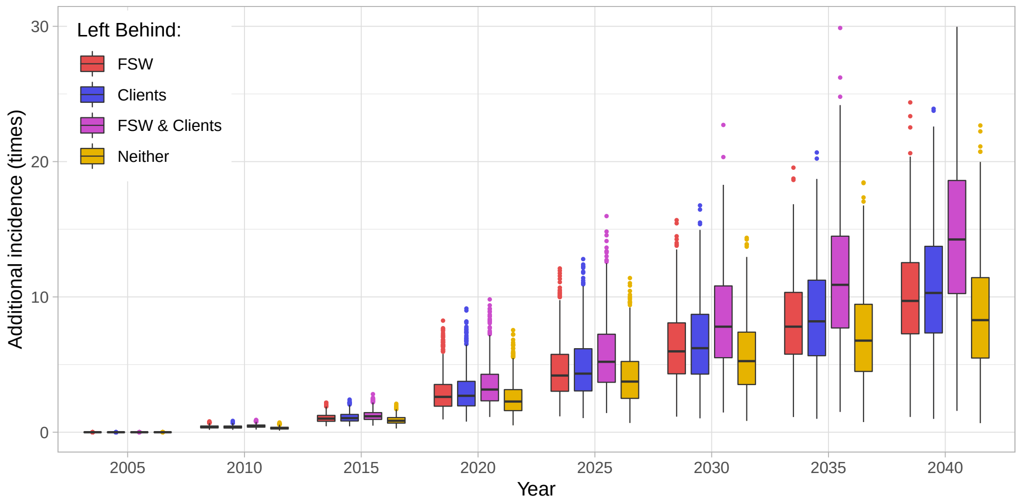
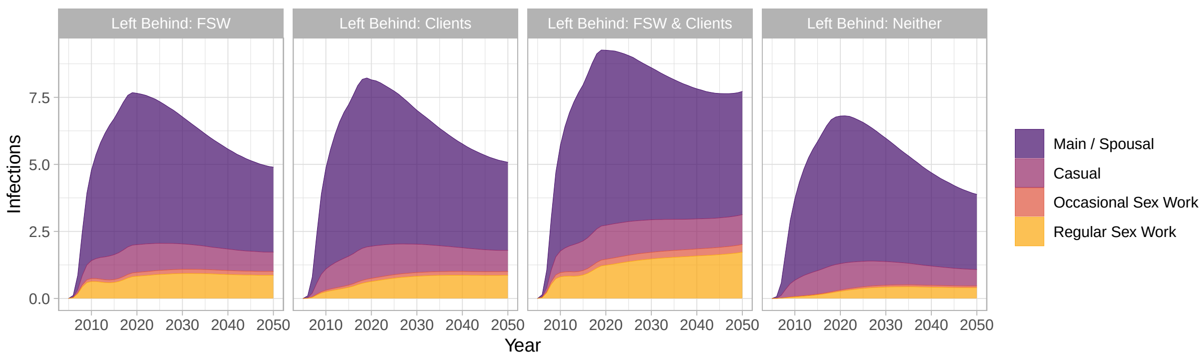


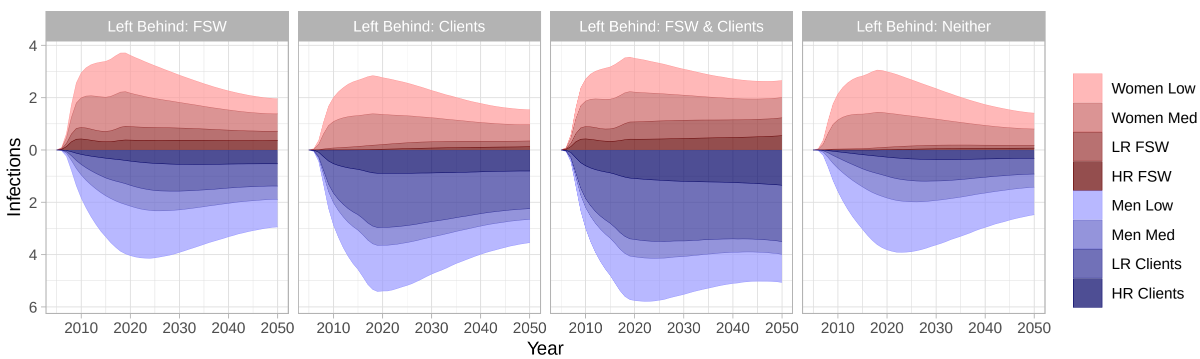
Figure B.5: Additional HIV incidence (times) in counterfactual scenarios (60-80-80 overall by 2020) vs the base case scenario (95-95-95 by 2020). Scenarios explore reduced cascades (40-60-80 by 2020) among FSW, clients of FSW, both, or neither as part of reduced cascade overall.

B.2.2 Distribution of Infections

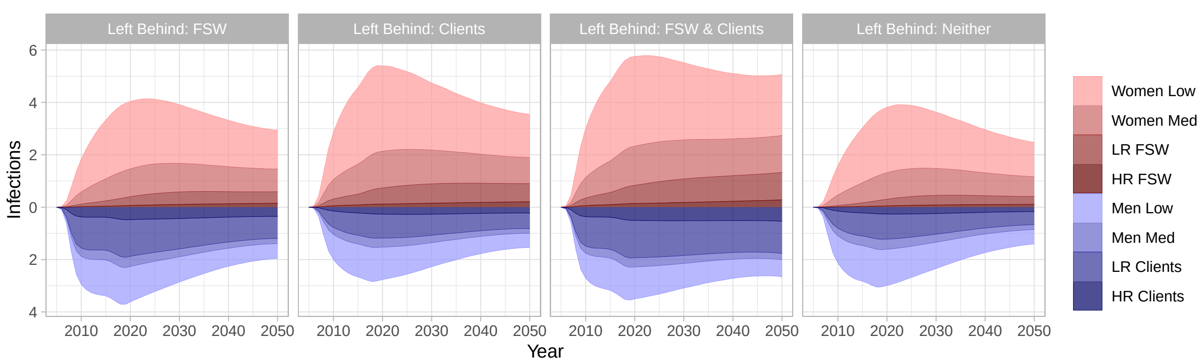
As in § B.1.1, Figure B.6 illustrates …



(a) Partnership type



(b) Transmitted from



(c) Acquired among

Figure B.6: Numbers of additional infections in each counterfactual scenario vs the base case, stratified by: (a) partnership type, (b) transmitting group, and (c) acquiring group

Notation — Low/LR: lower risk; Med: medium risk; HR: higher risk; FSW: female sex workers; Clients: of FSW. Median numbers of infections across all model fits are shown.

B.3 Objective 2

Figure B.7 illustrates the distribution of HIV treatment cascade attainment by 2020 in randomly sampled scenarios for Objective 2, stratified by sub-population. Median (95% CI) viral suppression (*VS*) among HIV+ were: 43 (15, 72)% among overall, 44 (13, 76)% among lower risk, 45 (18, 72)% among FSW, and 33 (9, 65)% among clients.

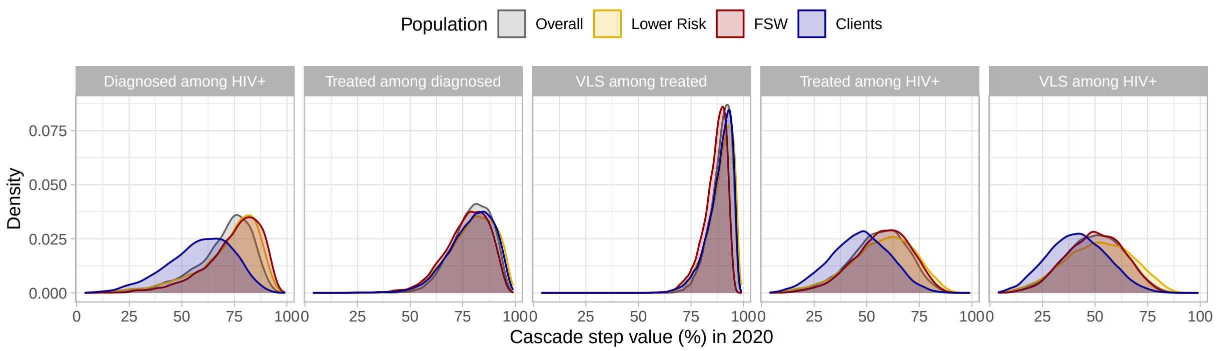


Figure B.7: Distribution of HIV treatment cascade attainment by 2020 in randomly sampled scenarios, stratified by sub-population

Figure B.8 expands on Figure 2 by illustrating effects over multiple time horizons (2020, 2030, 2040). Figure B.9 illustrates effects on additional incidence by 2040, rather than cumulative additional infections.

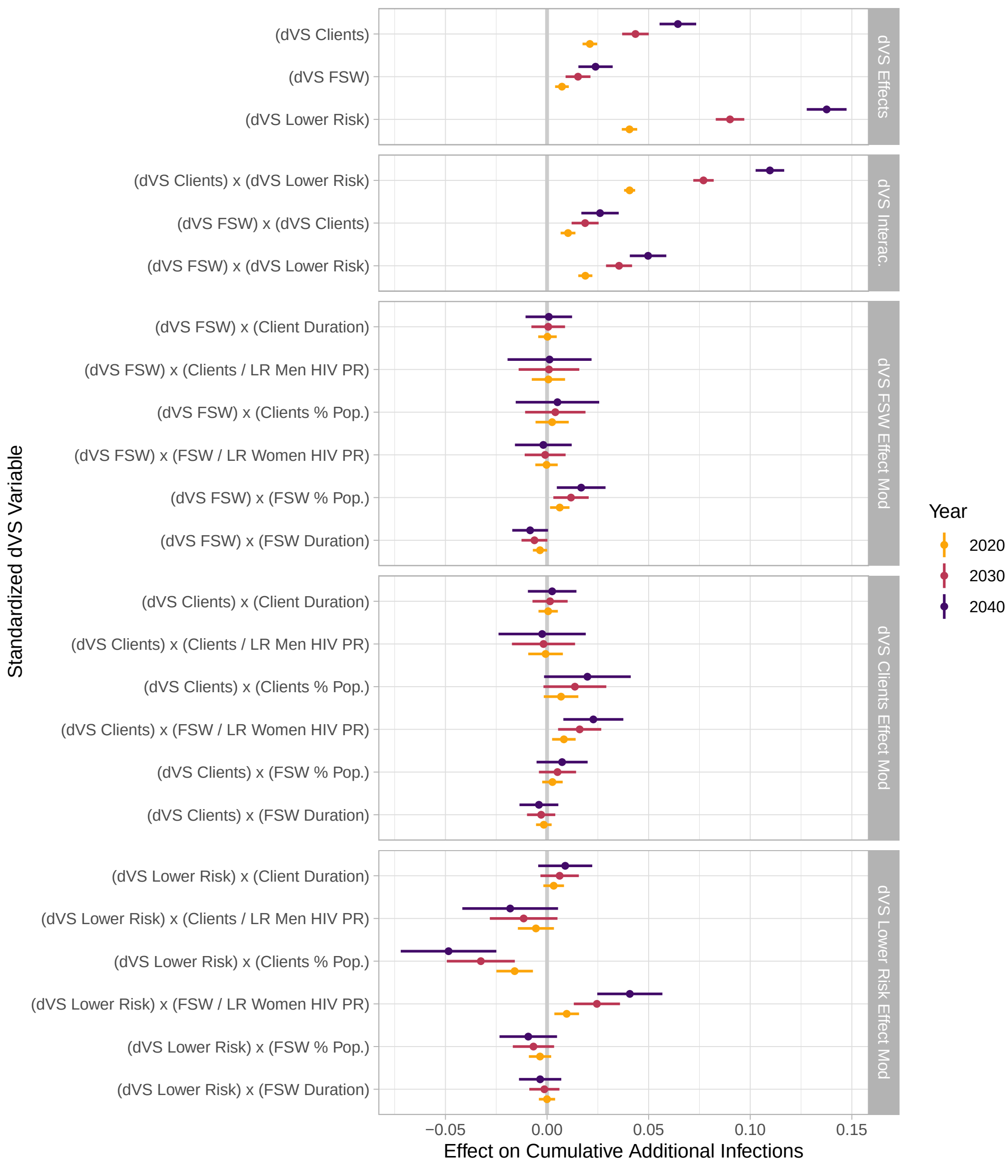


Figure B.8: Standardized effects of reduced viral suppression (dVS) among different populations on cumulative additional infections by 2020, 2030, and 2040, plus effect modification by epidemic conditions

dVS: absolute difference in viral suppression in each counterfactual scenario versus the base case; FSW: female sex workers; Clients: of FSW; LR: lower risk; Duration: average time spent in the risk group; % Pop: relative population size; HIV PR: HIV prevalence ratio. All model variables were standardized like $\hat{x}_k = (x_k - \mu_{x_k})/\sigma_{x_k}$ to reflect the relative influence of variables.

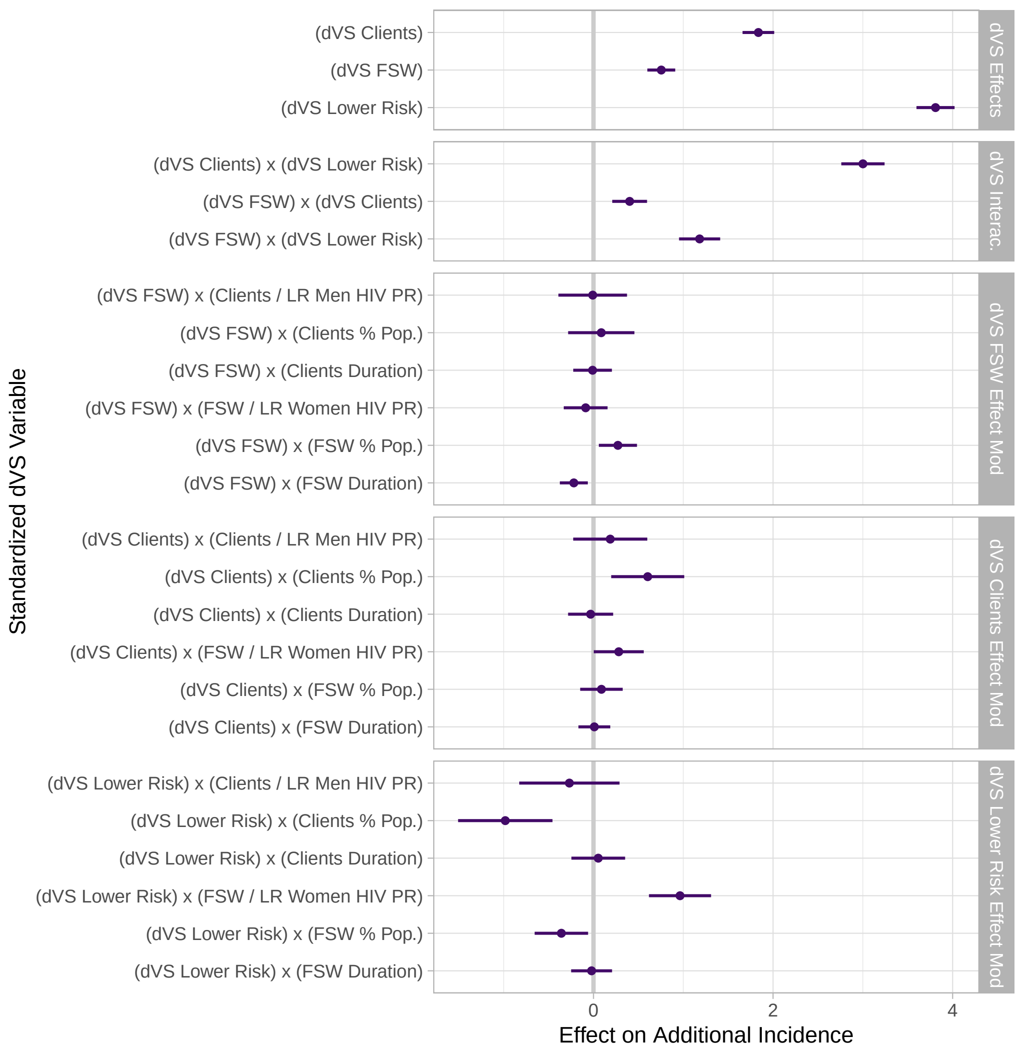


Figure B.9: Standardized effects of reduced viral suppression (dVS) among different populations on additional incidence by 2040, plus effect modification by epidemic conditions

dVS: absolute difference in viral suppression in each counterfactual scenario versus the base case; FSW: female sex workers; Clients: of FSW; LR: lower risk; Duration: average time spent in the risk group; % Pop: relative population size; HIV PR: HIV prevalence ratio. All model variables were standardized like $\hat{x}_k = (x_k - \mu_{x_k})/\sigma_{x_k}$ to reflect the relative influence of variables.