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

Short Title: Heterogeneity in transmission models

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

Abstract

Objective. 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. **Design**. Scoping review to identify common modelling assumptions and applications. **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 crude 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. Models without activity stratification predicted the largest ART prevention impacts, followed by models with key populations that had faster cascade transitions versus the wider population. **Conclusions**. Among compartmental transmission models applied to project ART prevention impacts, representations of risk heterogeneity and projected impacts varied considerably, where models with less heterogeneity tended to predict larger impacts. The potential influence of modelling assumptions about risk and intervention heterogeneity should be further explored.

Words: 250 / 250

Keywords: HIV, mathematical model, transmission, risk heterogeneity, key populations, antiretroviral therapy, universal test and treat

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]. Data suggest that key populations, including individuals engaged in sex work and men who have sex with men, experience disproportionate risks of HIV acquisition and onward transmission in SSA [2, 3, 4, 5]. HIV treatment to reduce onward transmission remains a key element of combination HIV prevention [6]. Effective HIV treatment with antiretroviral therapy (ART) leads to viral load suppression and has been shown to prevent HIV transmission between sex partners [7, 8, 9].

Following empirical evidence of partnership-level efficacy of ART in preventing HIV [7, 8, 9], and model-based evidence of "treatment as prevention" [10, 11, 12], several large-scale community-based trials of universal test-and-treat (UTT) were recently completed [13, 14, 15]. 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 [14, 15, 13]. Thus the population-level reductions in incidence anticipated from transmission modelling were not observed in these trials [16, 17].

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 [18, 16]. While viral suppression improved under UTT in all three trials, 21–54% of study participants remained unsuppressed [13, 14, 15]. It has been suggested that populations experiencing barriers to viral suppression under UTT may be at highest risk for onward transmission, including key populations like sex workers, men who have sex with men, and adolescent girls and young women [19, 20, 21]. While widespread UTT scale-up may fill some coverage gaps, equitable access to ART for marginalized populations remains an open challenge.

Given the upstream and complementary role of transmission modelling in estimating the prevention impacts of ART [11, 22], we sought to examine and appraise representations of risk heterogeneity in mathematical models used to assess the prevention impacts of ART in SSA. We conducted a scoping review with the following objectives. Among non-linear compartmental models of sexual HIV transmission that have been 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). First, we developed a conceptual framework to organize assumptions and representations of risk heterogeneity in compartmental HIV transmission models. Then, we designed and implemented the search strategy, and extracted data relevant to the framework to address our objectives.

2.1 Conceptual Framework for Risk Heterogeneity

We conceptualized "factors of risk heterogeneity", meaning epidemiological stratifications and phenomena which may/not be included in transmission models. Such factors could include if/how populations, rates, and probabilities are stratified along various dimensions. We defined the following 4 domains in which different factors of risk heterogeneity might influence the transmission impact of ART.

- **Biological Effects**: differential transmission risk within HIV disease course that may coincide with differential ART coverage [23]
- **Behaviour Change Effects**: differential transmission risk due to behavioural changes related to engagement in the ART cascade [24, 25]
- **Network Effects**: differential transmission risk within sub-populations that increases the challenge of epidemic control through core group dynamics [26, 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, 19, 21]

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

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 [25]	**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, 21]
Key Populations	c; κ	Any epidemiologically defined higher risk groups [38]	**Network & Coverage** higher transmission risk and barriers to viral suppression among key populations [19]
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 [19, 21]	**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 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 imported into Covidence [41] for screening. Duplicate studies were removed automatically by Ovid and by Covidence; four additional duplicates with subtly different titles were later identified and removed manually. Potentially relevant studies were identified by title and abstract screening, followed by full-text screening using the inclusion/exclusion criteria below. One reviewer (JK) conducted the search, screening, and data extraction.

2.2.1 Inclusion/Exclusion Criteria

We included peer-reviewed, primarily modelling studies that used non-linear models of sexual HIV transmission to project the prevention impacts of ART in any setting within SSA. See Table A.2 for complete inclusion/exclusion criteria. We only included studies published in English anytime before Jan 1, 2020. We excluded conference publications and those without primary modelling results and description of the methods, such as commentaries and reviews. If a model's details were provided in another peer-reviewed publication, we extracted data from both publications as required.

The following criteria were used for inclusion of studies: 1) Used a non-linear compartmental model of sexual HIV transmission at the population level. We defined a *non-linear model* as one where future projected infections are a function of previously projected infections [42], and a *compartmental model* as one where system variables represent the numbers of individuals in each state, rather than unique individuals [42]. Thus, statistical models, models without dynamic transmission, and individual-based models were excluded. 2) The model was parameterized/calibrated to reflect at least one setting within SSA (see Appendix B.1 for countries). 3) The study 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 specifically examined scale-up of ART coverage alone (versus combination intervention) for the whole population (versus ART prioritized to subgroups), and reported HIV incidence reduction or cumulative HIV infections averted over time 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. 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 and 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); and people who inject drugs (PWID). FSW were defined as any female activity group meeting 3 criteria: <5% of the female population; <1/3 the client population size; and having >50× the partners per year of the lowest sexually active female activity group [43, 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 or PWID.

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 (sex frequency and partnership duration) 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 relative to t_o.

Finally, 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 plotted the impacts versus time since t_o, stratified by factor levels, and explored whether projected impacts were the same under all factor levels, testing for significant differences using a Kruskal-Wallis test.

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. Most (61) of the 94 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 2 illustrates the number of studies by country. East Africa was the

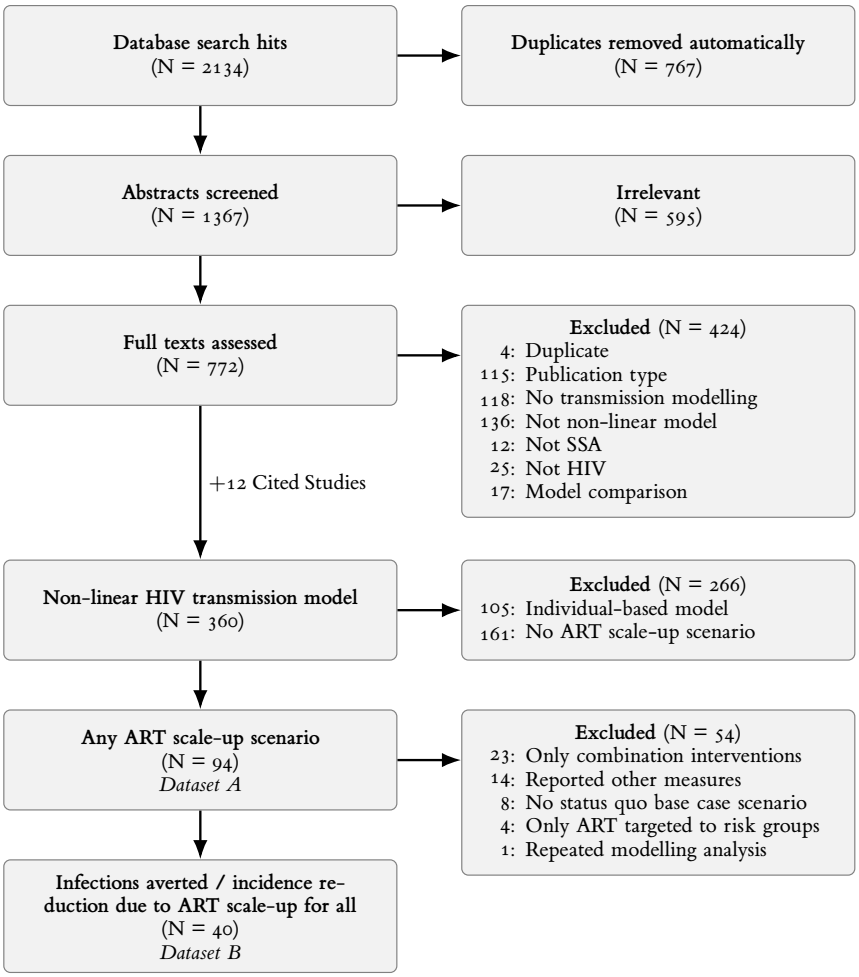


Figure 1: PRISMA flowchart of study identification

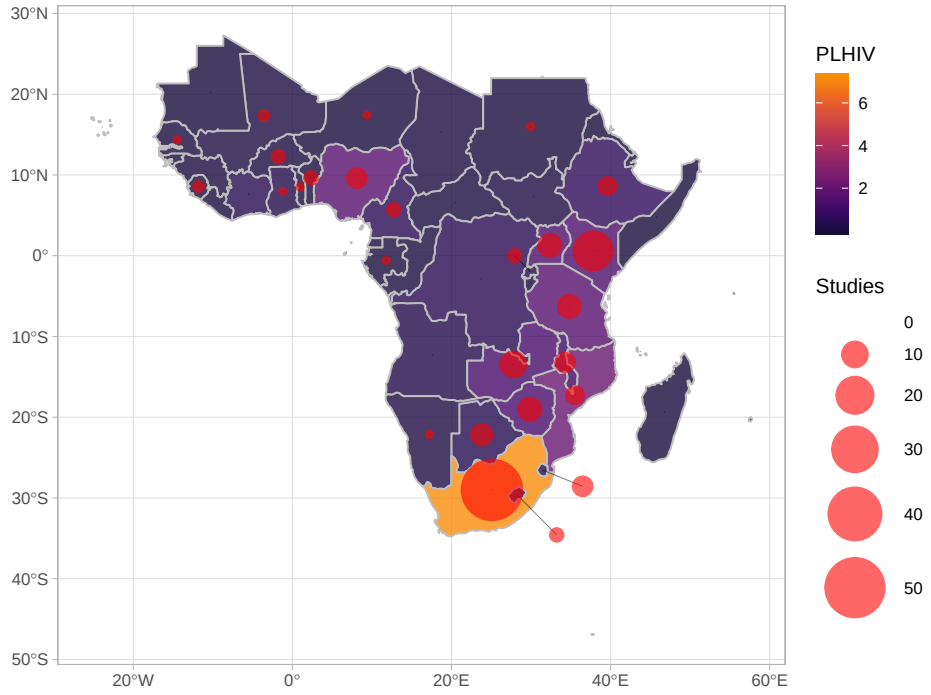


Figure 2: Map showing number of studies (of 94 total) applying HIV transmission modelling in each country vs the number of people living with HIV (PLHIV, millions)

most represented SSA region, being simulated in 77 studies, followed by Southern (73), 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.1). 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).

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	30
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
	PWID	11

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.

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; and people who inject drugs (PWID) in 11.

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 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 assumed to be 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); the lower activity partner (11); the 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. Overlapping partnership types had differential total sex acts and condom use across types.

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.

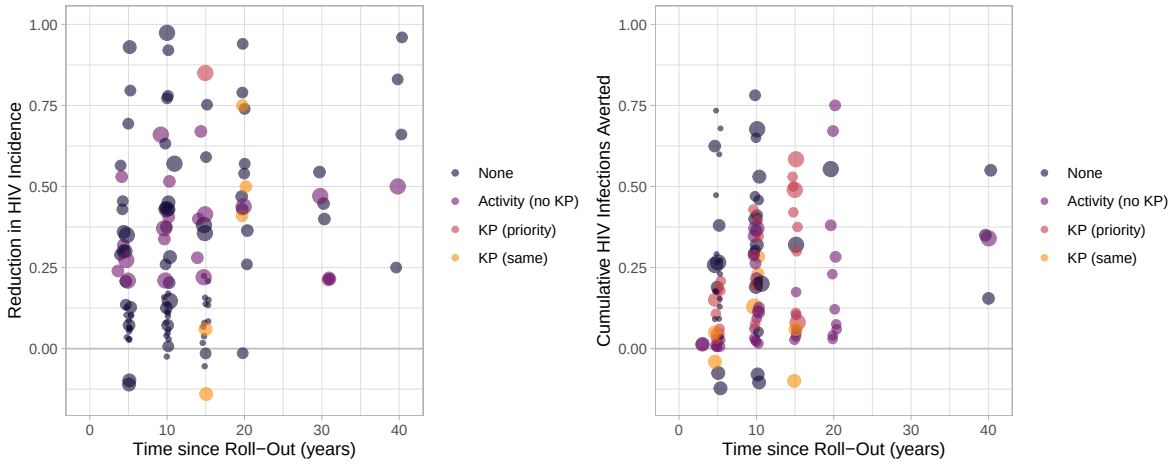
3.2.4 Coverage Effects

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 with ART scale-up as compared to a scenario without ART scale-up was reported in 23 studies (61 scenarios); the proportion of cumulative infections averted due to ART scale-up was reported in 24 (75); and 7 (11) reported both. Some scenarios reported these outcomes on multiple time horizons.

Figure 3 summarizes each outcome versus time since ART scale-up, stratified by a composite index of modelled risk heterogeneity. Ecological-level analysis across scenarios by degree of risk heterogeneity identified differences in proportions of infections averted, but not in relative incidence reduction (Table C.1). The largest proportions of infections averted were reported from scenarios without risk heterogeneity (median [IQR]% = 29 [18, 47]), followed by scenarios with key populations prioritized for ART (21 [11, 41]). The smallest impact was observed in scenarios with key populations who were not prioritized for ART (10 [3, 21]) and in models with risk heterogeneity but without key populations (6 [3, 22]). Only 11 scenarios from 7 studies provided both outcomes [44, 45, 46, 47, 48, 49, 50]; among which the pattern of incidence reduction



(a) Reduction in HIV incidence

(b) Cumulative HIV infections averted

Figure 3: Projected ART prevention benefits, stratified by factors of risk heterogeneity: whether models considered differences in sexual activity, key populations, and ART cascade prioritized to key populations

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 (Dataset B). If any study included multiple scenarios of ART scale-up, then each scenario was included as a separate data point, but the size of each data point was reduced in proportion to the number of scenarios in the study. Some scenarios have multiple data points if multiple time horizons were reported. A small random offset was added to all data points to reduce overlap. KP: key populations; priority: cascade transitions were faster for at least one step among KP vs overall; same: cascade transitions were assumed the same speed in KP as overall; no scenarios in Dataset B considered lower cascade among KP.

versus modelled heterogeneity was similar to the pattern of infections averted versus modelled heterogeneity (Figure C.11).

ART prevention impacts were larger with longer time horizon, lower HIV prevalence (Figure C.12), and greater ART eligibility (C.13); however patterns were not consistent across HIV incidence trajectory (C.14), ART coverage targets (C.15), or relative infectiousness on ART (C.16).

4 Discussion

Via scoping review, we found that representations of risk heterogeneity varied widely across transmission modelling studies of ART intervention in SSA, with stratification by sexual activity and key populations considered in approximately 2/3 and 2/5 of models, respectively. We also found that the projected pro-

portions of infections averted due to ART scale-up were larger under assumptions of homogeneous risk or prioritized ART to key populations, as compared to heterogeneous risk or without prioritized ART to key populations. Three notable themes emerged from our review.

First, modelling studies have an opportunity to keep pace with growing epidemiological data on risk heterogeneity. For example, 41% of the modelling studies reviewed included at least one key population, such as FSW and or MSM. Key populations continue to experience disproportionate risk of HIV, even in high-prevalence epidemics [1], and models examining the unmet needs of key populations suggest that these unmet needs play an important role in overall epidemic dynamics [51, 52]. Furthermore, the 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 the available data [27, 40]. Similarly, among studies with different partnership types, only 20% modelled main/spousal partnerships—with more sex acts/lower condom use—between two higher risk individuals, while 80% modelled only casual/commercial partnerships among higher risk individuals. However, data suggest female sex workers may form main/spousal partnerships with regular clients and boyfriends/spouses from higher risk groups [40]. Thus, future models can continue to include emerging data on these and other factors of heterogeneity, while nested model comparison studies can study how multiple factors might act together to influence projections of ART impact [28, 53].

Second, most models assumed equal ART cascade transition rates across subgroups, including diagnosis, ART initiation, and retention. Recent data suggest differential ART cascade by sex, age, and key populations [30, 54, 55, 21]. These differences may stem from the unique needs of population subgroups and is one reason why differentiated ART services are a core component of HIV programs [56, 57]. Moreover, barriers to ART may intersect with transmission risk, particularly among key populations, due to issues of stigma, discrimination, and criminalization [58, 16]. Thus, further opportunities exist to: incorporate differentiated cascade data, examine the intersections of intervention and risk heterogeneity, and to consider the impact of HIV services as they are delivered on the ground. Similar opportunities were noted regarding modelling of pre-exposure prophylaxis in SSA [59]. Finally, depending on the research question, the modelled treatment cascade may need expansion to include more cascade steps and states related to treatment failure/discontinuation.

Third, based on ecological analysis of scenarios, we found that modelling assumptions about risk and intervention heterogeneity may influence the projected proportion of infections averted by ART. We did not find similar evidence for relative incidence reduction due to ART, but studies reporting both outcomes were

largely distinct. Among studies reporting both, the overall pattern was consistent [44, 45, 46, 47, 48, 49, 50]. These findings highlight the limitations of ecological analysis to estimate the potential influence of modelling assumptions on projected ART prevention benefits, and motivate additional model comparison studies to better quantify this influence, such as [28, 53]. Our ecological analysis also suggested that the anticipated ART prevention impacts from homogeneous models may be achievable in the context of risk heterogeneity if testing and treatment resources are prioritized to higher risk groups.

Limitations of our scoping review include our examination of only a few key populations. In our conceptual framework for risk heterogeneity, we did not explicitly examine heterogeneity by type of sex act (i.e. anal sex) which is associated with higher probability of HIV transmission, nor structural risk factors like violence [60, 61]. The large number of differences between scenarios in the scoping review context also limited our ability to infer the influence of risk heterogeneity across scenarios.

In conclusion, representations of risk heterogeneity vary widely among models used to project the prevention impacts of ART in SSA. Such differences may partially explain the large variability in projected impacts. Opportunities exist to incorporate new and existing data on the intersections of risk and intervention heterogeneity. Moving forward, systematic model comparison studies are needed to estimate and understand the influence of various modelling assumptions on ART prevention impacts.

Conflicts of Interest

None declared.

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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.

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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.

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.

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.
G21	9730	Cote d'Ivoire/ OR Cote d'Ivoire.mp. OR Ivory Coast.mp.
G22	46,917	Kenya/ OR Kenya.mp.

continued ...

… continued

	Term	Hits
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 a 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 ?? for full country list). [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 Papers

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 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 Awa
[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, Anderson, and Hallett
[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 **??** 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.

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

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

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.

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 Risk Heterogeneity

C.1.1 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.

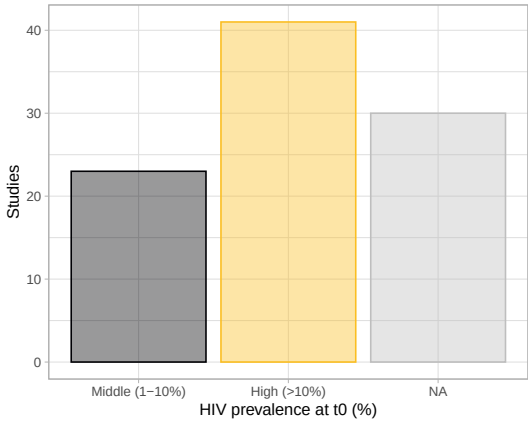


Figure C.1: HIV prevalence at t_0 (%)

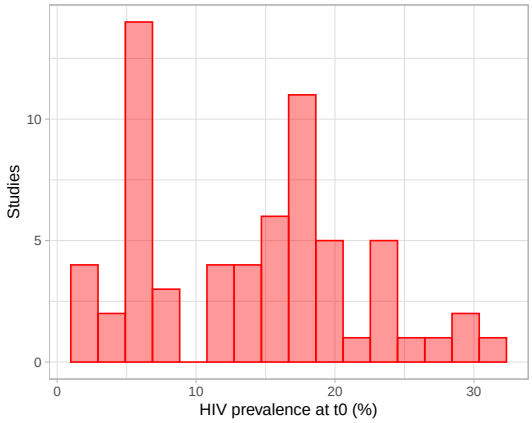


Figure C.2: HIV prevalence at t_0 (%)

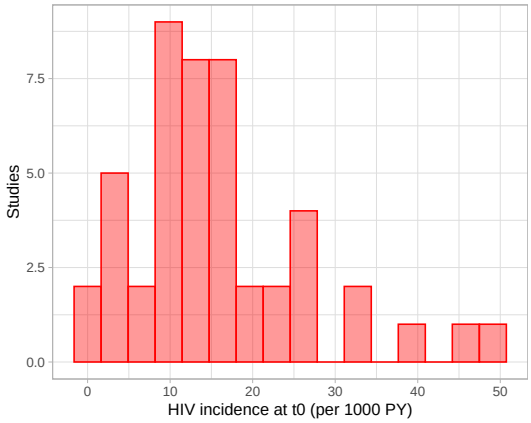


Figure C.3: HIV incidence at t_0 (per 1000 PY)

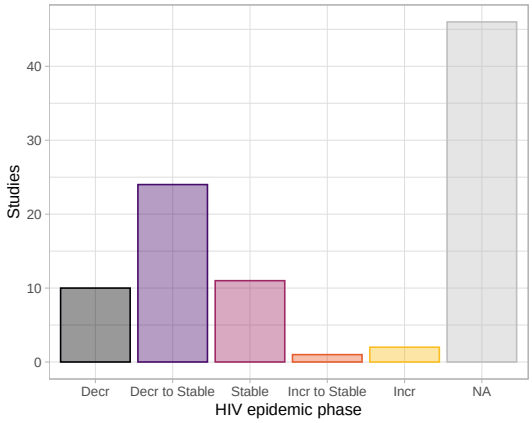


Figure C.4: HIV epidemic phase

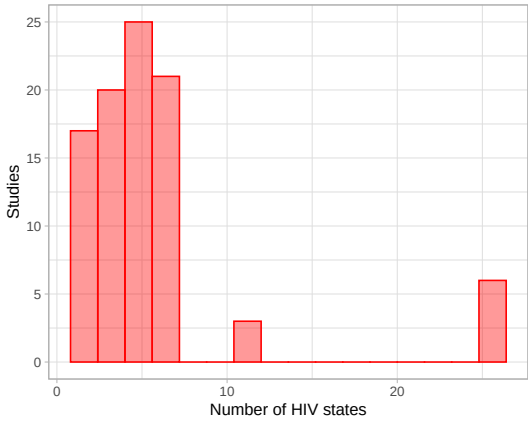


Figure C.5: Number of HIV states

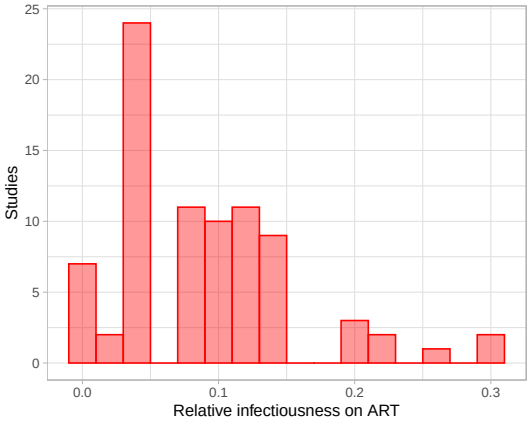


Figure C.6: Relative infectiousness on ART

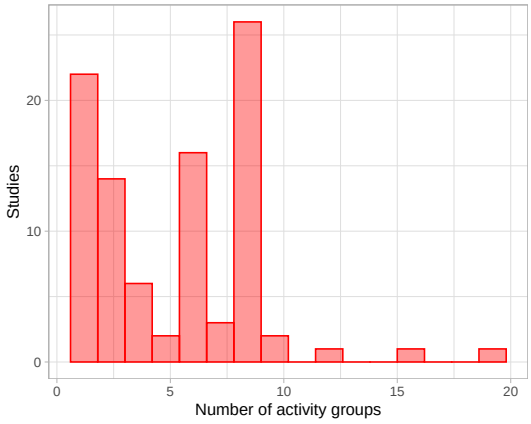


Figure C.7: Number of activity groups

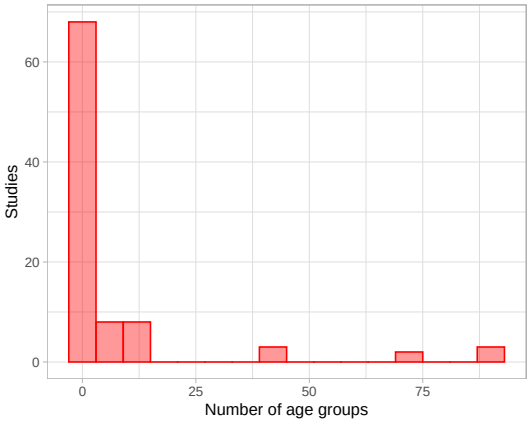


Figure C.8: Number of age groups

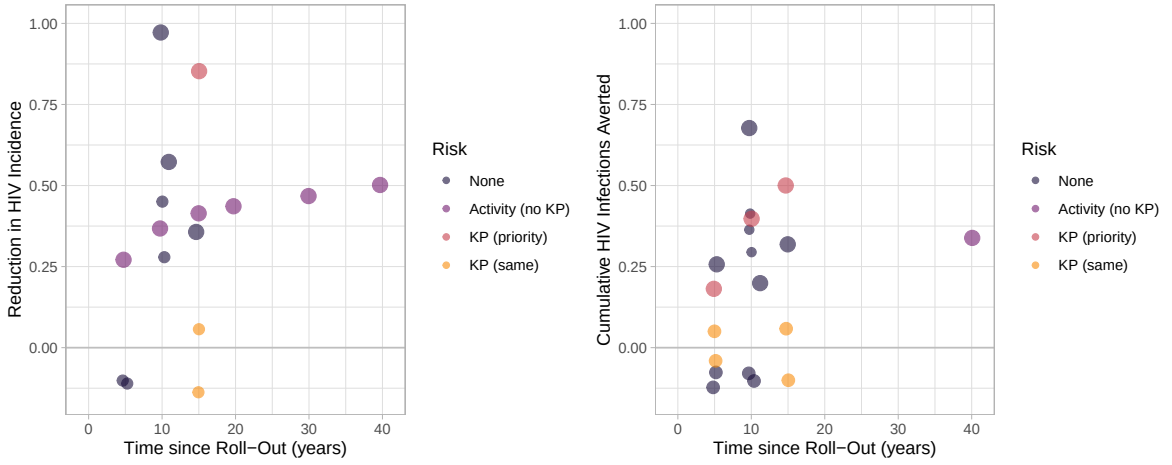
Figure C.9: Proportion of women in the highest female activity group

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

C.2 ART Prevention Impact

C.2.1 Figures

The following figures illustrate the projected ART prevention impact (Dataset B), stratified by various factors of heterogeneity and intervention contexts (colours). The left panels show the relative reduction in HIV incidence rate; the right panels show the relative reduction in cumulative new HIV infections; both as compared to a base-case scenario reflecting status quo. 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 study included multiple scenarios of ART scale-up, then each scenario was included separately, but the size of each data point was reduced in proportion to the number of scenarios; so studies with only one scenario have the largest data points. Some scenarios have multiple data points if multiple time horizons were reported. If any factor could not be quantified due to missing data or varying values, the data point is grey. A small random offset has been added to the data points to reduce overlap.



(a) Reduction in HIV incidence (%)

(b) Cumulative HIV infections averted (%)

Figure C.11: Projected ART prevention benefits, stratified by factors of risk heterogeneity: whether models considered differences in sexual activity, key populations, and ART cascade prioritized to key populations. Subset of studies reporting both outcomes.

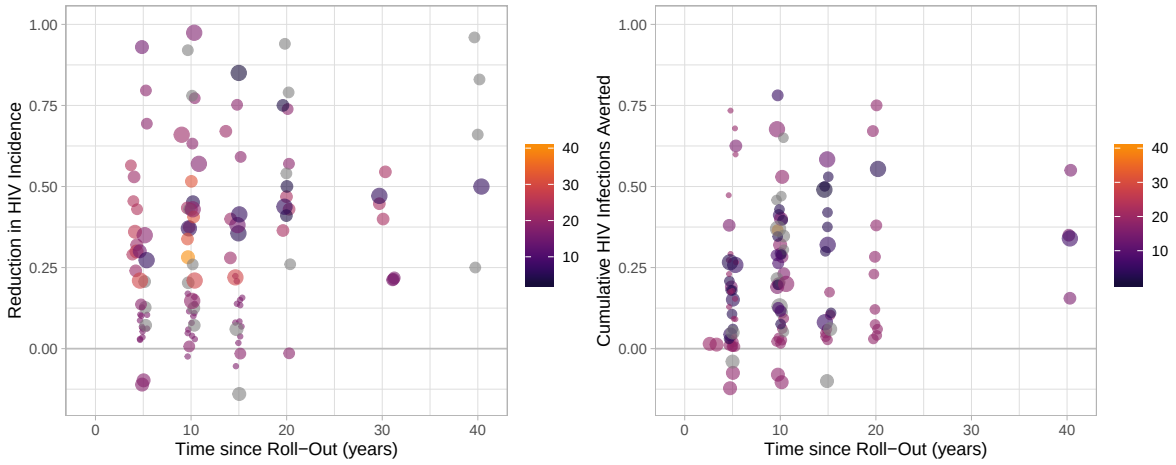


Figure C.12: HIV prevalence at t_0 (%)

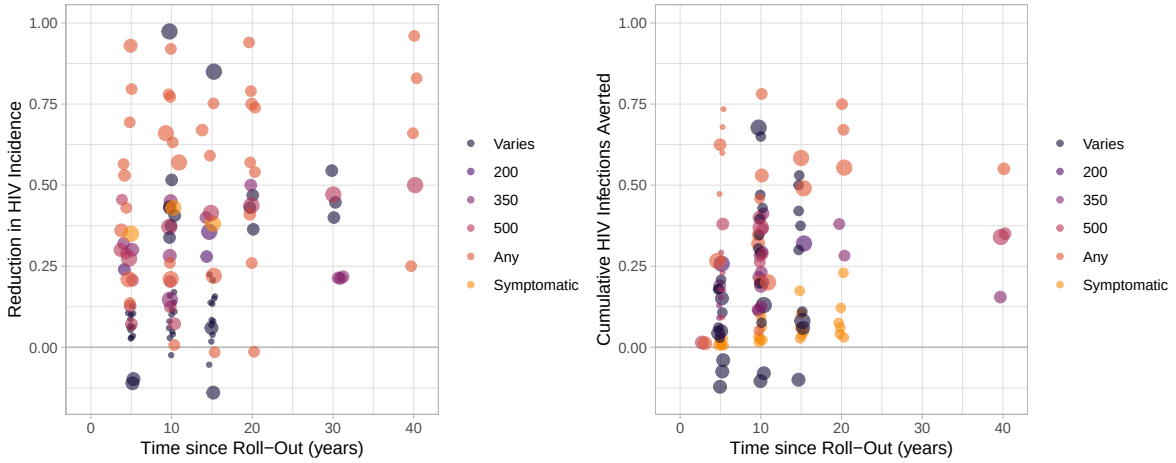


Figure C.13: CD4 initiation criteria

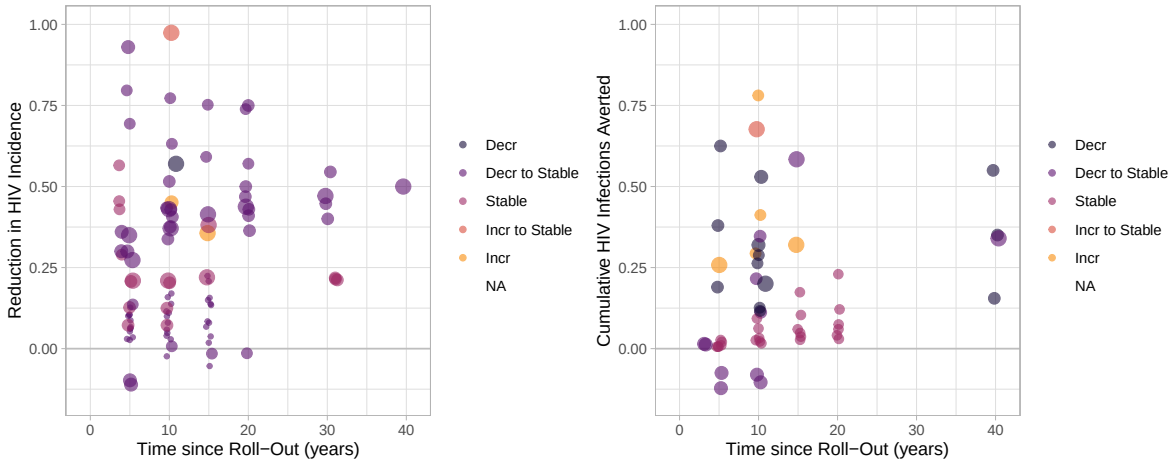


Figure C.14: HIV epidemic phase

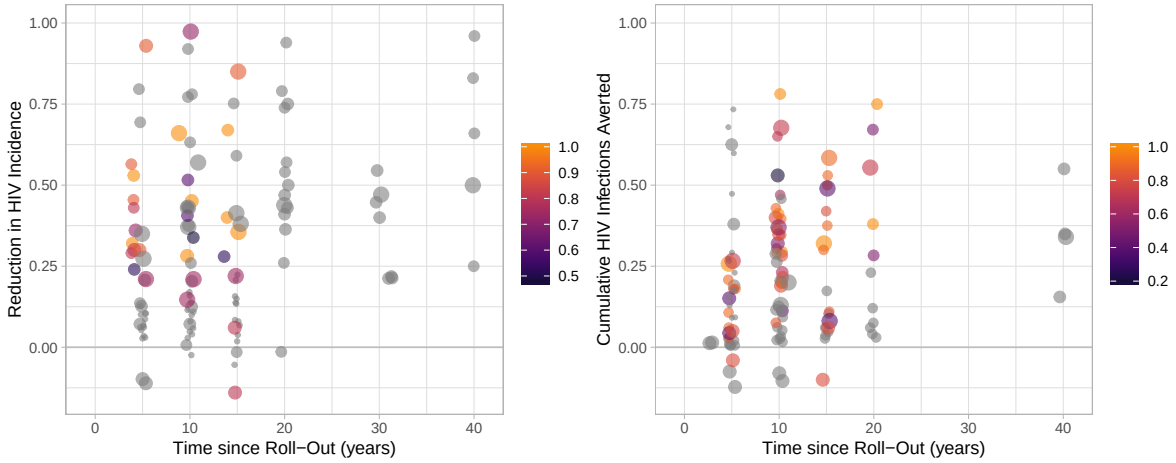


Figure C.15: ART intervention coverage target

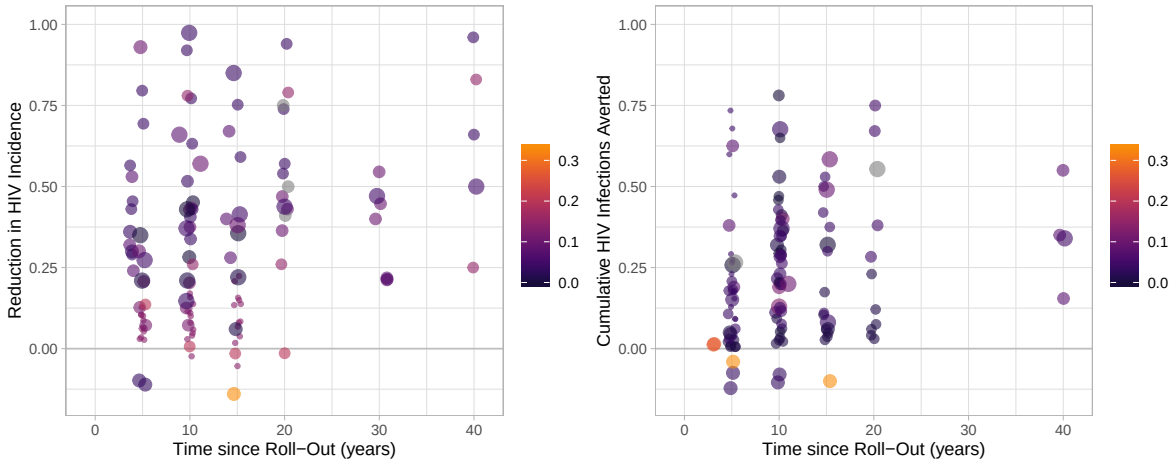


Figure C.16: Relative infectiousness on ART

C.2.2 Table

Table C.1 summarizes the median [IQR] projected ART prevention impact (Dataset B), stratified by various factors of heterogeneity and intervention conditions. Reported p-values for each factor are from non-parametric Kruskal-Wallis tests for differences in ART prevention impact under at least one of the factor levels.

Table C.1: Projected ART prevention benefits, stratified by factors of risk heterogeneity and contexts

		Incidence Reduction (%)				Cum. Infections Averted (%)			
Factor	Level	Median	(IQR)	N [a]	p [b]	Median	(IQR)	N [a]	p [b]
Time Horizon (years)	0–10	17	(7, 35)	36	0.002	14	(3, 26)	40	0.05
	11–20	20	(8, 42)	63		22	(8, 38)	60	
	21–30	47	(39, 65)	15		23	(7, 47)	11	
	31+	46	(24, 57)	12		34	(29, 40)	4	
HIV Prevalence (%)	0–1	—	(—, —)	0	0.002	49	(49, 49)	1	0.033
	1–10	44	(40, 50)	12		27	(13, 38)	33	
	10+	21	(7, 43)	94		15	(3, 31)	66	
HIV Incidence	Increasing	40	(38, 43)	2	0.156	32	(29, 41)	5	< 0.001
	Inc-to-stable	97	(97, 97)	1		68	(68, 68)	1	
	Stable	21	(20, 29)	17		4	(2, 7)	24	
	Dec-to-stable	15	(6, 43)	81		1	(−8, 28)	11	
	Decreasing	57	(57, 57)	1		29	(19, 38)	13	
RR Transmission on ART	0.0–0.039	22	(14, 35)	11	< 0.001	6	(2, 27)	44	< 0.001
	0.4–0.099	49	(34, 67)	42		27	(15, 38)	60	
	0.1+	11	(5, 26)	70		13	(1, 20)	9	
CD4 Threshold for ART Initiation	200	28	(26, 32)	3	< 0.001	28	(24, 30)	4	< 0.001
	350	29	(21, 38)	10		18	(13, 27)	18	
	500	29	(16, 43)	15		29	(23, 35)	13	
	Any	56	(22, 75)	41		51	(28, 62)	22	
ART Coverage Target (%)	0–59	28	(26, 31)	3	0.018	30	(13, 43)	11	0.173
	60–84	29	(21, 41)	13		22	(8, 39)	22	
	85+	46	(36, 66)	13		36	(26, 43)	21	
Acute Infection	No	22	(10, 57)	35	0.967	38	(24, 50)	15	0.001
	Yes	26	(9, 44)	91		16	(5, 32)	100	
Late-Stage Infection	No	39	(13, 56)	38	0.25	36	(20, 48)	12	0.013
	Yes	22	(8, 43)	88		18	(5, 34)	103	
Trans. Drug Resist.	No	21	(7, 43)	114	< 0.001	18	(5, 36)	102	0.171
	Yes	72	(39, 85)	12		26	(20, 30)	13	
HIV Morbidity	No	21	(7, 45)	102	0.088	27	(13, 42)	73	< 0.001
	Any	34	(22, 46)	24		6	(3, 23)	42	
HTC Behav. Change	No	21	(7, 45)	112	0.031	23	(11, 38)	81	0.001
	Any	41	(29, 49)	14		6	(3, 22)	34	
Risk Definition	None	19	(7, 44)	98	0.065	29	(18, 47)	45	< 0.001
	Activity (No KP)	35	(22, 46)	22		6	(3, 22)	39	
	KP (Priority)	85	(85, 85)	1		21	(11, 41)	23	
	KP (Same)	41	(6, 50)	5		10	(3, 21)	8	
Activity Turnover	No	26	(8, 45)	117	0.649	20	(5, 35)	87	0.881
	Yes	22	(21, 50)	9		18	(7, 38)	28	
Partnership Types	Generic	21	(8, 44)	107	0.098	28	(15, 42)	48	0.001
	By Groups	33	(22, 52)	16		11	(3, 28)	66	
	Overlapping	50	(46, 62)	3		58	(58, 58)	1	
Sex Stratification	No	21	(7, 44)	97	0.076	29	(18, 44)	39	< 0.001
	Yes	36	(22, 52)	29		11	(3, 29)	76	

[a] N: number of unique scenarios and time horizons. [b] P-values from non-parametric Kruskal–Wallis test for differences in ART prevention impact under at least one of the factor levels. 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.	2
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.	3
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.	3-4
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.	6, A.4
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.	6, A.2
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6, A.2-A.3
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6, A.4
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.	7, A.6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	7-8, A.6-A.9
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.	7-8, A.6-A.9

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.	9, Fig.1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8-15, A.5
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.	8-15, A.10-A.27
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8-15, A.10-A.27
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.	15-17
Limitations	20	Discuss the limitations of the scoping review process.	17
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.	17
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.	18

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

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

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