Title: Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review

Running Head: Heterogeneity in transmission models

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Date: May 25, 2021

Funding: The study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC CGS-D); Ontario Early Researcher Award No. ER17-13-043; and the Canadian Institutes of Health Research Foundation Grant (FN-13455).

Conflicts of Interest: None declared.

Words: 3589

RISK HETEROGENEITY IN COMPARTMENTAL HIV TRANSMISSION MODELS OF ART AS PREVENTION IN SUB-SAHARAN AFRICA: A SCOPING REVIEW

Abstract

Background. Transmission models provide complementary evidence to clinical trials about the potential population-level incidence reduction attributable to ART (ART prevention impact). Different modelling assumptions about risk heterogeneity may influence projected ART prevention impacts. We sought to review representations of risk heterogeneity in compartmental HIV transmission models applied to project ART prevention impacts in Sub-Saharan Africa. **Methods**. We systematically reviewed studies published before January 2020 that used non-linear compartmental models of sexual HIV transmission to simulate ART prevention impacts in Sub-Saharan Africa. We summarized data on model structure/assumptions (factors) related to risk and intervention heterogeneity, and explored multivariate ecological associations of ART prevention impact with modelled factors. **Results**. Of 1384 search hits, 94 studies were included, which primarily modelled medium/high prevalence epidemics in East/Southern Africa. 64 studies considered sexual activity stratification and 39 modelled at least one key population. 21 studies modelled faster/slower ART cascade transitions (HIV diagnosis, ART initiation, or cessation) by risk group, including 8 with faster and 4 with slower cascade transitions among key populations versus the wider population. In ecological analysis, activity stratification alone had minimal effect on projected ART prevention benefits, but turnover of higher risk groups, and ART cascade differences by sex both reduced projected benefits. **Conclusion**. Among compartmental transmission models applied to project ART prevention impacts in Sub-Saharan Africa, representations of risk heterogeneity and projected impacts varied considerably. Future work should explore how assumptions about turnover and cascade differences amongst risk groups may influence projected ART prevention impacts.

Words: 244

Keywords: HIV, Mathematical Model, Computer Simulation, Antiretroviral Therapy, Population Heterogeneity, Risk Factors, Healthcare Disparities

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 [1]. HIV treatment to reduce onward transmission remains a key element of combination HIV prevention [2]. Following empirical evidence of partnership-level efficacy of ART in preventing HIV transmission [3, 4, 5], and model-based evidence of "treatment as prevention" [6, 7, 8], several large-scale community-based trials of universal test-and-treat (UTT) were recently completed. These trials found that over 2-to-4 years, cumulative incidence under UTT did not significantly differ from cumulative incidence under ART according to national guidelines [9, 10, 11]. Thus the population-level reductions in incidence anticipated from transmission modelling were not observed in these trials [12, 13].

One theme in the proposed explanations for limited population-level ART prevention effectiveness was heterogeneity in intervention coverage and its intersection with heterogeneity in transmission risks [14, 12]. While viral suppression improved under UTT in all three trials, 21–54% of study participants remained unsuppressed [11, 9, 10]. Populations experiencing barriers to viral suppression under UTT may be at highest risk for acquisition and onward transmission, including key populations like sex workers and men who have sex with men [15, 16]. Other sub-populations, including youth and heterosexual men, also experience barriers to engagement in ART care [17, 18] that could undermine treatment as prevention. While widespread UTT scale-up may fill some coverage gaps, equitable access to ART for all populations remains an open challenge.

Risk heterogeneity, defined by various factors affecting acquisition and onward transmission risk, is a well-established determinant of epidemic persistence and controllability with a basis in the modelling literature [19, 20]. Model comparison studies by Hontelez et al. [21] and Rozhnova et al. [22] found that projected prevention impacts of ART scale-up were smaller with greater heterogeneity. Given the upstream and complementary role of transmission modelling in estimating the prevention impacts of ART [7, 23], 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 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 for all?

2 Methods

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

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 [24]
- **Behaviour Change Effects**: differential transmission risk due to behavioural changes related to engagement in the ART cascade [25, 26]
- **Network Effects**: differential transmission risk within sub-populations that increases the challenge of epidemic control through core group dynamics [20, 27, 28]
- **Coverage Effects**: differential transmission risk within sub-populations who experience barriers to ART care and achieving viral suppression, such as youth and key populations [29, 30, 15, 17]

We then compiled a list of key factors of risk heterogeneity, and their possible mechanisms of influence on ART prevention impact (Table 1).

2.2 Search

We searched MEDLINE and EMBASE via Ovid using search terms related to Sub-Saharan Africa (SSA), HIV, and transmission modelling (Table A.1). Search results were de-duplicated and screened by title and abstract in Covidence [41], followed by full-text screening using the criteria below. One reviewer (JK) conducted the search, screening, and data extraction.

Table 1: Factors of heterogeneity in HIV transmission and their possible mechanisms of influence on the prevention impact of ART interventions

Factor	MP [a]	Definition	Possible mechanism(s) of influence on ART prevention impact
Acute Infection	β_i	Increased infectiousness immediately following infection [31, 32]	**Biological**: transmissions during acute infection are unlikely to be prevented by ART
Late-Stage Infection	β_i	Increased infectiousness during late-stage infection [31, 32]	**Biological**: transmissions during late-stage are more likely to be prevented by ART
Drug Resistance	β_i	Transmitted factor that requires regimen switch to achieve viral suppression [33]	**Biological**: transmissions during longer delay to achieving viral suppression will not be prevented by ART
HIV Morbidity	c; η	Reduced sexual activity during late-stage disease [34, 35]	**Behaviour Change**: reduced morbidity via ART could increase HIV prevalence among the sexually active population
HIV Counselling	c; η; κ	Reduced sexual activity and/or increased condom use after HIV diagnosis [26]	**Behaviour Change**: increased HIV testing with ART scale up can contribute to prevention even before viral suppression is achieved
Activity Groups	c; κ	Any stratification by rate of partnership formation [36]	**Network**: higher transmission risk among higher activity
Age Groups	c; κ	Any stratification by age	**Network & Coverage**: higher transmission risk and barriers to viral suppression among youth [37, 17]
Key Populations	c; κ	Any epidemiologically defined higher risk groups [38]	**Network & Coverage** higher transmission risk and barriers to viral suppression among key populations [15]
Group Turnover	ϕ	Individuals move between activity groups and/or key populations reflecting sexual lifecourse [27]	**Network & Coverage**: counteract effect of stratification due to shorter periods in higher risk [39]; viral suppression may be achieved only after periods of higher risk
Assortative Mixing	m	Any degree of assortative mixing (like-with-like) by age, activity, and/or key populations	**Network**: assortative sexual networks compound effect of stratification [36]
Partnership Types	η; κ	Different partnership types are simulated, with different numbers of sex acts and/or condom usage [40]	**Network**: longer duration and lower condom use among main versus casual/sex work partnerships counteracts effect of stratification
ART Cascade Gaps	τ; α	Slower ART cascade transitions among higher activity groups or key populations [15, 17]	**Coverage**: ART prevention benefits may be allocated differentially among risk groups

[a] MP: Model Parameters — β_i, β_s: transmission probability per act (infectiousness, susceptibility); η: number of sex acts of each type per partnership; κ: proportion of sex acts unprotected by a condom; c: partnership formation rate; m: mixing matrix (probability of partnership formation); μ: mortality rate; ν: entry rate; ϕ: internal turnover between activity groups; τ: testing rate; α: ART initiation rate (and retention-related factors).

2.2.1 Inclusion/Exclusion Criteria

See Table A.2 for complete inclusion/exclusion criteria and definitions. We included peer-reviewed, primary modelling studies that used non-linear compartmental models of sexual HIV transmission to project the prevention impacts of ART in any setting within SSA. We included studies published in English anytime before Jan 1, 2020, that simulated at least one scenario with increasing ART coverage, possibly alongside other interventions. The included studies formed Dataset A, used to complete objectives 1 and 2. A subset of Dataset A formed Dataset B, used to complete objective 3. Studies in Dataset B met three additional criteria: 1) examined scale-up of ART coverage alone (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.

2.3 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.

2.3.1 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 [42, 40]. 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.

2.3.2 Factors of Risk Heterogeneity

For objective 2, we examined if/how the factors of risk heterogeneity outlined in Table 1 were simulated in each study. We examined the number of *risk groups* defined by sex 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, activity, key populations, and/or age), and if so, how they differed.

2.3.3 ART Prevention Impact

For objective 3, we extracted the following data for each intervention scenario within Dataset B: the years that ART scale-up started (t_o) 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_o.

For each factor of 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 [43] to control for clustering due to multiple estimates per study/scenario. Time since t_o was included as a covariate, and two variables were removed due to missingness. No variable selection was used to avoid biasing effect estimates [44]. We also plotted impacts versus time since t_o, stratified by factor levels.

3 Results

The search yielded 1384 publications, of which 94 studies were included (Figure 1). These studies (Dataset A, Appendix A.3) 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).

3.1 Epidemic Context

Table 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 C.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 C.2). No studies reported overall HIV prevalence of <1% at time of intervention, although for 30 studies, HIV prevalence was not reported or varied across simulated contexts/scenarios. The median [min, (IQR), max] year of intervention was 2014 [1990, (2010, 2015), 2040]; at which time HIV prevalence (%) was 15 [2, (6, 19), 32] (Figure C.2); and incidence (per 1000 person-years) was 14 [1, (9, 20), 50] (Figure C.3). Most reported incidence trends were decreasing or stable (45 of 48 reporting, Figure C.4).

3.1.1 Key Populations

Groups representing FSW were described 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. Activity groups representing men who have sex with men (MSM) were noted in 28 studies; transgender in 0; people who inject drugs (PWID) in 11; and prisoners in 2.

3.2 Heterogeneity Factors

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 C.5), and 2 studies represented HIV along a continuous dimension

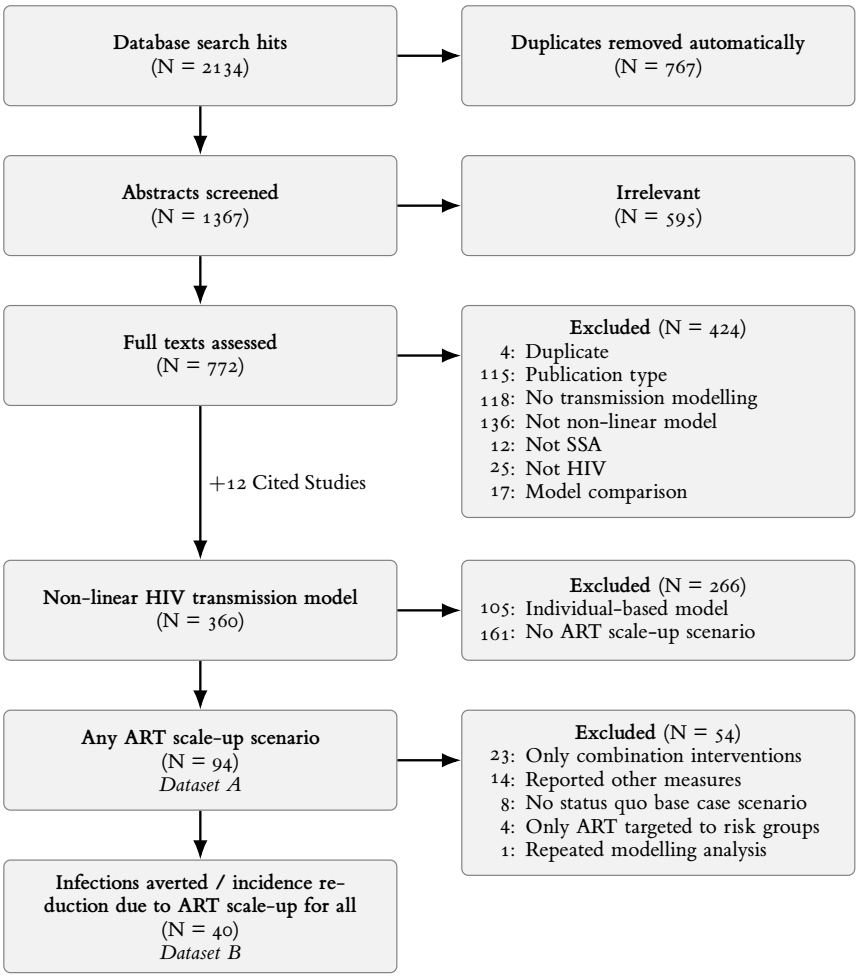

Figure 1: PRISMA flowchart of study identification

Table 2: Summary of epidemic contexts within Sub-Saharan Africa where the prevention impacts of ART have been modelled

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

Total studies: 94. FSW: female sex workers; Clients: clients of sex workers; MSM: men who have sex with men; PWID: people who inject drugs. [a] Does not sum to 94 as some studies modelled multiple countries. [b] Groups described as FSW, not considering the epidemiological definitions given in Appendix B.2.1. [c] Likewise for clients, and excluding studies where clients were modelled as a proportion of another risk group.

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 C.6), 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-naive; and 1 where such individuals transitioned back to a generic "off-treatment" state. Another 6 studies included a similar transition that was not identified as treatment failure versus ART cessation. Transmissible drug resistance was simulated in 9 studies.

3.2.2 Behavioural Effects

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

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

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

3.2.3 Network Effects

Populations were stratified by activity (different rates and/or types of partnerships formed) in 59 studies, and by sex in 64. The number of groups defined by sex and/or activity was 6 [1, (2, 9), 19] (Figure C.7); and by activity alone (maximum number of groups among: heterosexual women, heterosexual men, MSM, or overall if sex 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 C.9 and C.10).

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 C.8), 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.

3.2.4 Coverage Effects

Differential transition rates along the ART cascade were considered in 21 studies, including differences between sexes 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 sexes 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.

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 was reported in 24 (75); and 7 (11) reported both. Some scenarios included multiple time horizons.

Table 3 summarizes projected ART prevention impacts (IR, CIA), stratified by heterogeneity and contextual factors, plus adjusted effect estimates for each factor from multivariate analysis. Figures C.11–C.19 illustrate unadjusted impacts stratified by factor levels, while Figures C.20 and 2 (subset) illustrate effect estimates.

Table 3: Projected ART prevention impacts, stratified by factors of risk heterogeneity and contexts

		Incidence Reduction (%)					Cumulative Infections Averted (%)				
Factor	Level	N[a]	Median	(IQR)	Effect[b]	(95% CI)[b]	N[a]	Median	(IQR)	Effect[b]	(95% CI)[b]
Risk Stratif. & Cascade Diff.	None	98	19	(7, 44)	REF		45	29	(18, 47)	REF	
	Activity (No KP)	22	35	(22, 46)	4	(-14, 22)	39	6	(3, 22)	24	(12, 36)
	+ KP (Same)	5	41	(6, 50)	72	(-31, 175)	8	10	(3, 21)	20	(11, 28)
	+ KP (Priority)	1	85	(85, 85)	136	(73, 199)	23	21	(11, 41)	131	(97, 166)
Activity Turnover	No	117	26	(8, 45)	REF		87	20	(5, 35)	REF	
	Yes	9	22	(21, 50)	-82	(-153, -11)	28	18	(7, 38)	-86	(-103, -70)
Sex Stratif. & Cascade Diff.	No	97	21	(7, 44)	REF		39	29	(18, 44)	REF	
	Yes (Same)	22	41	(30, 53)	-4	(-32, 23)	48	8	(3, 24)	-49	(-62, -36)
	Yes (Men Low)	7	21	(2, 22)	5	(-41, 50)	28	16	(4, 35)	-125	(-143, -108)
Partnership Types	Generic	107	21	(8, 44)	REF		48	28	(15, 42)	REF	
	By Groups	16	33	(22, 52)	-22	(-53, 9)	66	11	(3, 28)	34	(20, 49)
	Overlapping	3	50	(45, 62)	8	(-52, 69)	1	58	(58, 58)	-9	(-60, 43)
Time Horizon (years)	0–10	36	17	(7, 35)	REF		40	14	(3, 26)	REF	
	11–20	63	20	(8, 42)	3	(-3, 9)	60	22	(8, 38)	9	(2, 17)
	21–30	15	47	(39, 65)	3	(-7, 13)	11	23	(7, 47)	12	(6, 19)
	31+	12	46	(24, 57)	12	(5, 20)	4	34	(29, 40)	5	(1, 8)
HIV Prevalence (%)	11+	112	22	(8, 44)	REF		75	18	(4, 35)	REF	
	1–10	14	43	(36, 49)	-9	(-49, 31)	39	26	(11, 36)	-9	(-20, 2)
	0–1	0	—	(—, —)			1	49	(49, 49)	-3	(-30, 24)
HIV Incidence Trend[c]	Increasing	2	40	(38, 43)			5	32	(29, 41)		
	Inc-to-stable	1	97	(97, 97)			1	68	(68, 68)		
	Stable	17	21	(20, 29)			24	4	(2, 7)		
	Dec-to-stable	81	15	(6, 43)			11	1	(-8, 28)		
	Decreasing	1	57	(57, 57)			13	29	(19, 38)		
RR Transmission on ART	0.0–0.039	11	22	(14, 35)	REF		44	6	(2, 27)	REF	
	0.04–0.099	42	49	(34, 67)	55	(22, 89)	60	27	(15, 38)	-41	(-54, -29)
	0.1+	73	12	(5, 30)	9	(-31, 48)	11	19	(1, 33)	-20	(-26, -13)
CD_4 Threshold for ART Initiation	Symptomatic	3	38	(37, 41)	47	(25, 68)	24	4	(2, 7)	-30	(-46, -15)
	200	3	28	(26, 32)	REF		4	28	(24, 30)	REF	
	350	10	29	(22, 38)	15	(3, 28)	18	18	(13, 27)	3	(-2, 7)
	500	15	29	(16, 43)	27	(8, 45)	13	29	(23, 35)	17	(10, 24)
	Any	41	56	(22, 75)	30	(14, 47)	22	51	(28, 62)	42	(37, 48)
	Mixed	54	10	(5, 31)	1	(-31, 32)	34	16	(5, 37)	63	(54, 72)
ART Coverage Target (%)[c]	0–59	3	28	(26, 31)			11	30	(13, 43)		
	60–84	13	29	(21, 41)			22	22	(8, 39)		
	85+	13	46	(36, 66)			21	36	(26, 43)		
Acute Infection	No	35	22	(10, 57)	REF		15	38	(24, 50)	REF	
	Yes	91	26	(9, 44)	52	(13, 91)	100	16	(5, 32)	51	(36, 66)
Late-Stage Infection	No	38	39	(13, 56)	REF		12	36	(20, 48)	REF	
	Yes	88	22	(8, 43)	-23	(-37, -8)	103	18	(5, 34)	-37	(-65, -9)
Trans. Drug Resist.	No	114	21	(7, 43)	REF		102	18	(5, 36)	REF	
	Yes	12	72	(39, 85)	-4	(-46, 39)	13	26	(20, 30)	-3	(-8, 3)
HIV Morbidity	No	102	21	(7, 45)	REF		73	27	(13, 42)	REF	
	Any	24	34	(22, 46)	35	(16, 54)	42	6	(3, 23)	-20	(-26, -14)
HTC Behav. Change	No	112	21	(7, 45)	REF		81	23	(11, 38)	REF	
	Any	14	41	(29, 49)	-39	(-73, -4)	34	6	(3, 22)	-13	(-18, -7)

[a] N: number of unique scenarios and time horizons; sums across factor levels may be less than 126 and 115 due to missing variables.
[b] Effect estimates from linear multivariate regression with generalized estimating equations [43]; effects are illustrated in Figure C.20.
[c] Omitted from regression model due to missing data. RR: relative risk; HTC: HIV testing and counselling; KP: key populations. priority: modelled ART cascade transitions were faster in KP vs overall due to prioritized programs; same: cascade transitions were assumed the same in KP as overall. Factor definitions are given in Appendix B.

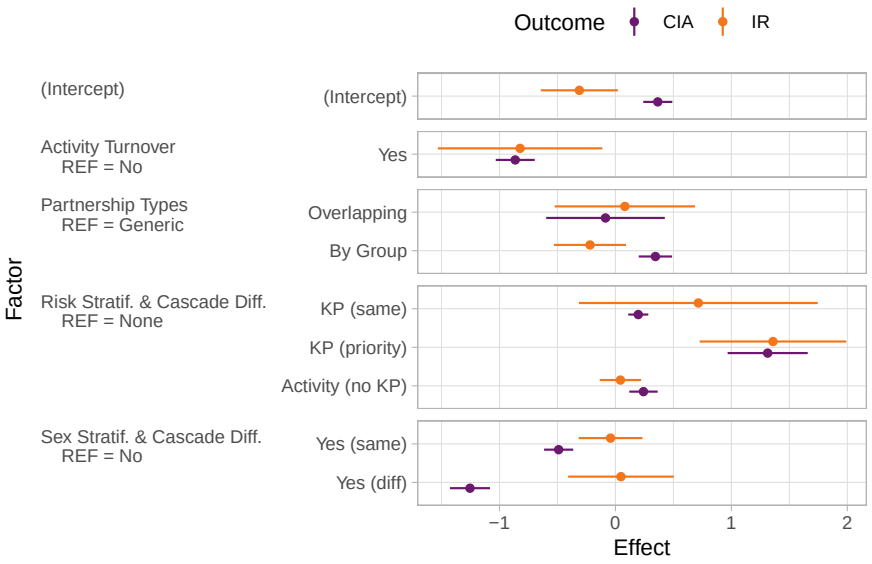

Figure 2: Effect estimates for selected factors of heterogeneity on incidence reduction (%, IR) and cumulative infections averted (%, CHI) from linear multivariate regression with generalized estimating equations.

Numerical results given in Table 3. 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; diff: cascade transitions were slower among men. Factor definitions are given in Appendix B.

Including activity groups without key populations slightly increased projected ART prevention impacts—adjusted effect (95% CI): 4 (-14, 22)% IR, 24 (12, 36)% CIA. Including key population(s) without prioritized ART cascade had a similar effect: 72 (-31, 175)% IR, 20 (11, 28)% CIA. However, including turnover of one or more higher risk group(s) reduced ART prevention impacts: -82 (-153, -11)% IR, -86 (-103, -70)% CIA, such that overall, including activity groups and/or key population(s) with turnover reduced ART prevention impacts.

Including ART cascade prioritized to any key population(s) increased the projected ART prevention impacts 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). Stratifying by sex, and considering lower ART cascade among men was estimated to reduce CIA: -49 (-62, -36)% and -125 (-143, -108)%, respectively; although similar effects were not observed for IR: -4 (-32, 23)% and 5 (-41, 50)%.

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 2/3 and 2/5 of studies to date, respectively; 1/3 considered risk group turnover and 1/4 considered differential ART cascade by any risk group. In multivariate ecological analysis, we found that projected incidence reductions and propoportions of infections averted were minimally affected by risk heterogeneity directly, but were reduced by risk group turnover and differential ART cascade.

Within-person variability in sexual risk has been illustrated among key populations, including MSM, FSW, and clients of FSW [45, 46, 47], as well as in the wider population [48]. This risk variability is often reflected in compartmental models as risk group turnover. Previous modelling suggested that turnover could make treatment as prevention *more* feasible [49]; however, the model in [49] 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 than without turnover, and the reproduction number may actually increase [39]. 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 [39]. The proportion of onward transmission prevented through ART may thus be reduced via turnover. Consistent inclusion of turnover in HIV transmission models would be supported by additional data on individual-level trajectories of sexual risk behaviour [27].

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

[30, 50, 51, 17]. These differences may stem from the unique needs of subpopulations and is one reason why differentiated ART services are a core component of HIV programs [52, 53]. Moreover, barriers to ART may intersect with transmission risk, particularly among key populations, due to issues of stigma, discrimination, and criminalization [54, 12]. 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 [55]. Depending on the research question, the modelled treatment cascade may need to include more cascade steps and states related to treatment failure/discontinuation.

Key populations often reflect intersections of risk heterogeneity, turnover, and cascade differences. For example, a sexual network comprising FSW with high turnover and FSW clients with low ART coverage could remain outside the reach of ART as prevention. Key populations continue to experience disproportionate risk of HIV, even in high-prevalence epidemics [56, 57], and models suggest that unmet needs of key populations play an important role in overall epidemic dynamics [58, 59]. Although recent and/or context-specific key populations data are often lacking [60], further opportunities exist to include key populations more consistenly in transmission models, and to improve modelling assumptions in the absence of such data. For example, 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 [27, 40]. Similarly, 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 [40]. Such modelling assumptions may influence the overall epidemic dynamics and the predicted ability of treatment to prevent population-level transmission.

Our scoping review has several limitations. First, we focused on classically defined key populations, although other priority groups like mobile populations and adolescent girls and young women will remain important for treatment as prevention [61, 62]. 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 structural risk factors like violence [63, 64]. Third, we did not extract data on model fitting, which could explain some counterintuitive effect estimates. For example, modelling increased infectiousness in late-stage HIV reduced ART prevention impacts. However, in most studies, newly ART-eligible patients via scale-up had earlier stage HIV; therefore, such patients would have lower modelled infectiousness than late-stage HIV, and lower infectiousness than in a model with uniform infectiousness fitted to the same

data. A similar mechanism could explain increased ART prevention impacts when including acute infection. Finally, the strength of our multivariate analysis was limited by the small number of studies/scenarios relative to the number of factors explored.

In conclusion, model-based evidence of ART prevention impacts could likely be improved by: 1) consistenly including risk group turnover, to reflect prevention challenges associated with the dynamic nature of sexual risk; 2) integrating emerging data on differences in ART cascade between sexual risk groups, to reflect services as delivered on the ground; and 3) routinely incorporating key populations, to reflect intersections of transmission risk and barriers to care that may undermine treatment as prevention. Model comparison studies like [28, 21] that explore the influence of these factors in detail would also be welcome.

Conflicts of Interest

None declared.

Funding

The study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC CGS-D); Ontario Early Researcher Award No. ER17-13-043; and the Canadian Institutes of Health Research Foundation Grant (FN-13455).

Acknowledgements

We thank: Kristy Yiu (Unity Health Toronto) for research coordination support; Linwei Wang (Unity Health Toronto) for feedback on elements of the paper; and Kaitlin Fuller (University of Toronto) for her help designing the search strategy.

Contributions

JK and SM conceptualized and designed the study, and developed the search strategy. JK performed the search, extracted the data, conducted the analysis, and generated the results. JK and SM drafted the manuscript and appendix. All authors (JK, RK, and SM) reviewed the results and contributed to writing the manuscript.

References

[1] UNAIDS. *AIDSinfo*. 2020.

[2] WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. 2016.

[3] J. D. Lundgren, A. G. Babiker, F. Gordin, et al. "How achievable is immediate ART for all?" In: *The Lancet HIV* 2.9 (Aug. 2015), pp. 795–807.

[4] The TEMPRANO ANRS 12136 Study Group. "A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa". In: *New England Journal of Medicine* 373.9 (Aug. 2015), pp. 808–822.

[5] M. S. Cohen, Y. Q. Chen, M. McCauley, et al. "Antiretroviral Therapy for the Prevention of HIV-1 Transmission". In: *New England Journal of Medicine* 375.9 (Sept. 2016), pp. 830–839.

[6] R. M. Granich, C. F. Gilks, C. Dye, et al. "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model". In: *The Lancet* 373.9657 (2009), pp. 48–57.

[7] J. W. Eaton, L. F. Johnson, J. A. Salomon, et al. "HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa". In: *PLoS Medicine* 9.7 (July 2012), e1001245.

[8] A. Cori, H. Ayles, N. Beyers, 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". In: *PLoS ONE* 9.1 (2014), e84511.

[9] D. V. Havlir, L. B. Balzer, E. D. Charlebois, et al. "HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa". In: *New England Journal of Medicine* 381.3 (July 2019), pp. 219–229.

[10] R. J. Hayes, D. Donnell, S. Floyd, et al. "Effect of universal testing and treatment on HIV incidence - HPTN 071 (popart)". In: *New England Journal of Medicine* 381.3 (July 2019), pp. 207–218.

[11] C. C. Iwuji, J. Orne-Gliemann, J. Larmarange, et al. "Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial". In: *The Lancet HIV* 5.3 (Mar. 2018), e116–e125.

[12] S. Baral, A. Rao, P. Sullivan, et al. "The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment". In: *The Lancet HIV* 6 (July 2019), e632–638.

[13] D. Havlir, S. Lockman, H. Ayles, et al. "What do the Universal Test and Treat trials tell us about the path to HIV epidemic control?" In: *Journal of the International AIDS Society* 23.2 (Feb. 2020), e25455.

[14] S. S. Abdool Karim. "HIV-1 Epidemic Control – Insights from Test-and-Treat Trials". In: *New England Journal of Medicine* 381.3 (July 2019), pp. 286–288.

[15] A. J. Hakim, V. MacDonald, W. Hladik, et al. "Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response". In: *Journal of the International AIDS Society* 21 (July 2018), e25119.

[16] D. Nyato, S. Nnko, A. Komba, 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". In: *PLoS ONE* 14.11 (Nov. 2019), e0219032.

[17] D. Green, D. M. Tordoff, B. Kharono, 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". In: *Journal of the International AIDS Society* 23.3 (Mar. 2020).

[18] C. Quinn, D. T. Kadengye, C. C. Johnson, et al. "Who are the missing men? Characterising men who never tested for HIV from population-based surveys in six sub-Saharan African countries". In: *Journal of the International AIDS Society* 22.10 (2019), e25398.

[19] R. M. Anderson, G. F. Medley, R. M. May, et al. "A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS". In: *Mathematical Medicine and Biology* 3.4 (1986), pp. 229–263.

[20] M.-C. Boily and B. Masse. "Mathematical models of disease transmission: A precious tool for the study of sexually transmitted diseases". In: *Canadian Journal of Public Health* 88.4 (1997), pp. 255–265.

[21] J. A. C. C. Hontelez, M. N. Lurie, T. Barnighausen, et al. "Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study". In: *PLoS Medicine* 10.10 (Oct. 2013), e1001534.

[22] G. Rozhnova, M. F. S. van der Loeff, J. C. M. Heijne, et al. "Impact of Heterogeneity in Sexual Behavior on Effectiveness in Reducing HIV Transmission with Test-and-Treat Strategy". In: *PLoS Computational Biology* 12.8 (2016), e1005012.

[23] W. Delva, D. P. Wilson, L. Abu-Raddad, et al. "HIV treatment as prevention: Principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation". In: *PLoS Medicine* 9.7 (July 2012), e1001239.

[24] C. D. Pilcher, H. C. Tien, J. J. Eron, et al. "Brief but efficient: Acute HIV infection and the sexual transmission of HIV". In: *Journal of Infectious Diseases* 189.10 (May 2004), pp. 1785–1792.

[25] S. Ramachandran, S. Mishra, N. Condie, et al. "How do HIV-negative individuals in sub-Saharan Africa change their sexual risk behaviour upon learning their serostatus? A systematic review". In: *Sexually Transmitted Infections* 92.8 (Dec. 2016), pp. 571–578.

[26] R. Tiwari, J. Wang, H. Han, et al. "Sexual behaviour change following HIV testing services: a systematic review and meta-analysis". In: *Journal of the International AIDS Society* 23.11 (Nov. 2020).

[27] C. Watts, C. Zimmerman, A. M. Foss, et al. "Remodelling core group theory: the role of sustaining populations in HIV transmission". In: *Sexually Transmitted Infections* 86.S3 (Dec. 2010), pp. iii85–iii92.

[28] P. J. Dodd, G. P. Garnett, and T. B. Hallett. "Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings". In: *AIDS* 24.5 (Mar. 2010), pp. 729–735.

[29] E. Mountain, S. Mishra, P. Vickerman, et al. "Antiretroviral therapy uptake, attrition, adherence and outcomes among hiv-infected female sex workers: A systematic review and meta-analysis". In: *PLoS ONE* 9.9 (Sept. 2014), e105645.

[30] K. E. Lancaster, D. Cernigliaro, R. Zulliger, et al. "HIV care and treatment experiences among female sex workers living with HIV in sub-Saharan Africa: A systematic review". In: *African Journal of AIDS Research* 15.4 (Dec. 2016), pp. 377–386.

[31] T. D. Hollingsworth, R. M. Anderson, and C. Fraser. "HIV-1 transmission, by stage of infection". In: *Journal of Infectious Diseases* 198.5 (Sept. 2008), pp. 687–693.

[32] M.-C. Boily, R. F. Baggaley, L. Wang, et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". In: *The Lancet Infectious Diseases* 9.2 (Feb. 2009), pp. 118–129.

[33] R. de Waal, R. Lessells, A. Hauser, et al. "HIV drug resistance in sub-Saharan Africa: public health questions and the potential role of real-world data and mathematical modelling." In: *Journal of virus eradication* 4.S2 (Nov. 2018), pp. 55–58.

[34] L. Myer, R. J. Carter, M. Katyal, et al. "Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: A cohort study". In: *PLoS Medicine* 7.2 (Feb. 2010), e1000229.

[35] N. McGrath, L. Richter, and M. L. 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". In: *Journal of the International AIDS Society* 16.1 (Jan. 2013), p. 18048.

[36] R. M. Anderson, R. M. May, M.-C. Boily, et al. "The spread of HIV-1 in Africa: Sexual contact patterns and the predicted demographic impact of AIDS". In: *Nature* 352.6336 (1991), pp. 581–589.

[37] I. Birdthistle, C. Tanton, A. Tomita, 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". In: *The Lancet Global Health* 7.11 (Nov. 2019), e1521–e1540.

[38] WHO. *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. 2016.

[39] J. Knight, S. D. Baral, S. Schwartz, et al. "Contribution of high risk groups' unmet needs may be underestimated in epidemic models without risk turnover: A mechanistic modelling analysis". In: *Infectious Disease Modelling* 5 (Jan. 2020), pp. 549–562.

[40] F. Scorgie, M. F. Chersich, I. Ntaganira, et al. "Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review". In: *AIDS and Behavior* 16.4 (May 2012), pp. 920–933.

[41] Veritas Health Innovation. *Covidence systematic review software*. 2020.

[42] J. Vandepitte, R. Lyerla, G. Dallabetta, et al. "Estimates of the number of female sex workers in different regions of the world". In: *Sexually Transmitted Infections* 82.S3 (June 2006).

[43] U. Halekoh, S. Hojsgaard, and J. Yan. "The R package geepack for generalized estimating equations". In: *Journal of Statistical Software* 15.2 (2006), pp. 1–11.

[44] F. E. Harrell. *Regression Modelling Strategies*. New York: Springer, 2001.

[45] E. Fazito, P. Cuchi, M. Mahy, et al. "Analysis of duration of risk behaviour for key populations: a literature review." In: *Sexually Transmitted Infections* 88.S2 (2012), pp. i24–i32.

[46] E. O. Romero-Severson, S. J. Alam, E. M. Volz, et al. "Heterogeneity in Number and Type of Sexual Contacts in a Gay Urban Cohort". In: *Statistical Communications in Infectious Diseases* 4.1 (2012), p. 4.

[47] E. Roberts, H. Ma, P. Bhattacharjee, et al. "Low program access despite high burden of sexual, structural, and reproductive health vulnerabilities among young women who sell sex in Mombasa, Kenya". In: *BMC Public Health* 20.1 (May 2020).

[48] B. Houle, S. A. Mojola, N. Angotti, et al. "Sexual behavior and HIV risk across the life course in rural South Africa: Trends and comparisons". In: *AIDS Care* 30.11 (2018), pp. 1435–1443.

[49] C. J. Henry and J. S. Koopman. "Strong influence of behavioral dynamics on the ability of testing and treating HIV to stop transmission". In: *Scientific Reports* 5.1 (2015), p. 9467.

[50] J. Stannah, E. Dale, J. Elmes, 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". In: *The Lancet HIV* 6.11 (Nov. 2019), e769–e787.

[51] H. Ma, L. Wang, P. Gichangi, 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". In: *Journal of Acquired Immune Deficiency Syndromes* 84.5 (Aug. 2020), pp. 470–479.

[52] C. D. Chikwari, S. Dringus, and R. A. Ferrand. "Barriers to, and emerging strategies for, HIV testing among adolescents in sub-Saharan Africa". In: *Current Opinion in HIV and AIDS* 13.3 (May 2018), pp. 257–264.

[53] P. Ehrenkranz, A. Grimsrud, and M. Rabkin. "Differentiated service delivery: Navigating the path to scale". In: *Current Opinion in HIV and AIDS* 14.1 (Jan. 2019), pp. 60–65.

[54] K. F. Ortblad, J. M. Baeten, P. Cherutich, et al. "The arc of HIV epidemics in sub-Saharan Africa: New challenges with concentrating epidemics in the era of 90-90-90". In: *Current Opinion in HIV and AIDS* 14.5 (Sept. 2019), pp. 354–365.

[55] K. K. Case, G. B. Gomez, and T. 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". In: *Journal of the International AIDS Society* 22.9 (Sept. 2019).

[56] S. D. Baral, C. Beyrer, K. Muessig, et al. "Burden of HIV among female sex workers in low-income and middle-income countries: A systematic review and meta-analysis". In: *The Lancet Infectious Diseases* 12.7 (July 2012), pp. 538–549.

[57] C. Beyrer, S. D. Baral, F. van Griensven, et al. "Global epidemiology of HIV infection in men who have sex with men". In: *The Lancet* 380.9839 (July 2012), pp. 367–377.

[58] L.-G. Bekker, L. Johnson, F. Cowan, et al. "Combination HIV prevention for female sex workers: What is the evidence?" In: *The Lancet* 385.9962 (2015), pp. 72–87.

[59] J. Stone, C. Mukandavire, M.-C. Boily, et al. "Estimating the contribution of key populations towards HIV transmission in South Africa". In: *Journal of the International AIDS Society* 24.1 (Dec. 2021), e25650.

[60] A. Rao, S. Schwartz, K. Sabin, et al. "HIV-related data among key populations to inform evidence-based responses: Protocol of a systematic review 11 Medical and Health Sciences 1117 Public Health and Health Services". In: *Systematic Reviews* 7.1 (2018), pp. 1–7.

[61] F. Tanser, T. Barnighausen, A. Vandormael, et al. "HIV treatment cascade in migrants and mobile populations". In: *Current Opinion in HIV and AIDS* 10.6 (Nov. 2015), pp. 430–438.

[62] R. C. Dellar, S. Dlamini, and Q. A. Karim. "Adolescent girls and young women: Key populations for HIV epidemic control". In: *Journal of the International AIDS Society* 18.2 (2015), pp. 64–70.

[63] J. G. Silverman. "Adolescent female sex workers: Invisibility, violence and HIV". In: *Archives of Disease in Childhood* 96.5 (May 2011), pp. 478–481.

[64] R. F. Baggaley, D. Dimitrov, B. N. Owen, et al. "Heterosexual Anal Intercourse: A Neglected Risk Factor for HIV?" In: *American Journal of Reproductive Immunology* 69.S1 (Feb. 2013), pp. 95–105.

APPENDIX

Title: Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review

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A Search Strategy

We designed our search strategy with guidance from an information specialist at our affiliate library (KF).

A.1 Search Terms

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

Table A.1: 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.
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	3512	Angola/ OR Angola.mp.
G2	9273	Benin/ OR Benin.mp.
G3	5809	Botswana/ OR Botswana.mp.
G4	9983	Burkina Faso/ OR Burkina Faso.mp.
G5	2055	Burundi/ OR Burundi.mp.
G6	16,822	Cameroon/ OR Cameroon.mp.
G7	1196	Cape Verde/ OR Cape Verde.mp.
G8	15,416	Central African Republic/ OR Central African Republic.mp. OR CAR.ti.
G9	3075	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	1131	Equatorial Guinea/ OR Equatorial Guinea.mp.
G14	1437	Eritrea/ OR Eritrea.mp.
G15	35,959	Ethiopia/ OR Ethiopia.mp.
G16	4500	Gabon/ OR Gabon.mp.
G17	6626	Gambia/ OR Gambia.mp.
G18	25,213	Ghana/ OR Ghana.mp.
G19	360,920	Guinea/ OR Guinea.mp.
G20	2625	Guinea-Bissau/ OR Guinea-Bissau.mp.

continued …

… continued

	Term	Hits
G21	9730	Cote d'Ivoire/ OR Cote d'Ivoire.mp. OR Ivory Coast.mp.
G22	46,917	Kenya/ OR Kenya.mp.
G23	1649	Lesotho/ OR Lesotho.mp.
G24	4239	Liberia/ OR Liberia.mp.
G25	11,386	Madagascar/ OR Madagascar.mp.
G26	16,367	Malawi/ OR Malawi.mp.
G27	9111	Mali/ OR Mali.mp.
G28	1573	Mauritania/ OR Mauritania.mp.
G29	2373	Mauritius/ OR Mauritius.mp.
G30	8502	Mozambique/ OR Mozambique.mp.
G31	3818	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	1545	Reunion/
G36	7597	Rwanda/ OR Rwanda.mp.
G37	342	"Sao Tome and Principe"/ OR "Sao Tome and Principe".mp.
G38	16,674	Senegal/ OR Senegal.mp.
G39	1566	Seychelles/ OR Seychelles.mp.
G40	5456	Sierra Leone/ OR Sierra Leone.mp.
G41	4667	Somalia/ OR Somalia.mp.
G42	114,536	South Africa/ OR South Africa.mp.
G43	1193	South Sudan/ OR South Sudan.mp.
G44	21,680	Sudan/ OR Sudan.mp.
G45	2409	Swaziland/ OR Swaziland.mp. OR Eswatini/ OR Eswatini.mp.
G46	32,442	Tanzania/ OR Tanzania.mp.
G47	3749	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	2190	M8 AND H8 AND G52
X2	2160	X1 NOT animal/
X3	2155	limit X2 to english language
X4	2125	limit X3 to yr="1860 - 2019"
X5	1384	remove duplicates from X4

A.2 Inclusion/Exclusion Criteria

Table A.2: Criteria for inclusion and exclusion

Include	Exclude
Publication Type	
• English language • published before 2020 • peer-reviewed journal article	• non-English language • published in or after 2020 • non-peer-reviewed article • review article [1] • textbook, grey literature • opinions, comments, correspondence • conference abstracts and proceedings • model comparison study
Mathematical Modelling of HIV Transmission	
• sexual HIV transmission model • non-linear HIV transmission model [2] • population-level dynamics • compartmental model [3]	• no sexual HIV transmission modelled • HIV transmission model is linear • only within-host/cellular/protein modelling • individual-based model
Context & Objectives	
• any region in Sub-Saharan Africa (SSA) [4] • assess prevention impact of ART scale-up for all [5]	• only regions outside SSA modelled • only theoretical context modelled • only individual-level benefits of ART modelled • only prevention benefits of other interventions • no base-case scenario reflecting status quo [*] • only ART-combination interventions [*] • only ART intervention targeted to some risk groups [*] • only ART prevention impacts reported for some risk groups [*] • ART prevention impacts not reported [5*]

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

A.3 Included Studies

A.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 de Montigny et al.
[40] 2019 Hauser et al.

A.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 Definitions & Extraction

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

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

B.1 Epidemic Context

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

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

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

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

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

B.2 Risk Heterogeneity

B.2.1 Key Populations

Female Sex Workers: Any female activity group meeting 3 criteria: representing <5% of the female population; and being <1/3 × the size of client population or highest heterosexual male activity group; and having >50 × the partners of the lowest sexually active female activity group [95, 96, 97]. 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 × the size of the FSW population [96]. 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.

[1] WebPlotDigitizer: https://apps.automeris.io/wpd/

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 Activity Groups

Activity groups were defined as any stratification based on sex 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 heterosexual women, heterosexual men, 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.2.3 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.2.4 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.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.4 Antiretroviral Therapy

B.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.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-naive 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.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.5 ART Prevention Impact

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

B.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_o 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 $t_o = t_f$. Impact time horizons were measured relative to t_o.

B.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_o (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_o, 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_o (time horizon). For example, if the baseline and intervention scenarios predicted 1000 and 700 new infections 5 years after t_o, then the proportion of infections averted for the 5-year time horizon would be 30%.

C Supplemental Results

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

C.1 Map

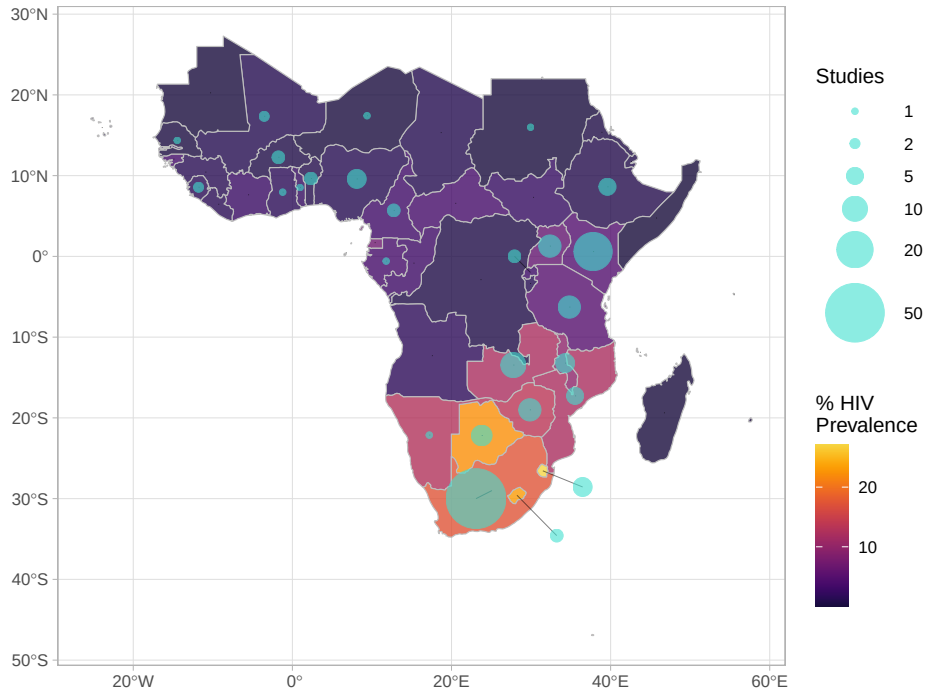

Figure C.1: Map showing number of studies (of 94 total) applying HIV transmission modelling in each country vs the number of people living with HIV (PLHIV, millions)

C.2 Risk Heterogeneity

C.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.

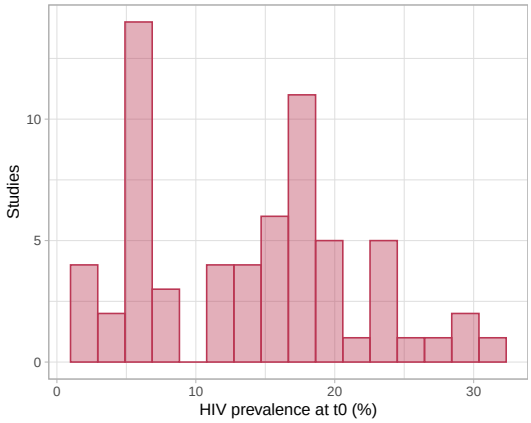

Figure C.2: HIV prevalence at t_0 (%)

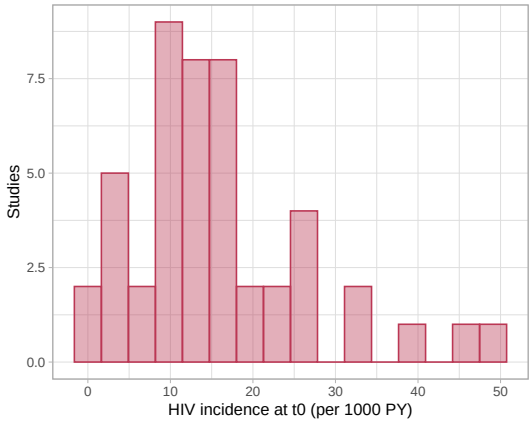

Figure C.3: HIV incidence at t_0 (per 1000 PY)

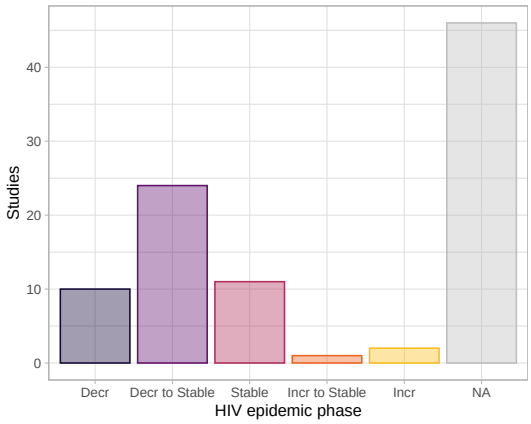

Figure C.4: HIV epidemic phase

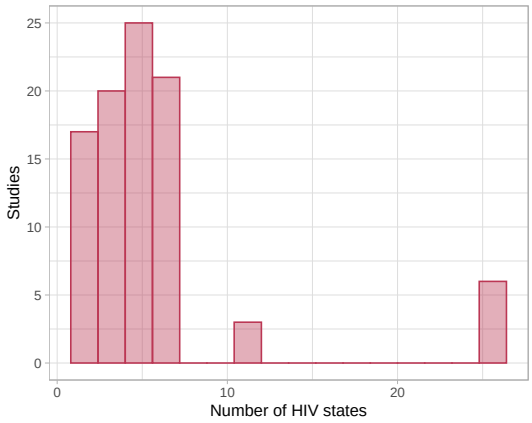

Figure C.5: Number of HIV states

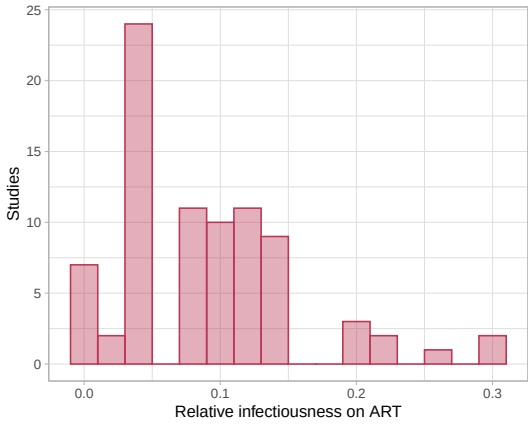

Figure C.6: Relative infectiousness on ART

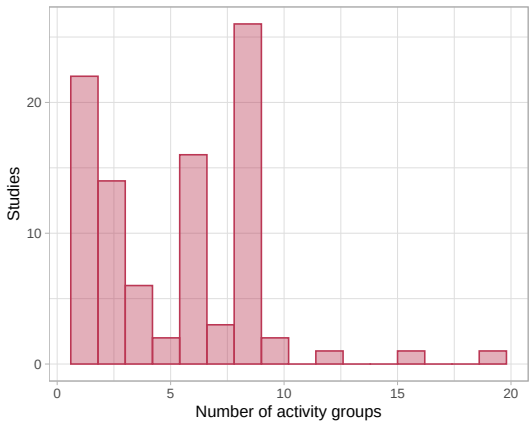

Figure C.7: Number of activity groups

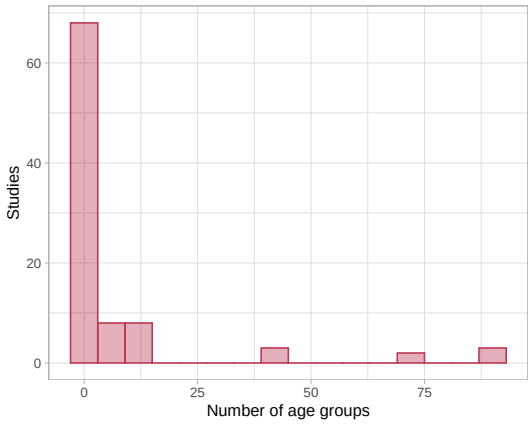

Figure C.8: Number of age groups

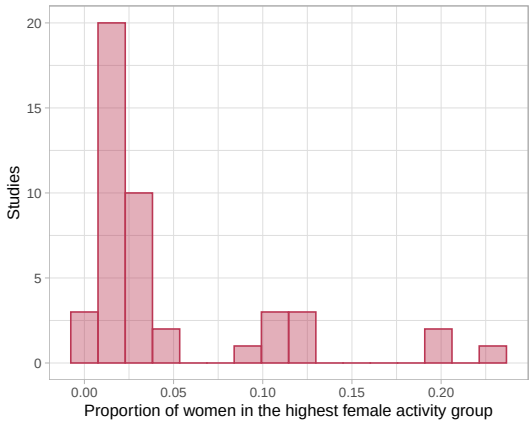

Figure C.9: Proportion of women in the highest female activity group

Figure C.10: Proportion of men in the client or highest activity male group

C.3 ART Prevention Impact

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

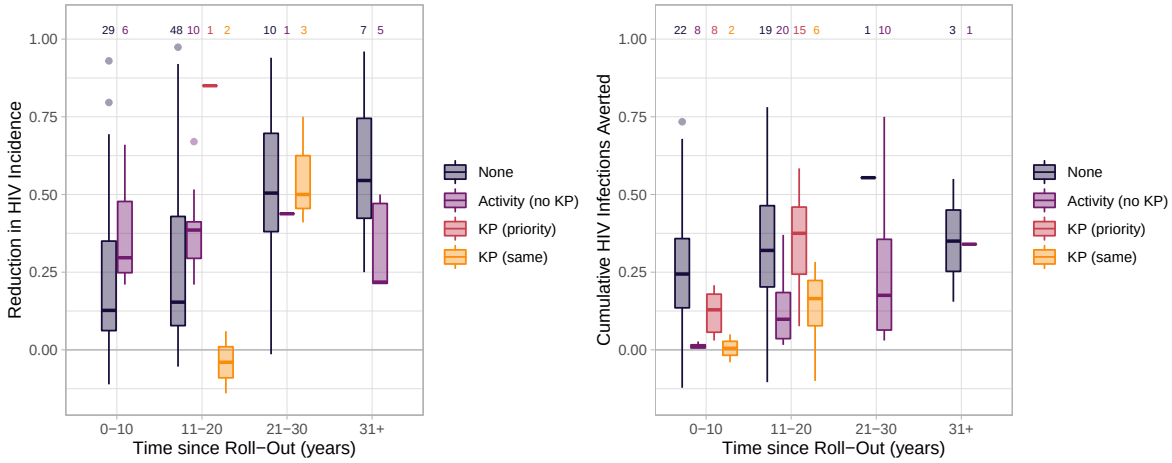

Figure C.11: Risk Stratification & ART cascade differences

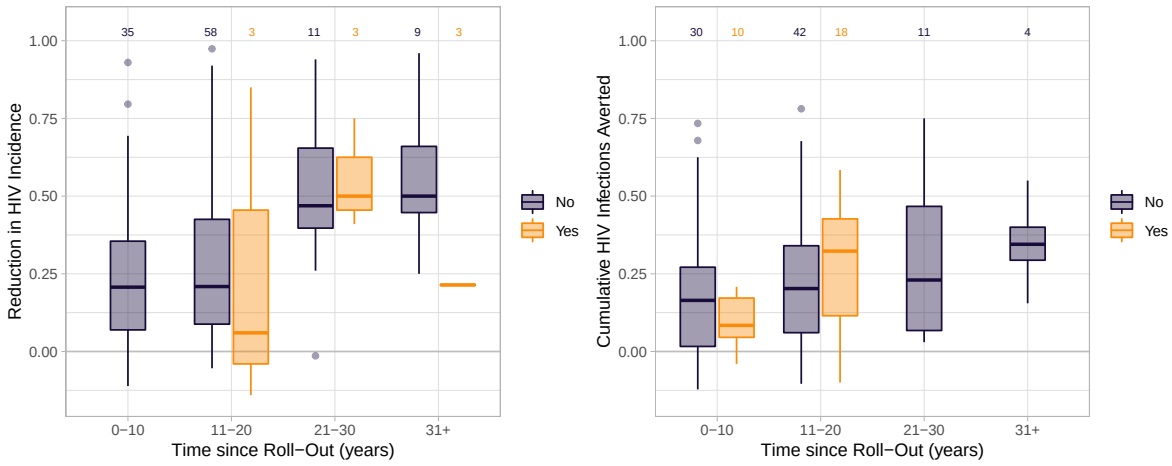

Figure C.12: Any activity group turnover

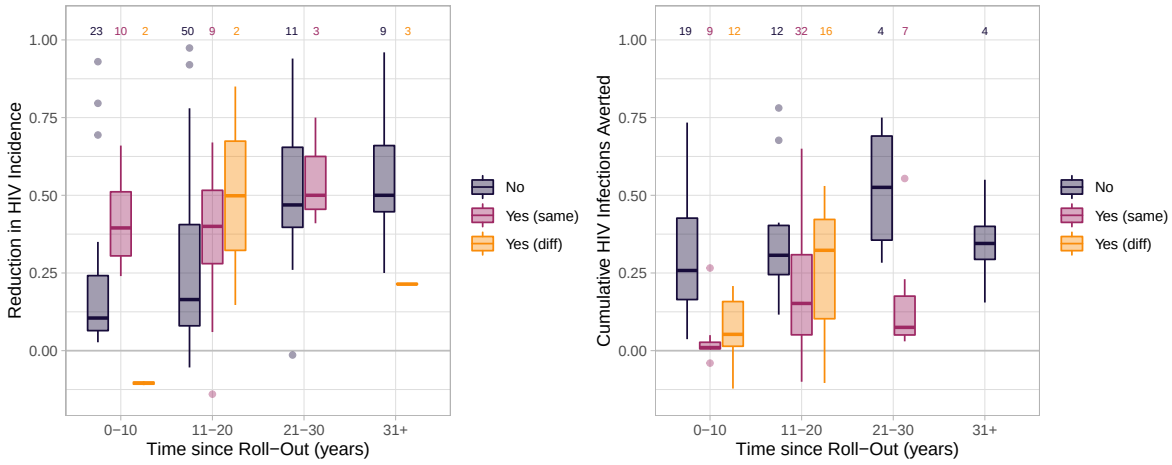

Figure C.13: Sex stratification & any ART cascade differences

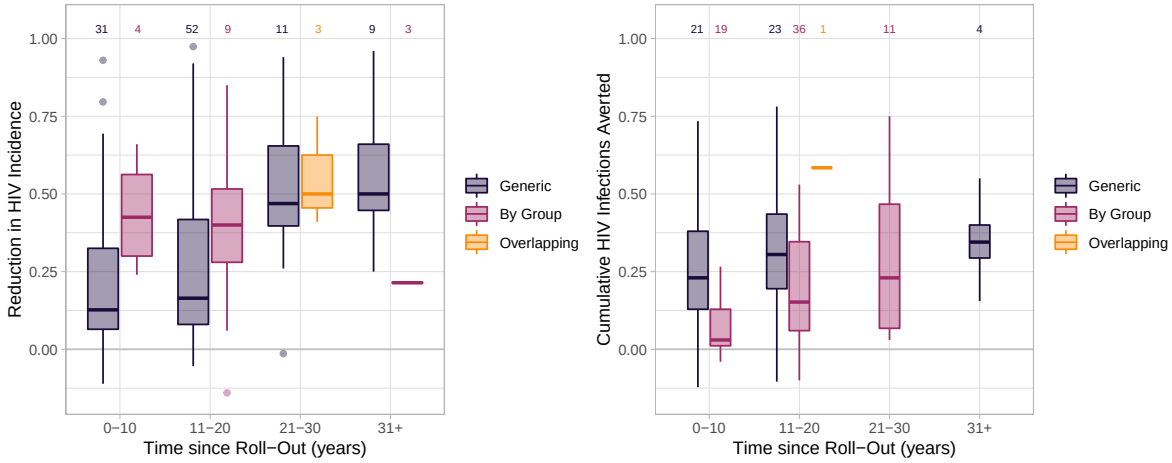

Figure C.14: Type of partnership definition

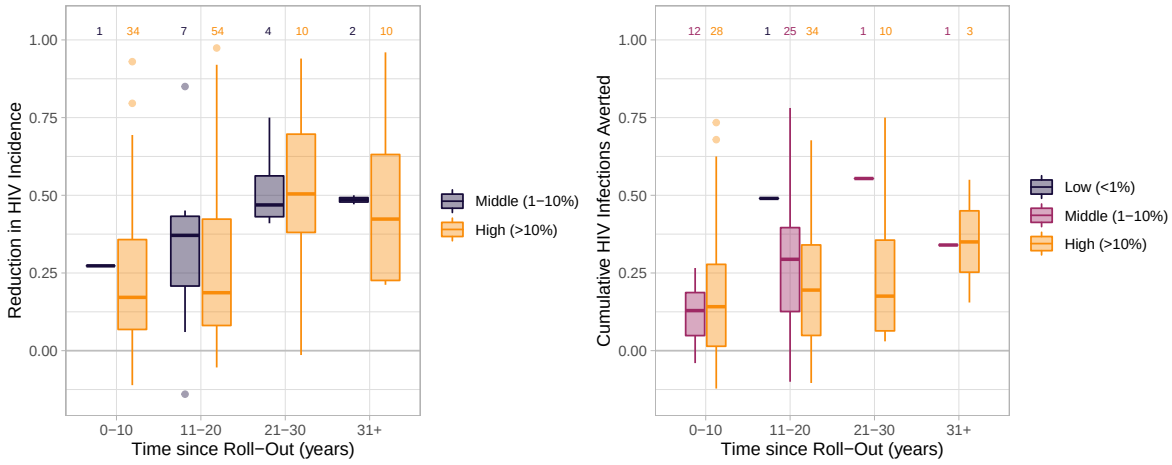

Figure C.15: HIV prevalence at t_0 (%)

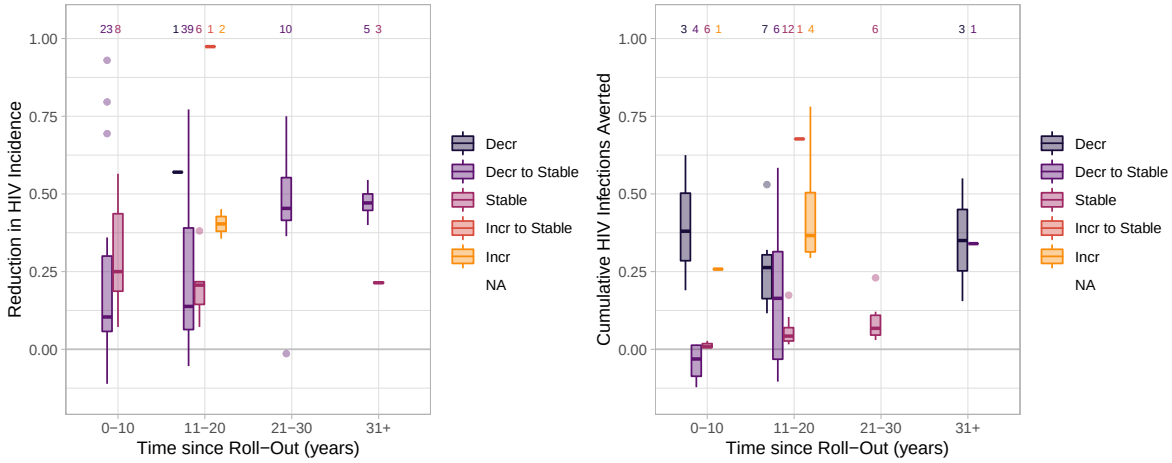

Figure C.16: HIV epidemic phase

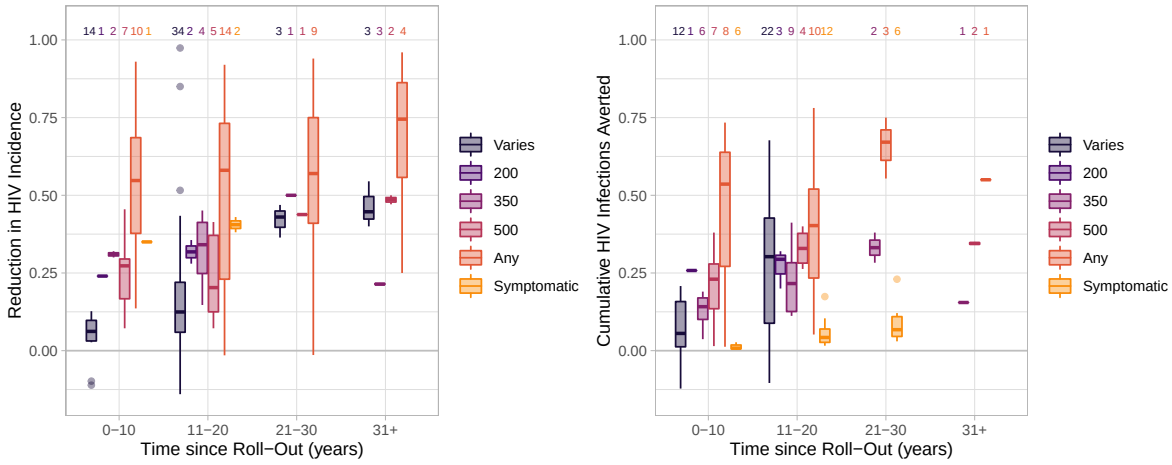

Figure C.17: CD4 initiation criteria

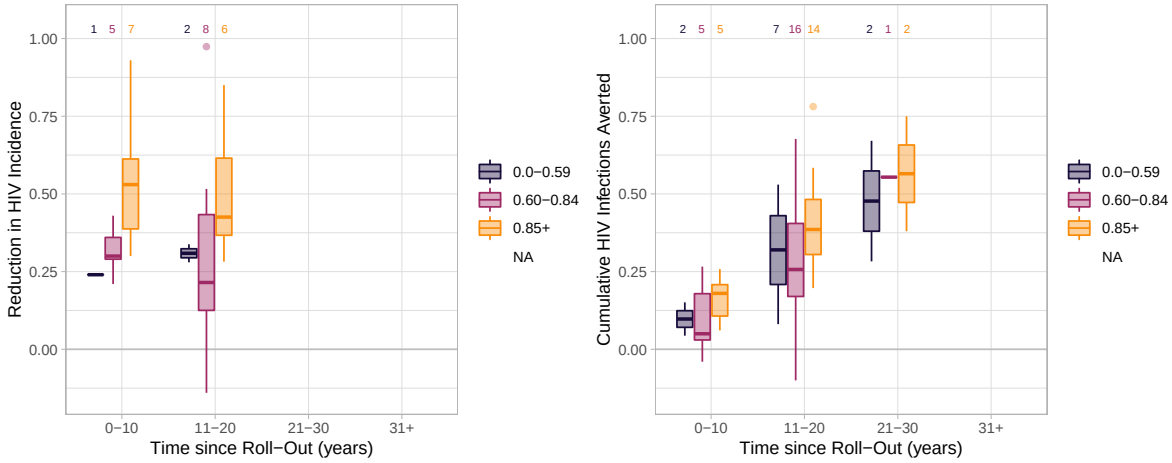

Figure C.18: ART intervention coverage target

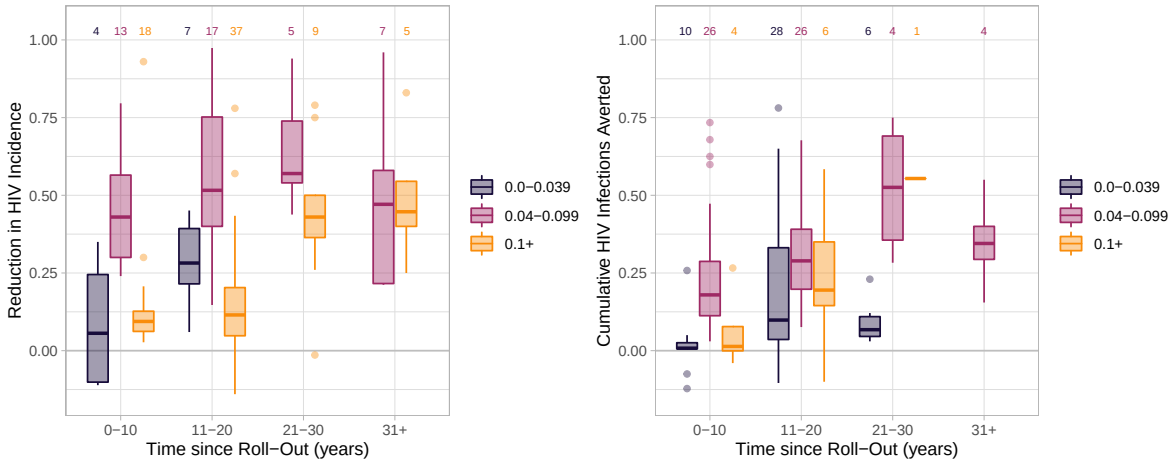

Figure C.19: Relative infectiousness on ART

Figure C.20: Effect estimates for factors of heterogeneity on incidence reduction (%, IR) and cumulative infections averted (%, CHI) from linear multivariate regression with generalized estimating equations.

Numerical results given in Table 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.

D PRISMA-ScR Checklist

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

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

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

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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

References

[1] J. A. Salomon, D. R. Hogan, J. Stover, et al. "Integrating HIV prevention and treatment: From slogans to impact". In: *PLoS Medicine* 2.1 (2005), pp. 0050–0056.

[2] U. L. Abbas, R. M. Anderson, and J. W. Mellors. "Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings." In: *Journal of Acquired Immune Deficiency Syndromes* 41.5 (2006), pp. 632–41.

[3] R. M. Granich, C. F. Gilks, C. Dye, et al. "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model". In: *The Lancet* 373.9657 (2009), pp. 48–57.

[4] T. B. Hallett, S. Dube, I. Cremin, et al. "The role of testing and counselling for HIV prevention and care in the era of scaling-up antiretroviral therapy". In: *Epidemics* 1.2 (2009), pp. 77–82.

[5] N. Bacaer, C. Pretorius, and B. Auvert. "An Age-Structured Model for the Potential Impact of Generalized Access to Antiretrovirals on the South African HIV Epidemic". In: *Bulletin of Mathematical Biology* 72.8 (2010), pp. 2180–2198.

[6] C. Pretorius, J. Stover, L. Bollinger, et al. "Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa". In: *PLoS ONE* 5.11 (2010), e13646.

[7] V. T. Metzger, J. O. Lloyd-Smith, and L. S. Weinberger. "Autonomous targeting of infectious superspreaders using engineered transmissible therapies". In: *PLoS Computational Biology* 7.3 (2011), e1002015.

[8] T. T. Yusuf and F. Benyah. "Optimal strategy for controlling the spread of HIV/AIDS disease: A case study of South Africa". In: *Journal of Biological Dynamics* 6.2 (2012), pp. 475–494.

[9] J. R. Andrews, R. Wood, L.-G. Bekker, et al. "Projecting the benefits of antiretroviral therapy for HIV prevention: the impact of population mobility and linkage to care." In: *The Journal of Infectious Diseases* 206.4 (2012), pp. 543–51.

[10] R. Granich, J. G. Kahn, R. Bennett, et al. "Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050". In: *PloS ONE* 7.2 (2012), e30216.

[11] W. G. Wagner and S. Blower. "Universal Access to HIV Treatment versus Universal 'Test and Treat': Transmission, Drug Resistance & Treatment Costs". In: *PLoS ONE* 7.9 (2012), e41212.

[12] U. L. Abbas, R. Glaubius, A. Mubayi, et al. "Antiretroviral therapy and pre-exposure prophylaxis: Combined impact on HIV transmission and drug resistance in South Africa". In: *The Journal of Infectious Diseases* 208.2 (2013), pp. 224–234.

[13] E. F. Long and R. R. Stavert. "Portfolios of biomedical HIV interventions in South Africa: A cost-effectiveness analysis". In: *Journal of General Internal Medicine* 28.10 (2013), pp. 1294–1301.

[14] I. Cremin, R. Alsallaq, M. Dybul, et al. "The new role of antiretrovirals in combination HIV prevention: A mathematical modelling analysis". In: *AIDS* 27.3 (2013), pp. 447–458.

[15] R. A. Alsallaq, J. M. Baeten, C. L. Celum, et al. "Understanding the Potential Impact of a Combination HIV Prevention Intervention in a Hyper-Endemic Community". In: *PLoS ONE* 8.1 (2013), e54575.

[16] B. E. Nichols, R. Baltussen, J. H. van Dijk, et al. "Cost-effectiveness of PrEP in HIV/AIDS control in Zambia: A stochastic league approach". In: *Journal of Acquired Immune Deficiency Syndromes* 66.2 (2014), pp. 221–228.

[17] B. E. Nichols, K. C. E. Sigaloff, C. Kityo, et al. "Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: A modeling study". In: *AIDS* 28.1 (2014), pp. 73–83.

[18] S. S. Alistar, P. M. Grant, and E. Bendavid. "Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa". In: *BMC Medicine* 12.1 (2014), p. 46.

[19] J. W. Eaton and T. B. Hallett. "Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence". In: *Proceedings of the National Academy of Sciences of the United States of America* 111.45 (2014), pp. 16202–16207.

[20] R. Ying, M. Sharma, R. Heffron, et al. "Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda". In: *Journal of the International AIDS Society* 18.S3 (2015), p. 20013.

[21] A. Low, N. Nagot, I. Konate, 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". In: *Journal of Acquired Immune Deficiency Syndromes* 68.S2 (2015), S180–S188.

[22] A. Khademi, S. Anand, and D. Potts. "Measuring the potential impact of combination HIV prevention in sub-Saharan Africa". In: *Medicine* 94.37 (2015), e1453.

[23] J. A. Gilbert, E. F. Long, R. P. Brooks, et al. "Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa". In: *PLoS ONE* 10.5 (2015), e0126267.

[24] L. M. Heaton, P. D. Bouey, J. Fu, et al. "Estimating the impact of the US President's Emergency Plan for AIDS Relief on HIV treatment and prevention programmes in Africa". In: *Sexually Transmitted Infections* 91.8 (2015), pp. 615–620.

[25] S. M. A. Rahman, N. K. Vaidya, and X. Zou. "Impact of early treatment programs on HIV epidemics: An immunity-based mathematical model". In: *Mathematical Biosciences* 280 (2016), pp. 38–49.

[26] J. A. Gilbert, S. V. Shenoi, A. P. Moll, et al. "Cost-effectiveness of community-based TB/HIV screening and linkage to care in rural South Africa". In: *PLoS ONE* 11.12 (2016), e0165614.

[27] S. Blaizot, D. Maman, B. Riche, et al. "Potential impact of multiple interventions on HIV incidence in a hyperendemic region in Western Kenya: A modelling study". In: *BMC Infectious Diseases* 16.1 (2016), p. 189.

[28] R. Ying, M. Sharma, C. L. Celum, et al. "Home testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modelling analysis". In: *The Lancet HIV* 3.6 (2016), e275–e282.

[29] T. Barnighausen, D. E. Bloom, and S. Humair. "Human resources for treating HIV/AIDS: Are the preventive effects of antiretroviral treatment a game changer?" In: *PLoS ONE* 11.10 (2016), e0163960.

[30] A. Heffernan, E. Barber, R. Thomas, et al. "Impact and cost-effectiveness of point-of-care CD4 testing on the HIV epidemic in South Africa". In: *PLoS ONE* 11.7 (2016), e0158303.

[31] M. Maheu-Giroux, J. F. Vesga, S. Diabate, et al. "Changing Dynamics of HIV Transmission in Cote d'Ivoire: Modeling Who Acquired and Transmitted Infections and Estimating the Impact of Past HIV Interventions (1976-2015)". In: *Journal of Acquired Immune Deficiency Syndromes* 75.5 (2017), pp. 517–527.

[32] M. Maheu-Giroux, J. F. Vesga, S. Diabate, et al. "Population-level impact of an accelerated HIV response plan to reach the UNAIDS 90-90-90 target in Cote d'Ivoire: Insights from mathematical modeling". In: *PLoS Medicine* 14.6 (2017), e1002321.

[33] E. M. Volz, N. Ndembi, R. Nowak, et al. "Phylodynamic analysis to inform prevention efforts in mixed HIV epidemics". In: *Virus Evolution* 3.2 (2017), vex014.

[34] S. Blaizot, H. Huerga, B. Riche, et al. "Combined interventions to reduce HIV incidence in KwaZulu-Natal: a modelling study". In: *BMC Infectious Diseases* 17.1 (2017), p. 522.

[35] C. Mukandavire, J. Walker, S. Schwartz, et al. "Estimating the contribution of key populations towards the spread of HIV in Dakar, Senegal". In: *Journal of the International AIDS Society* 21.S5 (2018), e25126.

[36] M. Guillon. "Success factors for universal access to antiretroviral treatments in South Africa". In: *The International Journal of Health Planning and Management* 33.4 (2018), e1160–e1178.

[37] G. Akudibillah, A. Pandey, and J. Medlock. "Optimal control for HIV treatment". In: *Mathematical Biosciences and Engineering* 16.1 (2018), pp. 373–396.

[38] R. M. Stuart, N. Fraser-Hurt, C. C. Kerr, et al. "The City of Johannesburg can end AIDS by 2030: Modelling the impact of achieving the Fast-Track targets and what it will take to get there: Modelling". In: *Journal of the International AIDS Society* 21.1 (2018), e25068.

[39] S. de Montigny, M.-C. Boily, B. R. Masse, et al. "Assessing the utility of the tipping point ratio to monitor HIV treatment programmes in the era of universal access to ART". In: *Infectious Disease Modelling* 3 (2018), pp. 85–96.

[40] A. Hauser, K. Kusejko, L. F. Johnson, et al. "Bridging the gap between hiv epidemiology and antiretroviral resistance evolution: Modelling the spread of resistance in south africa". In: *PLoS Computational Biology* 15.6 (2019), e1007083.

[41] L. F. Johnson and R. E. Dorrington. "Modelling the demographic impact of HIV/AIDS in South Africa and the likely impact of interventions". In: *Demographic Research* 14 (2006), pp. 541–574.

[42] R. F. Baggaley, G. P. Garnett, and N. M. Ferguson. "Modelling the Impact of Antiretroviral Use in Resource-Poor Settings". In: *PLoS Medicine* 3.4 (2006), pp. 493–504.

[43] D. P. Wilson, J. Kahn, and S. M. Blower. "Predicting the epidemiological impact of antiretroviral allocation strategies in KwaZulu-Natal: the effect of the urban-rural divide." In: *Proceedings of the National Academy of Sciences of the United States of America* 103.38 (2006), pp. 14228–33.

[44] N. Bacaer, R. Ouifki, C. Pretorius, et al. "Modeling the joint epidemics of TB and HIV in a South African township". In: *Journal of Mathematical Biology* 57.4 (2008), pp. 557–593.

[45] E. Chigidi and E. M. Lungu. "Hiv model incorporating differential progression for treatment-naive and treatment-experienced infectives". In: *Mathematical Biosciences and Engineering* 6.3 (2009), pp. 427–450.

[46] B. G. Williams, R. Granich, K. M. De Cock, et al. "Antiretroviral therapy for tuberculosis control in nine African countries". In: *Proceedings of the National Academy of Sciences of the United States of America* 107.45 (2010), pp. 19485–19489.

[47] F. Nyabadza and Z. Mukandavire. "Modelling HIV/AIDS in the presence of an HIV testing and screening campaign". In: *Journal of Theoretical Biology* 280.1 (2011), pp. 167–179.

[48] T. Barnighausen, D. E. Bloom, and S. Humair. "Is treatment as prevention the new game-changer?: Costs and effectiveness". In: *Journal of the International AIDS Society* 15.S3 (2012), p. 163.

[49] B. G. Wagner, B. J. Coburn, and S. Blower. "Increasing survival time decreases the cost-effectiveness of using "test & treat" to eliminate HIV epidemics". In: *Mathematical Biosciences and Engineering* 10.5-6 (2013), pp. 1673–1686.

[50] M. R. Decker, A. L. Wirtz, C. Pretorius, et al. "Estimating the impact of reducing violence against female sex workers on HIV epidemics in Kenya and Ukraine: a policy modeling exercise." In: *American Journal of Reproductive Immunology* 69 Suppl 1 (2013), pp. 122–132.

[51] A. L. Wirtz, D. G. Walker, L. Bollinger, 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". In: *International Journal of STD and AIDS* 24.1 (2013), pp. 18–30.

[52] L. A. Shafer, R. N. Nsubuga, R. Chapman, et al. "The dual impact of antiretroviral therapy and sexual behaviour changes on HIV epidemiologic trends in Uganda: A modelling study". In: *Sexually Transmitted Infections* 90.5 (2014), pp. 423–429.

[53] S. D. Hove-Musekwa, F. Nyabadza, H. Mambili-Mamboundou, et al. "Cost-Effectiveness Analysis of Hospitalization and Home-Based Care Strategies for People Living with HIV/AIDS: The Case of Zimbabwe." In: *International Scholarly Research Notices* 2014 (2014), p. 836439.

[54] R. S. Braithwaite, K. A. Nucifora, C. Toohey, et al. "How do different eligibility guidelines for antiretroviral therapy affect the cost–effectiveness of routine viral load testing in sub-Saharan Africa". In: *AIDS* 28.S1 (2014), S73–S83.

[55] B. E. Nichols, K. C. E. Sigaloff, C. Kityo, 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". In: *Journal of the International AIDS Society* 17 (2014), p. 19164.

[56] L. J. Abu-Raddad and S. F. Awad. "How does population viral load vary with the evolution of a large HIV epidemic in sub-Saharan Africa?" In: *AIDS* 28.6 (2014), pp. 927–929.

[57] S.-J. Anderson, P. Cherutich, N. Kilonzo, et al. "Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study". In: *The Lancet* 384.9939 (2014), pp. 249–256.

[58] S. S. Alistar, E. F. Long, M. L. Brandeau, et al. "HIV epidemic control-a model for optimal allocation of prevention and treatment resources". In: *Health Care Management Science* 17.2 (2014), pp. 162–181.

[59] A. Cori, H. Ayles, N. Beyers, 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". In: *PLoS ONE* 9.1 (2014), e84511.

[60] J. Stover, T. B. Hallett, Z. Wu, 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". In: *PloS ONE* 9.11 (2014), e111956.

[61] A. L. Wirtz, C. Pretorius, C. Beyrer, et al. "Epidemic impacts of a community empowerment intervention for HIV prevention among female sex workers in generalized and concentrated epidemics". In: *PLoS ONE* 9.2 (2014), e88047.

[62] E. L. Korenromp, B. Gobet, E. Fazito, et al. "Impact and cost of the HIV/AIDS national strategic plan for Mozambique, 2015-2019-projections with the spectrum/goals model". In: *PLoS ONE* 10.11 (2015), e0142908.

[63] G. M. Knight, P. J. Dodd, A. D. Grant, et al. "Tuberculosis Prevention in South Africa". In: *PLoS ONE* 10.4 (2015), e0122514.

[64] C. C. Kerr, R. M. Stuart, R. T. Gray, et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". In: *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376.

[65] N. Fraser, C. C. Kerr, Z. Harouna, et al. "Reorienting the HIV response in Niger toward sex work interventions: From better evidence to targeted and expanded practice". In: *Journal of Acquired Immune Deficiency Syndromes* 68.S2 (2015), S213–S220.

[66] S. M. Kassa and A. Ouhinou. "The impact of self-protective measures in the optimal interventions for controlling infectious diseases of human population". In: *Journal of Mathematical Biology* 70.1-2 (2015), pp. 213–236.

[67] L.-G. Bekker, L. Johnson, F. Cowan, et al. "Combination HIV prevention for female sex workers: What is the evidence?" In: *The Lancet* 385.9962 (2015), pp. 72–87.

[68] K. Shannon, S. A. Strathdee, S. M. Goldenberg, et al. "Global epidemiology of HIV among female sex workers: Influence of structural determinants". In: *The Lancet* 385.9962 (2015), pp. 55–71.

[69] S. Blaizot, B. Riche, D. Maman, et al. "Estimation and short-term prediction of the course of the HIV epidemic using demographic and health survey methodology-like data". In: *PLoS ONE* 10.6 (2015), e0130387.

[70] J. A. Smith, S.-J. Anderson, K. L. Harris, et al. "Maximising HIV prevention by balancing the opportunities of today with the promises of tomorrow: a modelling study". In: *The Lancet HIV* 3.7 (2016), e289–e296.

[71] R. Atun, A. Y. Chang, O. Ogbuoji, et al. "Long-term financing needs for HIV control in sub-Saharan Africa in 2015-2050: a modelling study." In: *BMJ Open* 6.3 (2016), e009656.

[72] A. J. Shattock, C. C. Kerr, R. M. Stuart, et al. "In the interests of time: Improving HIV allocative efficiency modelling via optimal time-varying allocations". In: *Journal of the International AIDS Society* 19.1 (2016), p. 20627.

[73] J. B. McGillen, S.-J. Anderson, M. R. Dybul, et al. "Optimum resource allocation to reduce HIV incidence across sub-Saharan Africa: a mathematical modelling study". In: *The Lancet HIV* 3.9 (2016), e441–e448.

[74] L. F. Johnson, C. Chiu, L. Myer, et al. "Prospects for HIV control in South Africa: a model-based analysis". In: *Global Health Action* 9 (2016), p. 30314.

[75] M. Sharma, C. Farquhar, R. Ying, et al. "Modeling the cost-effectiveness of homebased HIV testing and education (HOPE) for pregnant women and their male partners in Nyanza Province, Kenya". In: *AIDS Research and Human Retroviruses* 32.S1 (2016), p. 300.

[76] G. Akudibillah, A. Pandey, and J. Medlock. "Maximizing the benefits of ART and PrEP in resource-limited settings". In: *Epidemiology and Infection* 145.5 (2017), pp. 942–956.

[77] R. A. Alsallaq, J. Buttolph, C. M. Cleland, et al. "The potential impact and cost of focusing HIV prevention on young women and men: A modeling analysis in western Kenya". In: *PLoS ONE* 12.4 (2017), e0175447.

[78] S.-J. Anderson, P. D. Ghys, R. Ombam, et al. "HIV prevention where it is needed most: Comparison of strategies for the geographical allocation of interventions: Comparison". In: *Journal of the International AIDS Society* 20.4 (2017), e25020.

[79] C. Chiu, L. F. Johnson, L. Jamieson, et al. "Designing an optimal HIV programme for South Africa: Does the optimal package change when diminishing returns are considered?" In: *BMC Public Health* 17.1 (2017), p. 143.

[80] L. F. Johnson, M. T. May, R. E. Dorrington, et al. "Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study". In: *PLoS Medicine* 14.12 (2017), e1002468.

[81] R. M. Stuart, C. C. Kerr, H. Haghparast-Bidgoli, et al. "Getting it right when budgets are tight: Using optimal expansion pathways to prioritize responses to concentrated and mixed HIV epidemics". In: *PLoS ONE* 12.10 (2017), e0185077.

[82] J. B. McGillen, A. Sharp, B. Honermann, et al. "Consequences of a changing US strategy in the global HIV investment landscape". In: *AIDS* 31.18 (2017), F19–F23.

[83] I. Cremin, L. McKinnon, J. Kimani, et al. "PrEP for key populations in combination HIV prevention in Nairobi: a mathematical modelling study". In: *The Lancet HIV* 4.5 (2017), e214–e222.

[84] J. M. Ross, R. Ying, C. L. Celum, et al. "Modeling HIV disease progression and transmission at population-level: The potential impact of modifying disease progression in HIV treatment programs." In: *Epidemics* 23 (2018), pp. 34–41.

[85] S.-J. Anderson, P. D. Ghys, R. Ombam, et al. "Frontloading HIV financing maximizes the achievable impact of hiv prevention". In: *Journal of the International AIDS Society* 21.3 (2018), e25087.

[86] S.-J. Anderson, G. P. Garnett, J. Enstone, et al. "The importance of local epidemic conditions in monitoring progress towards HIV epidemic control in Kenya: a modelling study". In: *Journal of the International AIDS Society* 21.11 (2018), e25203.

[87] E. O. Omondi, R. W. Mbogo, and L. S. Luboobi. "Mathematical analysis of sex-structured population model of HIV infection in Kenya". In: *Letters in Biomathematics* 5.1 (2018), pp. 174–194.

[88] B. Woods, C. Rothery, S.-J. Anderson, et al. "Appraising the value of evidence generation activities: an HIV modelling study." In: *BMJ Global Health* 3.6 (2018), e000488.

[89] E. R. Stevens, L. Li, K. A. Nucifora, et al. "Cost-effectiveness of a combination strategy to enhance the HIV care continuum in Swaziland: Link4health". In: *PLoS ONE* 13.9 (2018), e0204245.

[90] I. J. Stopard, J. B. McGillen, K. Hauck, et al. "The influence of constraints on the efficient allocation of resources for HIV prevention". In: *AIDS* 33.7 (2019), pp. 1241–1246.

[91] L. Beacroft and T. B. Hallett. "The potential impact of a "curative intervention" for HIV: a modelling study." In: *Global Health Research and Policy* 4 (2019), p. 2.

[92] M. Reidy, E. Gardiner, C. Pretorius, et al. "Evaluating the potential impact and cost-effectiveness of dapivirine vaginal ring pre-exposure prophylaxis for HIV prevention". In: *PLoS ONE* 14.6 (2019), e0218710.

[93] E. O. Omondi, R. W. Mbogo, and L. S. Luboobi. "A mathematical modelling study of HIV infection in two heterosexual age groups in Kenya". In: *Infectious Disease Modelling* 4 (2019), pp. 83–98.

[94] M. Maheu-Giroux, S. Diabate, M.-C. Boily, et al. "Cost-Effectiveness of Accelerated HIV Response Scenarios in Cote d'Ivoire". In: *Journal of Acquired Immune Deficiency Syndromes* 80.5 (2019), pp. 503–512.

[95] J. Vandepitte, R. Lyerla, G. Dallabetta, et al. "Estimates of the number of female sex workers in different regions of the world". In: *Sexually Transmitted Infections* 82.S3 (June 2006).

[96] M. Carael, E. Slaymaker, R. Lyerla, et al. "Clients of sex workers in different regions of the world: Hard to count". In: *Sexually Transmitted Infections* 82.S3 (June 2006), pp. iii26–iii33.

[97] F. Scorgie, M. F. Chersich, I. Ntaganira, et al. "Socio-demographic characteristics and behavioral risk factors of female sex workers in sub-Saharan Africa: A systematic review". In: *AIDS and Behavior* 16.4 (May 2012), pp. 920–933.