Risk heterogeneity in compartmental HIV transmission models applied to assess ART as prevention in Sub-Saharan Africa: A scoping review

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March 10, 2021

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.

Design. Scoping review to identify common modelling assumptions and applications.

Methods. We systematically reviewed studies published before 2020 that used dynamical compartmental models of sexual HIV transmission to simulate the prevention impacts of ART in Sub-Saharan Africa. We extracted and summarized data on model structure and assumptions (factors) related to risk heterogeneity. We also explored crude associations of reported ART prevention impact with modelled factors of risk heterogeneity.

Results. Of 1384 search hits, 94 studies were included. Studies mainly modelled medium/high prevalence epidemics in East and Southern Africa. 64 studies considered stratification by sexual activity and 39 modelled at least one key population. 21 studies modelled differential ART cascade by risk group, including 8 with higher and 4 with lower cascade among key populations versus the general population. Models without activity stratification predicted the largest proportion of infections averted by ART, followed by models with key populations that had higher ART cascade versus the general population.

Conclusions. Among compartmental transmission models applied to project the prevention impacts of ART, representations of risk heterogeneity and the projected impacts both varied considerably. The potential influence of modelling assumptions about differential ART cascade among risk groups should be further explored.

1 Introduction

Sub-Saharan Africa continues to bear the largest burden of HIV. As of 2019, two thirds (25.7 million) of all people living with HIV globally are in Sub-Saharan Africa, where an estimated one million new HIV infections were acquired in 2019.[1] Data suggest that key populations, such as individuals engaged in sex work and men who have sex with men experience disproportionate risks of HIV acquisition and onward transmission in Sub-Saharan Africa.[2–5] 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.[7–9]

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

One theme in the proposed explanations for limited population-level ART effectiveness was heterogeneity in intervention coverage and its intersection with heterogeneity in transmission risks.[16,18] While viral suppression improved under UTT in all three trials, 21–54% of study participants remained unsuppressed.[13–15] 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 female sex workers, men who have sex with men, and adolescent girls and young women.[19–21] While widespread UTT scale-up may fill some of these 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 impact of ART as prevention,[11,22], we sought to critically appraise and examine the type and scope of risk heterogeneity captured in mathematical models used to assess the prevention impacts of ART in Sub-Saharan Africa. We conducted a scoping review with the following objectives. Among dynamical compartmental models of sexual HIV transmission that have been used to simulate the prevention impacts of ART in Sub-Saharan Africa:

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 (see Appendix D for checklist). First, we developed a conceptual framework to organize the assumptions and representations of risk heterogeneity in compartmental HIV transmission models. Then, we designed and implemented the search strategy, and extracted the data relevant to the framework to address the objectives.

2.1 Conceptual Framework for Risk Heterogeneity

For the review, 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 health, structural, and behavioural 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 increase the challenge of epidemic control through core group dynamics[26–29]
- **Coverage Effects:** differential transmission risk within sub-populations who also experience barriers to engaging in ART care and achieving viral suppression, such as youth and key populations[19,21,30,31]

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 (Appendix A.1). Search results were imported into Covidence[32] for screening. Duplicate studies were removed automatically by Ovid and by Covidence; four additional duplicates that were not identified automatically, possibly due to subtle changes to the title, 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 listed 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[23]	**Biological**: transmissions during acute infection are unlikely to be prevented by ART
Late Stage Infection	β_i	Increased infectiousness during late stage infection	**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	**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	**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	**Behaviour Change**: increased HIV testing with ART scale up can contribute to prevention even before viral suppression is achieved
Morbidity Reduction	c; η	Increased sexual activity use after ART initiation	**Behaviour Change**: increased risk behaviour if viral suppression is not sustained could increase transmission risk
Activity Groups	c; κ	Any stratification by rate of partnership formation	**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
Key Populations	c; κ	Any epidemiologically defined higher risk groups	**Network & Coverage** higher transmission risk and barriers to viral suppression among key populations
Group Turnover	ϕ	Individuals move between activity groups and/or key populations reflecting sexual lifecourse	**Network & Coverage**: counteract effect of stratification due to shorter periods in higher risk; viral suppression may be achieved only after periods of higher risk
Assortative Mixing	m	Any degree of assortative mixing by age, activity, and/or key populations	**Network**: assortative sexual networks compound effect of stratification
Partnership Types	η; κ	Different partnership types are simulated, with different volumes of sex and/or condom usage	**Network**: longer duration and lower condom use among main versus casual/sex work partnerships counteracts effect of stratification
ART Cascade Gaps	τ; α	Lower ART cascade coverage among higher activity groups or key populations	**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

We included peer-reviewed, primarily modelling studies that used dynamical models of sexual HIV transmission to project the prevention impacts of ART in any one or more settings within SSA. Complete inclusion/exclusion criteria are given in Appendix A.2 We only included studies communicated in English and published between XXX and Dec 31, 2019. We excluded publications without primary modelling results and their description of the methods, such as commentaries and reviews. We excluded conference publications. If a model's details were provided in a separate peer-reviewed publication, we extracted data from both publications.

The following criteria were used for inclusion of studies: 1) used a dynamical compartmental model of sexual HIV transmission at the population level. We defined a *dynamical 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. We defined a *compartmental model* as one where the system variables represent the numbers of individuals in each state, rather than unique individuals. Thus, statistical models, non-dynamical models, and individual-based models without dynamic transmission were excluded. 2) the model was calibrated or parameterized to reflect at least one setting within SSA. (see Table A.4 for full country list). 3) the study simulated at least one scenario with increasing ART coverage, possibly alongside scale-up of other interventions. The included studies formed Dataset A, used to answer research questions 1 and 2.

A subset of Dataset A formed Dataset B, which used to answer research question 3. Studies in Dataset B specifically examined scale-up of ART coverage alone (vs combination intervention) for the whole population (vs ART prioritized to subgroups), and reported HIV incidence reduction or cumulative HIV infections averted over time as compared to a base-case scenario reflecting the status quo.

2.3 Data Extraction

Data extraction used the full text and all available supplementary material. For research questions 1 and 2, data were extracted per-article. For research question 3, data were extracted per-scenario within the article. Additional variables definitions are given in Appendix B.

2.3.1 Epidemic Context

To answer Research Question 1, we extracted data on geography, epidemic phase, and subgroups explicitly considered in the model. Specifically, we categorized studies by the geographic location (country and SSA region), scale of the simulated population (city, sub-national, national, regional), and whether the study included multiple geographic settings. We classified epidemic size at time of ART intervention using the overall HIV prevalence at that time (low: $< 1\%$, medium: $1 - 10\%$, high: $> 10\%$), and classified epidemic phase at the time of ART intervention using the trend in incidence at that time (increasing, increasing but stabilizing, stable/equilibrium, decreasing but stabilizing,

and decreasing). Subgroups of interest included the following key populations: 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: begin < 5 % of the female population; being $< 1/3$ the size of the client population; and having $> 50\times$ the partners per year of the lowest sexually active female activity group. Likewise, clients were defined as any male activity group meeting 2 criteria: being described as clients of FSW; being $> 3\times$ the size of the FSW population. If it was not possible to evaluate any criteria due to lack of data, then we assumed the criteria was satisfied. No specific criteria were used to define MSM or PWID.

2.3.2 Factors of Risk Heterogeneity

For Research Question 2, we examined if and how the factors of risk heterogeneity outlined in Table 1 were simulated in each study.

Special focus was given to the factors related to Network and Coverage Effects, due to the large variability in how these factors were simulated. We examined the number and defining characteristics of *activity groups*, including sex, different rates of partnership formation, and different types of partnerships. We extracted whether each of the *key populations* noted above was included in the model. Any *turnover* of individuals between activity groups and/or key populations was noted.

We extracted whether multiple *partnership types* were simulated, and classified how such partnerships were defined: generic (all partnerships equal); based only on the activity groups involved; or reflecting identifiable types (main/spousal; casual; commercial/sex work; transactional), such that different partnership types could be formed between the same two activity groups. We extracted whether partnerships considered different volumes of sex (total number of coital acts per partnership) and levels of condom use. We extracted whether models simulated any degree of assortative vs proportionate *mixing* between activity groups. The number of unique *age groups* was extracted, as well as whether *mixing* by age groups was proportionate, strictly assortative, or assortative with age differences. We extracted whether age conferred any additional risk beyond mixing, such as higher rates of partnership formation.

Finally, we extracted whether rates of HIV diagnosis, ART initiation, and/or ART discontinuation differed across modelled risk strata (sex, activity, key populations, and/or age), and if so, how they differed.

2.3.3 ART Prevention Impact

For Research Question 3, we examined the subset of studies (Dataset B) reporting incidence reduction or infections averted due to population-wide ART scale-up. We extracted the following data for each scenario of ART scale-up within Dataset B: the years that ART scale-up started and stopped, corresponding to the time each scenario diverged from the base-case scenario (t_0) and the time ART coverage or initiation rates stabilized following scale-up (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. CD_4 count); and the relative reduction in transmission probability on ART. Then, we extracted relative reduction in incidence or proportion of infections averted reported for different time horizons relative to t_0. Figure data were extracted 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.[1]

Finally, for each factor of heterogeneity, we compared the projected ART prevention impacts across the different factor levels (whether or not, and how the factor was modelled). We plotted impact magnitude vs time since t_0, stratified by factor levels, and explored whether the distribution in magnitude of impact was the same under all factor levels (non-parametric Kruskal-Wallis test).

3 Results

The search yielded 1384 publications, of which 94 studies were included (Figure 1). 360 studies used dynamical HIV transmission models applied to SSA, of which 255 were compartmental models. 94 compartmental modeling studies simulated ART scale-up (Database A), of which 40 reported infections averted or incidence reduction due to population-wide ART scale-up without additional combination interventions, as compared to a base case reflecting status quo (Database B). Appendix A.3 lists the included papers, and Appendix C provides additional results.

3.1 Epidemic Context

Table 2 summarizes the 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, including 51 single-country and 10 multi-country analyses. Studies also explored regional (1), subnational (16), and city-level (16) epidemic scales. South Africa was the most common country simulated (52 studies), but was not disproportionately represented among SSA countries: the number of studies per million PLHIV as of 2019 in South Africa (7.22) was similar to the SSA median (6.27). Figure 2 illustrates the number of studies by country. East Africa was the most represented SSA region being simulated in 75 studies, followed by Southern (69), Central (25), and West Africa (1).

ART prevention impacts were most often modelled in high-prevalence epidemics ($>$ 10% HIV prevalence, 41 studies) and medium-prevalence epidemics ($1-10\%$, 23 studies). No studies reported overall HIV prevalence of $<1\%$ at time of ART scale-up, although for 30 studies, HIV prevalence was either not reported or varied across independently simulated contexts/scenarios. The median [min, (IQR), max] year of scenario ART scale-up was 2014 [1990, (2010, 2015), 2040]; at which time HIV prevalence (%) was 15 [2, (6, 19), 32]; and incidence (per 1000 PY) was 14 [1, (9, 20), 50]. Most contexts reporting incidence trends had decreasing or stable incidence (45 of 48 reporting).

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

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]	28
	Clients [c]	22
	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] FSW as defined by three epidemiological criteria in Appendix B.2.1; 11 met all three FSW criteria while 17 were described as FSW but the criteria could not be evaluated; another 11 were described as FSW but did not meet the criteria. [c] Likewise for clients, the counts were: 8, 14, and 9, respectively.

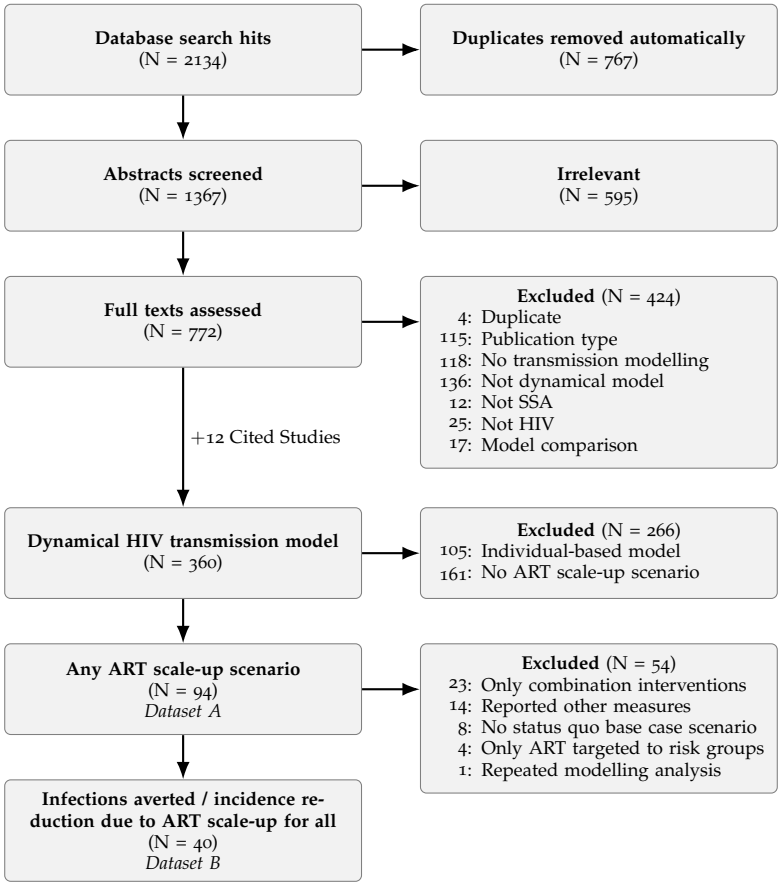


Figure 1: PRISMA flowchart of study identification

3.1.1 Key Populations

FSW were defined based on a combination of being described as FSW by the study and three epidemiological criteria. Among 39 studies describing FSW activity groups: all three criteria were satisfied in 11 studies; the criteria were either satisfied or indeterminate and assumed to be satisfied in another 17; and were not satisfied in 11. Among studies that did not describe FSW activity groups, none satisfied all three criteria.

Among 31 studies describing clients of FSW: 8 met the epidemiological criteria; 14 were indeterminate and assumed to meet the criteria; and 9 did not meet the criteria. Another 7 described clients as a proportion of another male risk group.

Activity groups described as representing men who have sex with men (MSM) were noted in 28 studies; people who inject drugs (PWID) in 11.

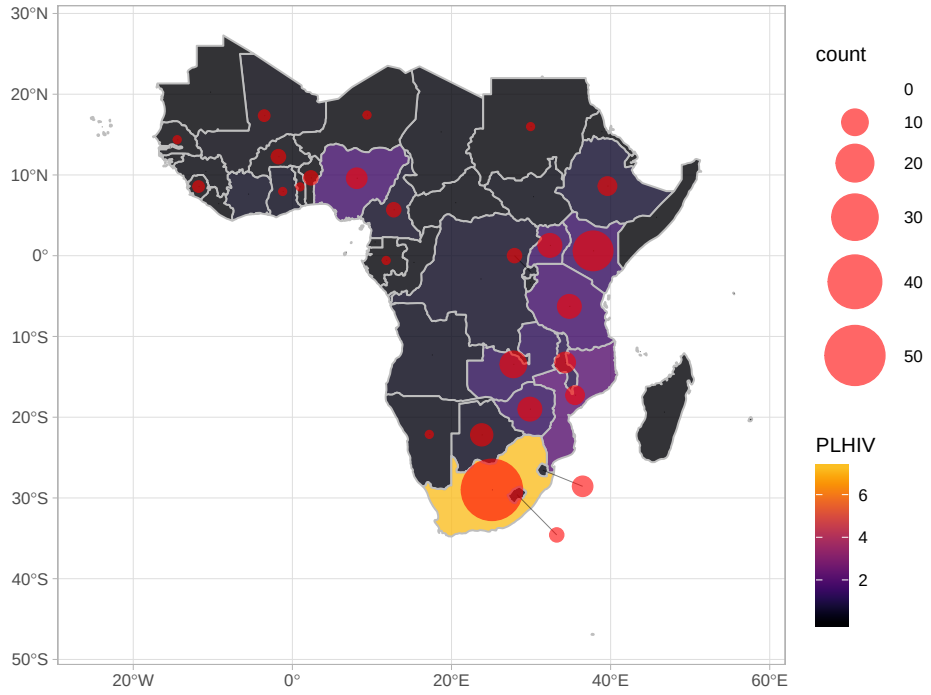


Figure 2: Map showing number of studies (of 94 total) applying HIV transmission modelling in each country vs the number of people living with HIV (PLHIV, millions)

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], and 2 studies represented HIV along a continuous dimension using a partial differential equations model. Most HIV states were defined by CD_4 count to reflect clinical progression and/or historical ART eligibility, often with additional states to represent acute infection and/or development of AIDS. 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], representing an average "on-treatment" state in 78 studies, vs a "virally suppressed" state specifically in 15 studies. Treatment failure due to drug resistance was simulated in 30 studies, including: 23 using a separate "treatment failure" compartment; 23 using a transition back into a generic "off-treatment" HIV state; and another 6 in which a similar transition was not clearly identified as treatment failure vs dropout. Transmissible drug resistance was simulated in 9 studies.

3.2.2 Behavioural Effects

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

Separate health states representing diagnosed HIV but not yet on treatment and on treatment but not yet virally suppressed were simulated in 30 and 17 studies, respectively. 22 studies modelled changes in behaviour following awareness of HIV status among PLHIV: 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 cessasation was simulated in 30 studies, including: 16 using a separate compartment; 19 using a flow back into a generic "off-treatment" HIV state; and again 6 in which a similar flow was not clearly identified as treatment failure vs ART cessasation.

3.2.3 Network Effects

Representations of risk heterogeneity varied widely. Risk groups defined at least in part by activity (different rates and/or types of partnerships formed) were simulated in 59 studies, and at least in part by sex in 64 studies. Considering both activity and sex, the number of risk groups simulated was 6 [1, (2, 9), 19]; considering activity alone (maximum number of groups in either men or women), it was 3 [1, (3, 4), 18]. The highest activity groups (including FSW and clients, where applicable) for females and males comprised 2 [0, (2, 4), 23] and 9 [0, (2, 14), 35] % of female and male populations, respectively.

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 activity groups into higher activity groups to re-balance group sizes against disproportionate HIV mortality in higher activity groups.

Among 59 studies with activity groups, sexual mixing was assumed to be assortative in 57 and proportionate in 2. Regarding the three approaches to partnership types: First, partnerships were considered to have equal probability of transmission in 39 studies, including all studies without activity groups. Second, partnerships were defined by the activity groups involved (44 studies). In such partnerships, transmission was usually lower in high-with-high activity partnerships than in low-with-low, due to a combination of fewer sex acts (31) and increased condom use (23). The transmission risk in mixed high-with-low activity partnerships was defined by: the susceptible partner (9); the lower activity partner (11); the higher activity partner (3); or the unique combination of both partners' activity groups (15). Third, partnerships could be defined based on phenomenological types (main/spousal, casual, and sex work), such that different partnership types could be formed between the same two activity groups (11 studies). All models with phenomenological partnerships defined differential total sex volume and condom use between types.

Age groups were simulated in 32 studies. Among studies with age groups, the number of age groups was 10 [2, (4, 34), 91], 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 occurred in 29 of these 32 studies.

3.2.4 Coverage Effects

Differential progression along the ART cascade was considered in 21 studies, including differences between sexes in 15; age groups in 7; and key populations in 12. No studies considered differences among activity groups beyond key populations. Another 2 studies did not simulate differential progression but specifically justified the simplification using data relevant to the simulated context.

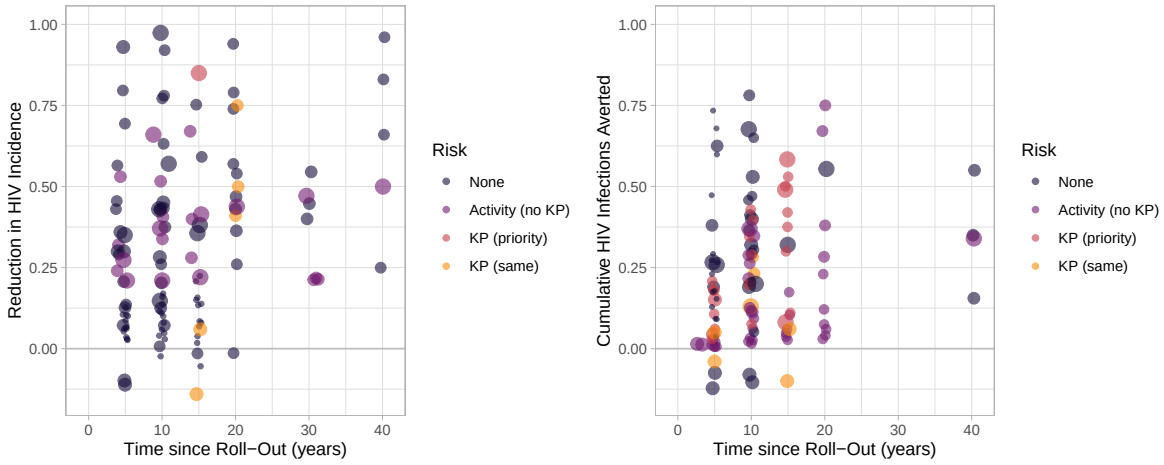
Differences between sexes included rates of diagnosis (11); ART initiation (6); and retention (1), with cascade engagement higher among women, in most cases attributed to antenatal services. Differences between age groups also affected rates of diagnosis (6); ART initiation (1); but not retention (0). 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. Reported impact on incidence ranged from 93% reduction over 10 years[10] to 14% increase over 15 years,[33] while impact on cumulative infections ranged from 78% reduction over 10 years[34] to 12% increase over 5 years.[35]

Figure 3 summarizes each outcome versus time since ART scale-up, stratified by a composite index of modelled risk heterogeneity. Ecological level analyses across scenarios by degree of risk heterogeneity did not identify a difference in the relative incidence reduction. However, there was an ecological-level difference in the reported proportions of infections averted across scenarios by the degree of risk heterogeneity. 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 access (21 [11, 41]). The smallest impact (proportion of infections averted) was observed in scenarios with key populations who were not prioritized for ART(10 [3, 21]) and in models with some risk heterogeneity but without key populations (6 [3, 22]). Only 11 scenarios provided both outcomes;[33–39] within which the pattern of incidence reduction versus modelled heterogeneity was generally similar to the pattern of infections averted vs modelled heterogeneity (Figure C.41).

Appendix C.2 and Table C.1 summarizes the reported ART prevention impacts (relative incidence



(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.

reduction and proportion of infections averted), stratified by: other factors of risk heterogeneity; epidemic contexts; and intervention conditions. For example, reported incidence reduction and proportion of infections averted were both larger with longer time horizon, greater ART eligibility, and higher ART coverage.

4 Discussion

Via scoping review, we found that representations of risk heterogeneity varied widely across transmission modelling studies of ART in SSA, with stratification by sexual activity and key populations considered in approximately two thirds and one third of models, respectively. We also found that the projected proportions 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, models can go further in keeping pace with epidemiological data on risk heterogeneity. For example, the majority of models did not consider key populations. Even in high-prevalence epidemics, especially with declining overall incidence, core groups continue to influence epidemic dynamics.[40,41] Among studies that considered female sex workers, parameterization of that modelled risk group did not always reflect epidemiological definitions, such as representing a smaller popula-

tion than their clients, and having much higher sexual activity than other women in the model.[28,42] Many models also defined partnership types based on the risk groups involved, precluding the formation of longer partnerships with lower condom use between two higher risk individuals. In fact, female sex workers may form such partnerships with regular clients and boyfriends/spouses from higher risk groups.[42] Overall, it is likely important that models reflect established factors of risk heterogeneity because nested model comparison studies suggest that multiple factors can each influence the challenge of epidemic control through ART scale-up.[29,43]

Second, emerging evidence of differential ART cascade by sex, age, and key populations[21,30,31] has not yet been regularly incorporated into modelling assumptions and scenarios. It is important to incorporate these data because barriers to ART may intersect with transmission risk, particularly among key populations, due to issues of stigma, discrimination, and criminalization.[16,41] A recent review of PrEP modelling in SSA[44] identified similar opportunities to better leverage programmatic data. Context-specific key population cascade data to support these efforts are often lacking.[30] However, sensitivity analyses of modelling assumptions related to cascade equity would likely be well-justified based on existing data,[21,30] and considering that unmeasured key population cascades may be lowest.[45] Modelled representations of the treatment cascade may also need expansion to include more cascade steps and states related to treatment failure and discontinuation.

Finally, based on ecological analysis of scenarios, we found evidence that modelling assumptions about risk and intervention heterogeneity may influence the projected proportion of future infections averted by ART. We did not find similar evidence for relative incidence reduction due to ART, but studies reporting these two outcomes were largely distinct. Among studies reporting both, the overall pattern was consistent. 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 answer this question. 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.

Our review has four main limitations. First, the key populations we considered did not include adolescent girls and young women, transgender people, or mobile populations, even though such populations may experience similar risks of transmission and barriers to care as other key populations[46,47] We also did not document representations of violence, coercion, or anal sex, which may similarly coincide with transmission risks and barriers to care.[48,49] Future work should explore representations of such groups and phenomena in transmission models. Second, we did not document which (if any) model parameters were fitted or to which calibration targets. As shown previously[50,51], model fitting can produce parameter values which compensate for differences in model structure, and thereby underpin counterintuitive associations between model structure and modelling results. Third, we did not compare modelled factors of heterogeneity to context-specific epidemiological data, which in some cases may justify model assumptions of homogeneity. However, we did note when authors specifically justified such assumptions. Finally, we did not estimate the effect size of individual heterogeneity factors on the projected ART prevention impact. Such

an effect estimate could be biased by confounding factors in univariate analysis, while exploratory work found challenges in multivariate analysis of our data, due to the small number of scenarios and high data collinearity.

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 the projected impacts. Many opportunities also remain to incorporate new and existing data on the intersections of risk heterogeneity and intervention heterogeneity. Step-wise model comparison studies are likely needed to estimate and understand the relative influence of various modelling assumptions on the prevention impacts of ART.

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Acknowledgements

We are grateful to: Kristy Yiu (Unity Health Toronto) for administrative support; Kaitlin Fuller (University of Toronto) for her help designing the search strategy.

Contributions

TODO

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.

Conflicts of Interest

None.

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 `[section]` refers to the result from another section, `term/` denotes a MeSH term, and `.mp` searches the main text fields, including title, abstract, and heading words.

Table A.1: Exclusion

	Term	Hits
1	2190	`[model] AND [hiv] AND [ssa]`
2	2160	`1 NOT animal/`
3	2155	`limit 2 to english language`
4	2125	`limit 3 to yr="1860 - 2019"`
5	1384	`remove duplicates from 4`

Table A.2: Search Terms related to modelling ("model")

	Hits	Term
1	238,076	`model, theoretical/`
2	334,921	`model, biological/`
3	302,802	`computer simulation/`
4	196,814	`patient-specific modeling/`
5	67,459	`monte carlo method/`
6	32,801	`exp stochastic processes/`
7	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.`
8	1,369,153	`OR/ 1-7`

Table A.3: Search Terms related to HIV ("HIV")

	Term	Hits
1	290,863	`exp HIV/`
2	651,624	`exp HIV infections/`
3	753,274	`(HIV OR HIV1* OR HIV2* OR HIV-1* OR HIV-2*).mp.`
4	369,182	`hiv infect*.mp.`
5	538,214	`(human immun*deficiency virus OR human immun* deficiency virus).mp.`
6	216,228	`exp Acquired Immunodeficiency Syndrome/`
7	235,971	`(acquired immun*deficiency syndrome OR acquired immun* deficiency syndrome).mp.`
8	954,470	`OR/ 1-7`

Table A.4: Search Terms related to SSA ("SSA")

	Term	Hits
1	3512	Angola/ OR Angola.mp.
2	9273	Benin/ OR Benin.mp.
3	5809	Botswana/ OR Botswana.mp.
4	9983	Burkina Faso/ OR Burkina Faso.mp.
5	2055	Burundi/ OR Burundi.mp.
6	16,822	Cameroon/ OR Cameroon.mp.
7	1196	Cape Verde/ OR Cape Verde.mp.
8	15,416	Central African Republic/ OR Central African Republic.mp. OR CAR.ti.
9	3075	Chad/ OR Chad.mp.
10	995	Comoros/ OR Comoros.mp.
11	13,737	Democratic Republic of the Congo/ OR Democratic Republic of the Congo.mp. OR DRC.mp.
12	959	Djibouti/ OR Djibouti.mp.
13	1131	Equatorial Guinea/ OR Equatorial Guinea.mp.
14	1437	Eritrea/ OR Eritrea.mp.
15	35,959	Ethiopia/ OR Ethiopia.mp.
16	4500	Gabon/ OR Gabon.mp.
17	6626	Gambia/ OR Gambia.mp.
18	25,213	Ghana/ OR Ghana.mp.
19	360,920	Guinea/ OR Guinea.mp.
20	2625	Guinea-Bissau/ OR Guinea-Bissau.mp.
21	9730	Cote d'Ivoire/ OR Cote d'Ivoire.mp. OR Ivory Coast.mp.
22	46,917	Kenya/ OR Kenya.mp.
23	1649	Lesotho/ OR Lesotho.mp.
24	4239	Liberia/ OR Liberia.mp.
25	11,386	Madagascar/ OR Madagascar.mp.
26	16,367	Malawi/ OR Malawi.mp.
27	9111	Mali/ OR Mali.mp.
28	1573	Mauritania/ OR Mauritania.mp.
29	2373	Mauritius/ OR Mauritius.mp.
30	8502	Mozambique/ OR Mozambique.mp.
31	3818	Namibia/ OR Namibia.mp.
32	35,455	Niger/ OR Niger.mp.
33	82,192	Nigeria/ OR Nigeria.mp.
34	13,547	Republic of the Congo/ OR Republic of the Congo.mp. OR Congo-Brazzaville.mp.
35	1545	Reunion/
36	7597	Rwanda/ OR Rwanda.mp.
37	342	"Sao Tome AND Principe"/ OR "Sao Tome AND Principe".mp.
38	16,674	Senegal/ OR Senegal.mp.
39	1566	Seychelles/ OR Seychelles.mp.
40	5456	Sierra Leone/ OR Sierra Leone.mp.
41	4667	Somalia/ OR Somalia.mp.
42	114,536	South Africa/ OR South Africa.mp.
43	1193	South Sudan/ OR South Sudan.mp.
44	21,680	Sudan/ OR Sudan.mp.
45	2409	Swaziland/ OR Swaziland.mp. OR Eswatini/ OR Eswatini.mp.
46	32,442	Tanzania/ OR Tanzania.mp.
47	3749	Togo/ OR Togo.mp.
48	37,399	Uganda/ OR Uganda.mp.
49	13,506	Zambia/ OR Zambia.mp.
50	15,755	Zimbabwe/ OR Zimbabwe.mp.
51	482,060	exp africa south of the sahara/ OR sub-saharan.mp. OR south of the sahara.mp.
52	982,505	OR/ 1-51

A.2 Inclusion/Exclusion Criteria

Table A.5: 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 • dynamical HIV transmission model [2] • population-level dynamics • compartmental model [3]	• no sexual HIV transmission modelled • HIV transmission model is not dynamical • only within-host/cellular/protein modelling • individual-based model
Context & Research Questions	
• any region in Sub-Saharan Africa (SSA) [4] • assess prevention impact of ART scale-up [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 targeted to some risk groups [*] • ART prevention benefits not reported [5*]

[1] Review articles were included if they also presented new HIV transmission modelling results fitting our criteria. [2] We define a *dynamical 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 A.4 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

[33] 2005 Salomon *et al.*
[34] 2006 Abbas *et al.*
[10] 2009 Granich *et al.*
[52] 2009 Hallett *et al.*
[53] 2010 Bacaer *et al.*
[36] 2010 Pretorius *et al.*
[54] 2011 Metzger *et al.*
[55] 2012 Yusuf & Benyah
[56] 2012 Andrews *et al.*
[57] 2012 Granich *et al.*
[58] 2012 Wagner & Blower
[59] 2013 Abbas *et al.*
[60] 2013 Long & Stavert
[61] 2013 Cremin *et al.*
[62] 2013 Alsallaq *et al.*
[37] 2014 Nichols *et al.*
[63] 2014 Nichols *et al.*
[64] 2014 Alistar *et al.*
[50] 2014 Eaton *et al.*
[65] 2015 Ying *et al.*
[66] 2015 Low *et al.*
[67] 2015 Khademi & Moody
[68] 2015 Gilbert *et al.*
[69] 2015 Heaton *et al.*
[70] 2016 Rahman *et al.*
[71] 2016 Gilbert *et al.*
[72] 2016 Blaizot *et al.*
[73] 2016 Ying *et al.*
[35] 2016 Barnighausen *et al.*
[74] 2016 Heffernan *et al.*
[75] 2017 Maheu-Giroux *et al.*
[38] 2017 Maheu-Giroux *et al.*
[76] 2017 Volz *et al.*
[77] 2017 Blaizot *et al.*
[78] 2018 Mukandavire *et al.*
[79] 2018 Guillon
[39] 2018 Akudibillah *et al.*
[80] 2018 Stuart *et al.*
[81] 2018 de Montigny *et al.*
[82] 2019 Hauser *et al.*

A.3.2 Dataset A less B

[83] 2006 Johnson & Dorrington
[84] 2006 Baggaley *et al.*
[85] 2006 Wilson *et al.*
[86] 2008 Bacaer *et al.*
[87] 2009 Chigidi & Lungu
[88] 2010 Williams *et al.*
[89] 2011 Nyabadza & Mukandavire
[90] 2012 Barnighausen *et al.*
[91] 2013 Wagner *et al.*
[92] 2013 Decker *et al.*
[93] 2013 Wirtz *et al.*
[94] 2014 Shafer *et al.*
[95] 2014 Hove-Musekwa *et al.*
[96] 2014 Braithwaite *et al.*
[97] 2014 Nichols *et al.*
[98] 2014 Abu-Raddad & Awa
[99] 2014 Anderson *et al.*
[100] 2014 Alistar *et al.*
[12] 2014 Cori *et al.*
[101] 2014 Stover *et al.*
[102] 2014 Wirtz *et al.*
[103] 2015 Korenromp *et al.*
[104] 2015 Knight *et al.*
[105] 2015 Kerr *et al.*
[106] 2015 Fraser *et al.*
[107] 2015 Kassa & Ouhinou
[108] 2015 Bekker *et al.*
[109] 2015 Shannon *et al.*
[110] 2015 Blaizot *et al.*
[111] 2016 Smith *et al.*
[112] 2016 Atun *et al.*
[113] 2016 Shattock *et al.*
[114] 2016 McGillen *et al.*
[115] 2016 Johnson *et al.*
[116] 2016 Sharma *et al.*
[117] 2017 Akudibillah *et al.*
[118] 2017 Alsallaq *et al.*
[119] 2017 Anderson *et al.*
[120] 2017 Chiu *et al.*
[121] 2017 Johnson *et al.*
[122] 2017 Stuart *et al.*
[123] 2017 McGillen *et al.*
[124] 2017 Cremin *et al.*
[125] 2018 Ross *et al.*
[126] 2018 Anderson *et al.*
[127] 2018 Anderson *et al.*
[128] 2018 Omondi *et al.*
[129] 2018 Woods *et al.*
[130] 2018 Stevens *et al.*
[131] 2019 Stopard *et al.*
[132] 2019 Beacroft & Hallett
[133] 2019 Reidy *et al.*
[134] 2019 Omondi *et al.*
[135] 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 in X". Data were assessed from figures with the help of a graphical measurement tool.[2]

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_0 be the time of ART scale-up/scenario divergence in the model.

HIV Prevalence: As reported at t_0: *Low*: $< 1\%$; *Medium*: $1 - 10\%$; *High*: $> 10\%$.

Epidemic Phase: Based on HIV incidence trend projected in the base case scenario between t_0 and roughly $t_0 + 10$ years. Increasing (linear or exponential); Increasing but stabilizing; Stable; Decreasing but stabilizing; Decreasing (linear or exponential).

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 $< 1/3\times$ the size of client population or highest heterosexual male activity group; and having $> 50\times$ the partners of the lowest sexually active female activity group. We also noted whether the authors described any activity groups as FSW. If it was not possible to evaluate any criteria due to lack of data, then we assumed the criteria was satisfied.

Clients of FSW: Any male activity group meeting 2 criteria: described as representing clients of FSW; being $> 3\times$ the size of the FSW population. 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.

Adolescent Girls and Young Women: TODO

Mobile Populations: TODO

B.2.2 Activity Groups

Activity groups were

Activity groups were counted separately for heterosexual women, heterosexual men, and MSM.

Age groups were counted separately, even when age influenced sexual activity.

B.2.3 Partnership Types

Generic: If only one type of partnership is simulated in the model.

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

Main:

Casual:

Sex Work:

Transactional:

Defined by the Partners:

B.2.4 Group Turnover

Turnover refers to movement of individuals between activity groups and/or key populations reflecting sexual life course. We defined the following five classifications of turnover: *N/A*: not applicable if no activity groups were modelled; *None*: no movement between activity groups; *High-Activity*: only movement between one high activity group or key population and one other activity group; *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.3 Antiretroviral Therapy

B.3.1 Transmission Reduction

The reduction in HIV transmission due to ART was defined as the relative reduction in probability of transmission among individuals who are virally suppressed (0 is perfect prevention, 1 is no effect).

B.3.2 States

Diagnosed: Individuals are aware of their HIV+ status, but have not yet started ART.

Not Yet Virally Suppressed: Individuals have started ART, but are not yet virally suppressed.

Treatment Failed Due to Resistance: Individuals have stopped experiencing the benefits of ART due to development of resistance; resuming ART is defined by or implies a 2+ line regimen.

Off ART: Individuals are not taking ART due to reasons unrelated to resistance; it may be possible to resume ART, possibly with the same regimen.

B.3.3 Behaviour Change

HIV Morbidity: Any reduced sexual activity in late-stage HIV states representing impact of symptoms, including: fewer sex acts per sex partnership; or fewer partnerships per year.

HIV Counselling: Any sexual behaviour change associated with HIV testing and counselling (HTC), applied to individuals in the diagnosed and/or on-ART states, including: increased condom use; fewer sex acts per sex partnership; fewer partnerships per year; or a generic reduction in per-act/per-partnership transmission probability due to counselling.

Morbidity Reduction: Must first include HIV morbidity. Morbidity reduction behaviour change is any return towards normal levels of sexual activity associated with ART due to reduced symptoms.

B.3.4 Transmitted Resistance

Any consideration of 1+ strains of HIV which are transmitted and for which ART has reduced benefits. We did not document the number of resistant strains, or characteristics of resistance and transmissibility.

C Supplemental Results

C.1 Risk Heterogeneity

C.1.1 Distributions

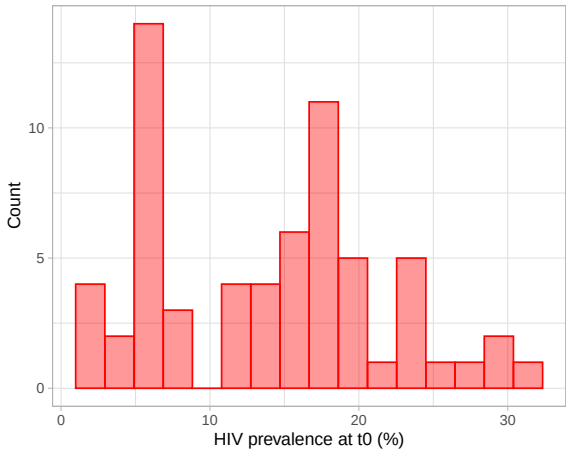


Figure C.1: HIV prevalence at t_0 (%)

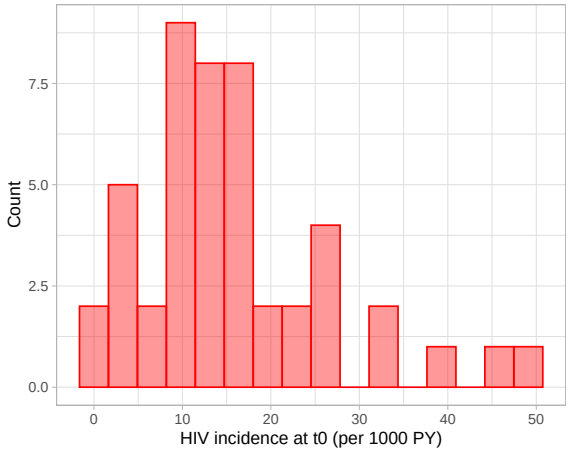


Figure C.2: HIV incidence at t_0 (per 1000 PY)

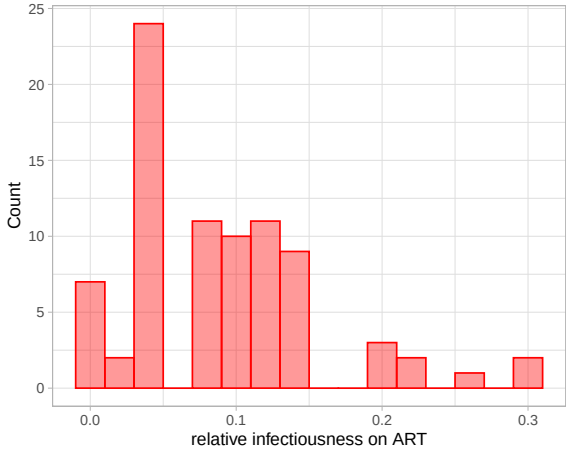


Figure C.3: relative infectiousness on ART

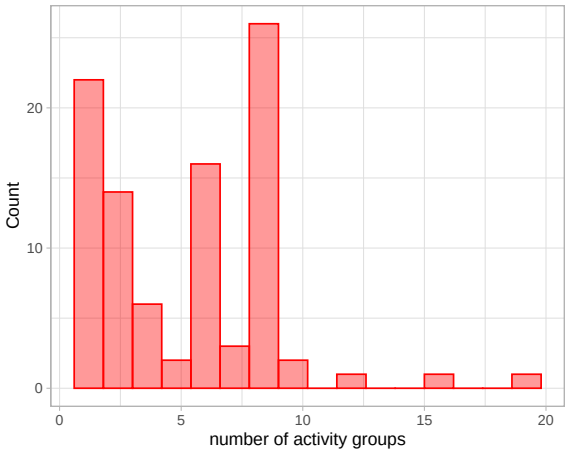


Figure C.4: number of activity groups

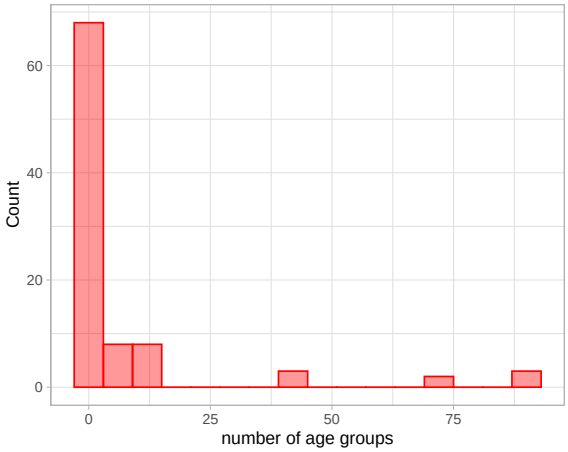


Figure C.5: number of age groups

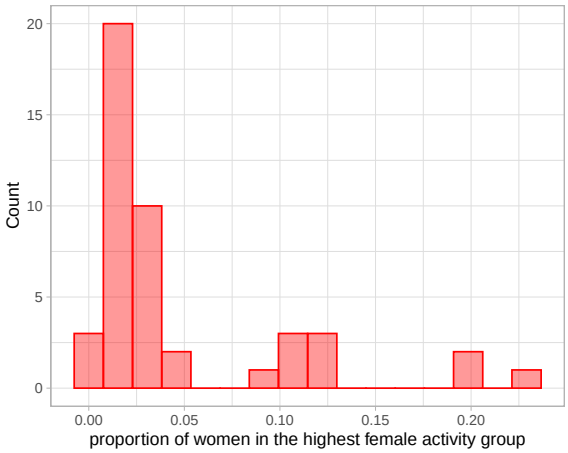


Figure C.6: proportion of women in the highest female activity group

Figure C.7: proportion of men in the client or highest activity male group

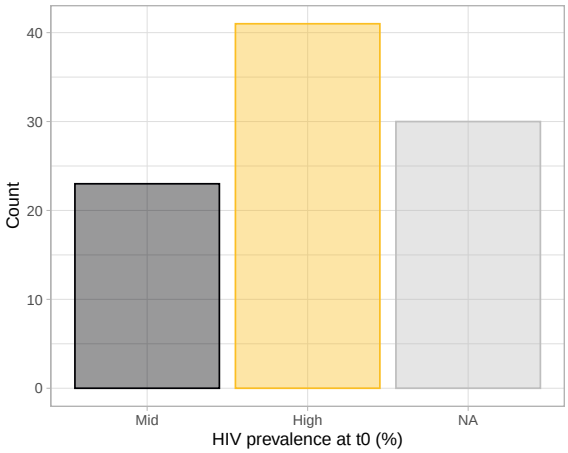


Figure C.10: HIV prevalence at t_0 (%)

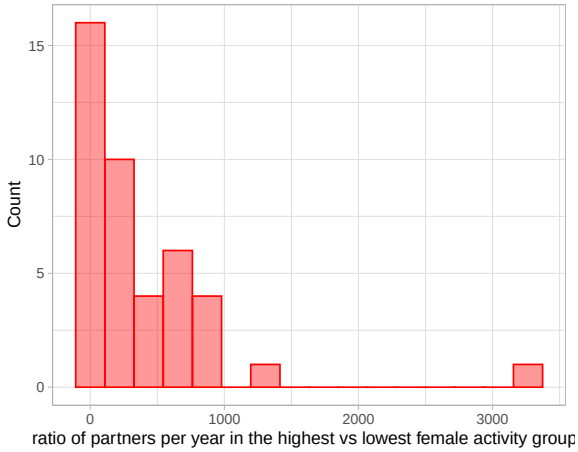


Figure C.8: ratio of partners per year in the highest vs lowest female activity groups

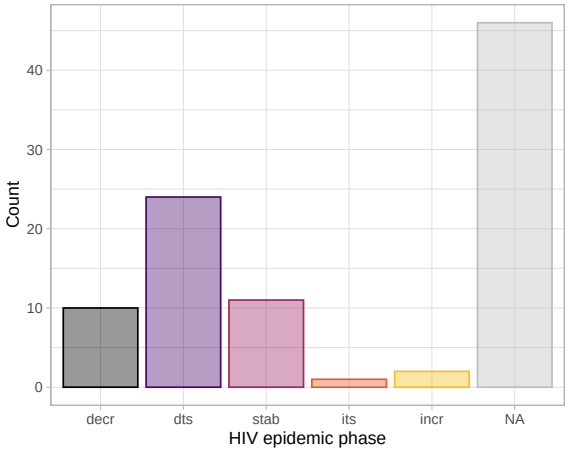


Figure C.11: HIV epidemic phase

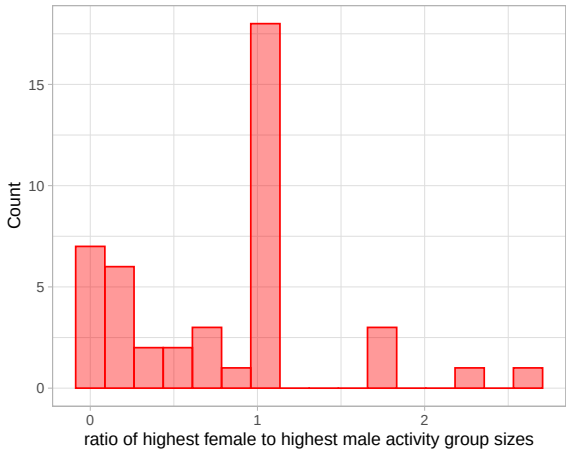


Figure C.9: ratio of highest female to highest male activity group sizes

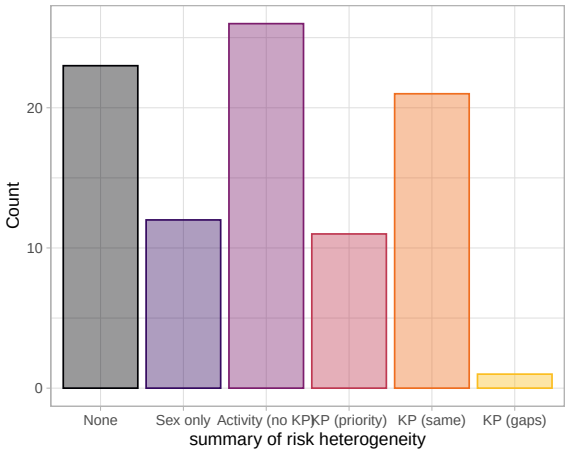


Figure C.12: summary of risk heterogeneity

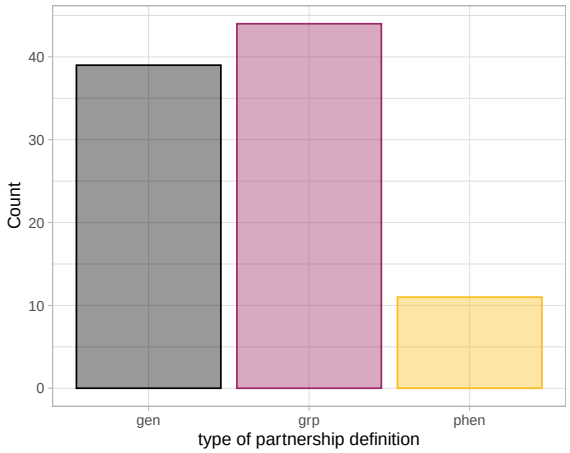


Figure C.13: type of partnership definition

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 conditions (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.

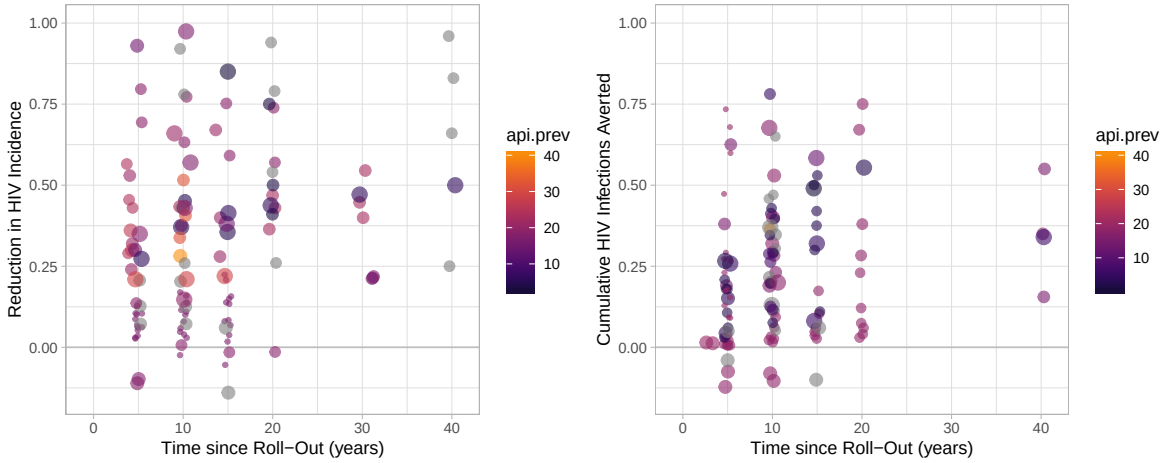


Figure C.14: HIV prevalence at t_0 (%)

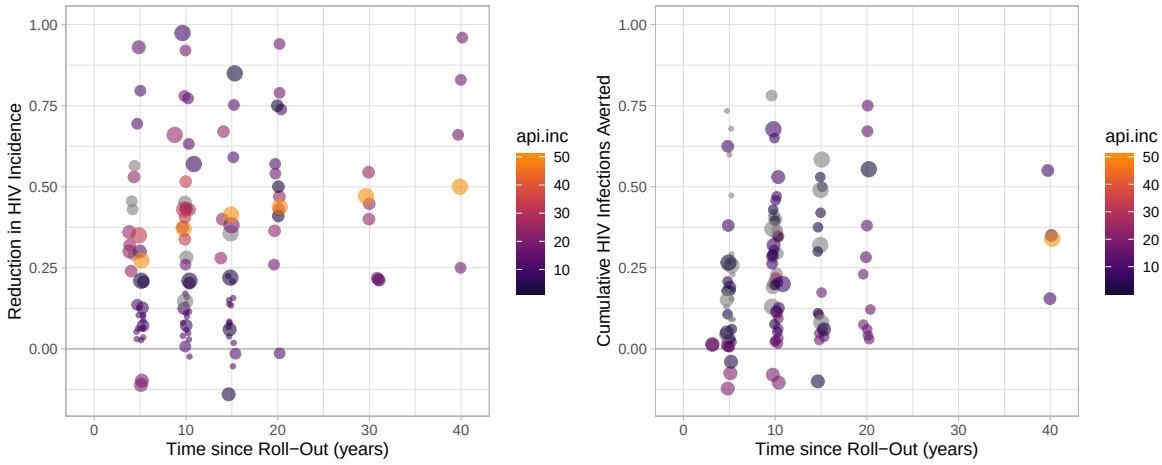


Figure C.15: HIV incidence at t_0 (per 1000 PY)

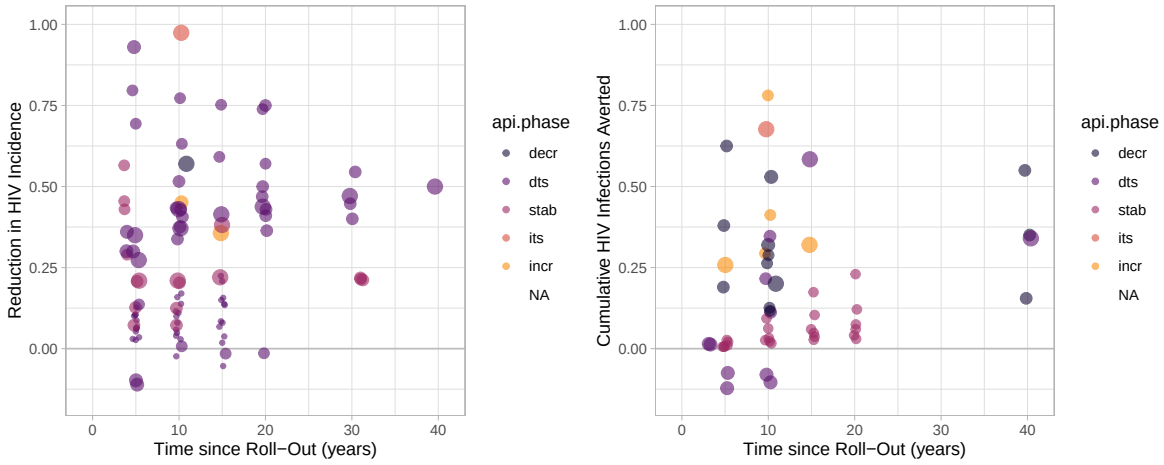


Figure C.16: HIV epidemic phase

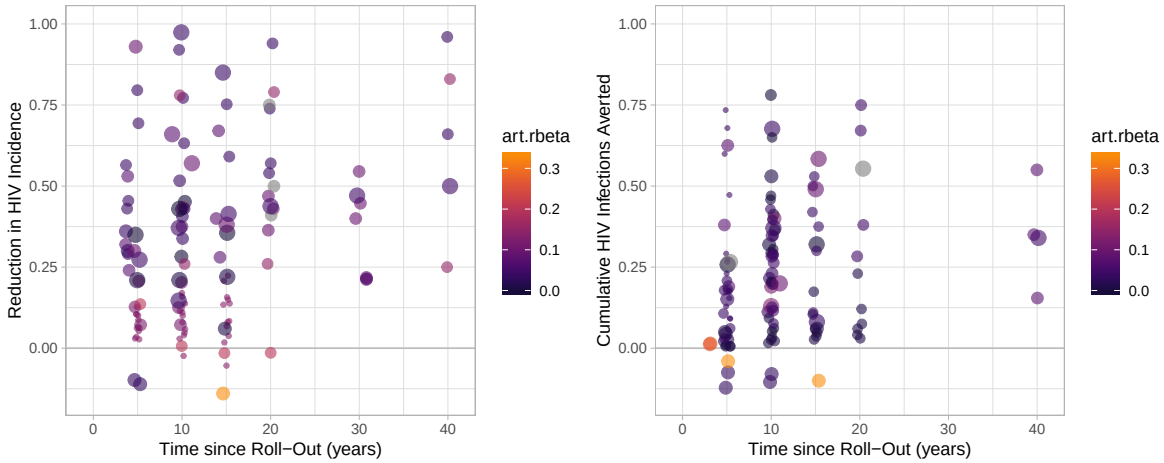


Figure C.17: relative infectiousness on ART

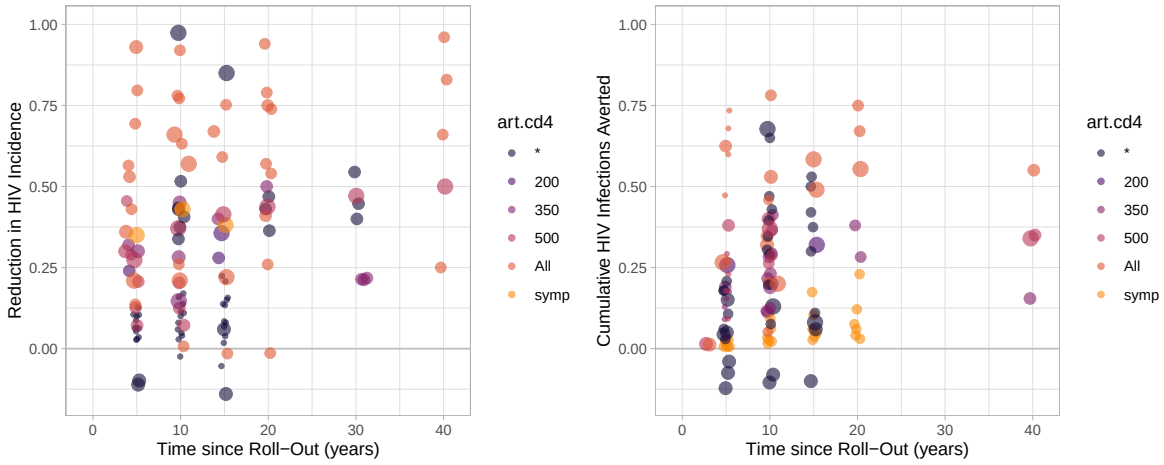


Figure C.18: CD4 initiation criteria (less than shown count)

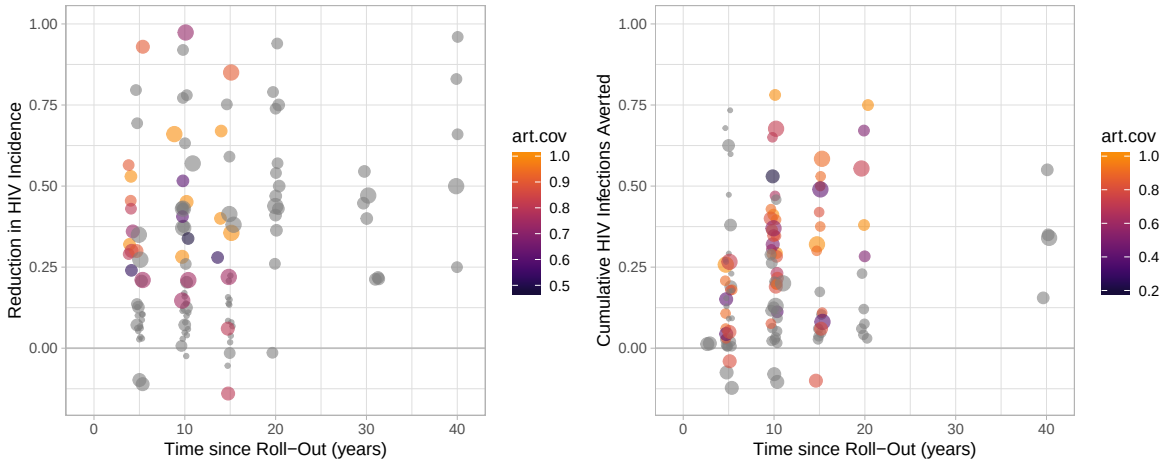


Figure C.19: ART coverage target

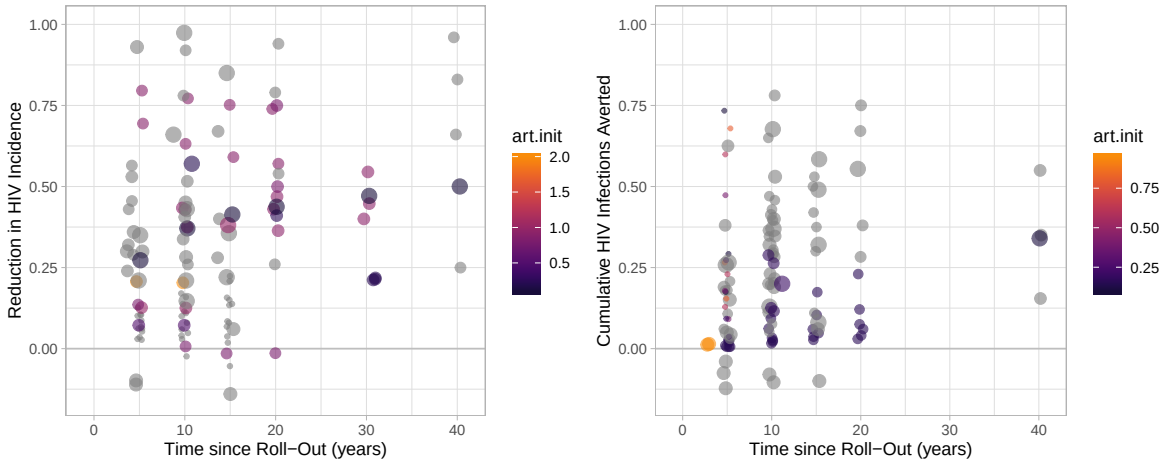


Figure C.20: ART initiation rate (per PY)

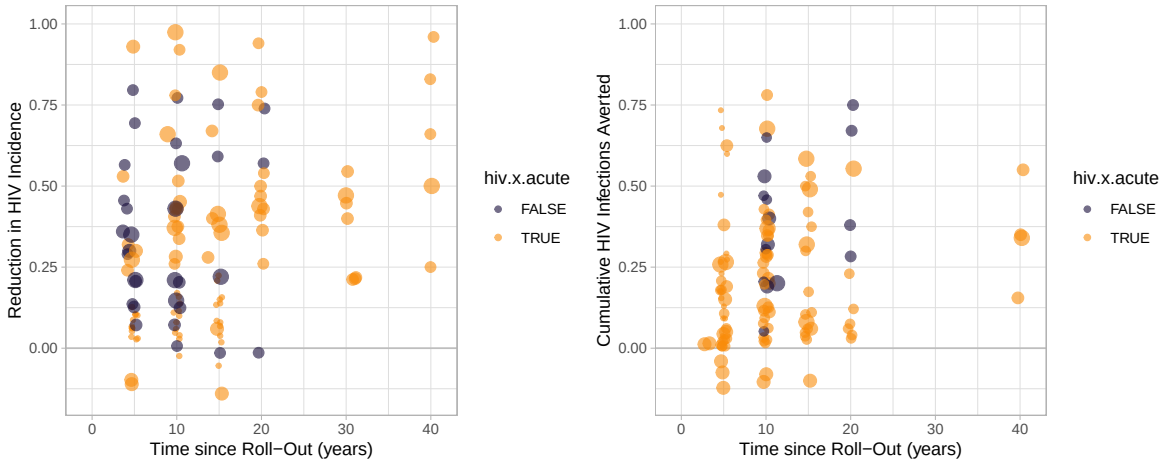


Figure C.21: increased infectiousness during acute infection

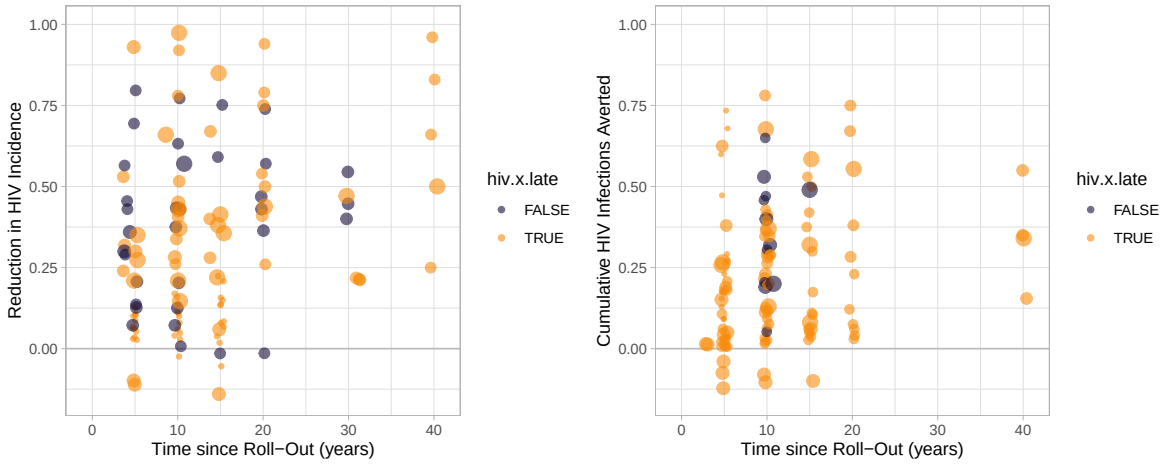


Figure C.22: increased infectiousness during late-stage infection

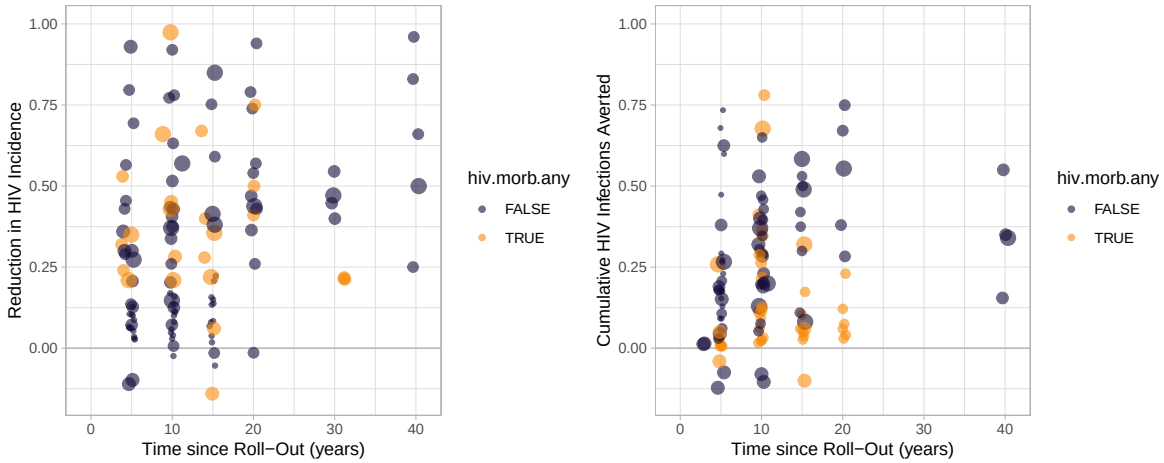


Figure C.23: decreased sexual activity during late-stage infection

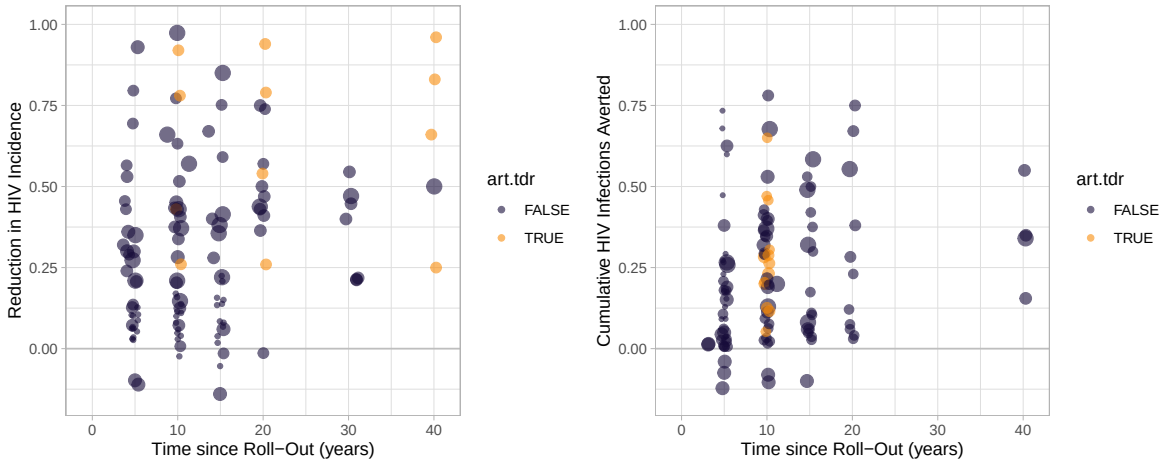


Figure C.24: any transmitted drug resistance

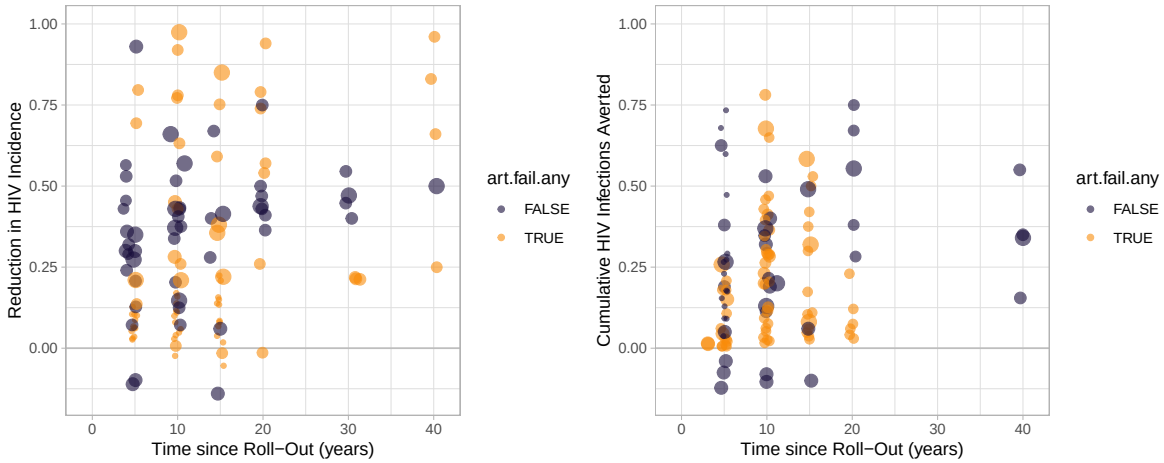


Figure C.25: any rate or state of ART failure

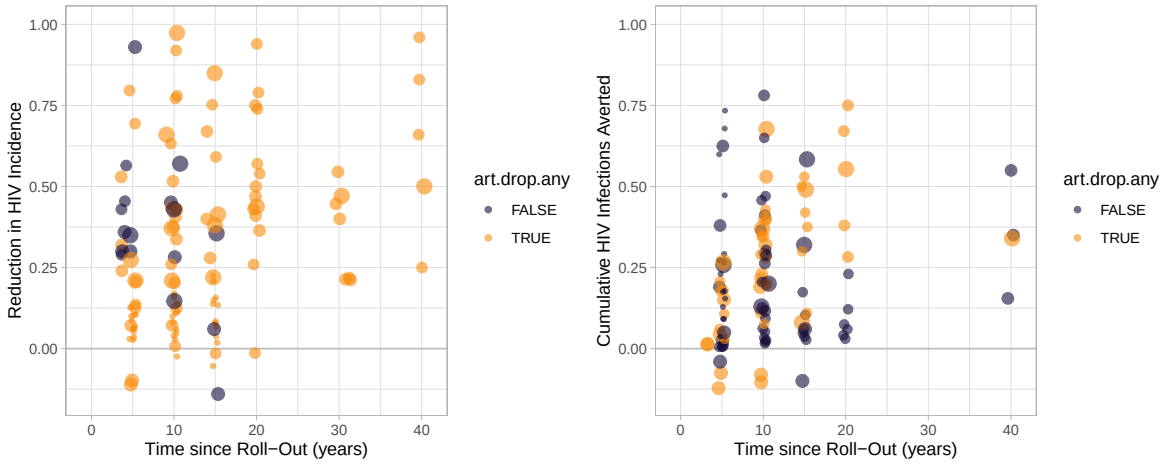


Figure C.26: any rate or state of ART dropout

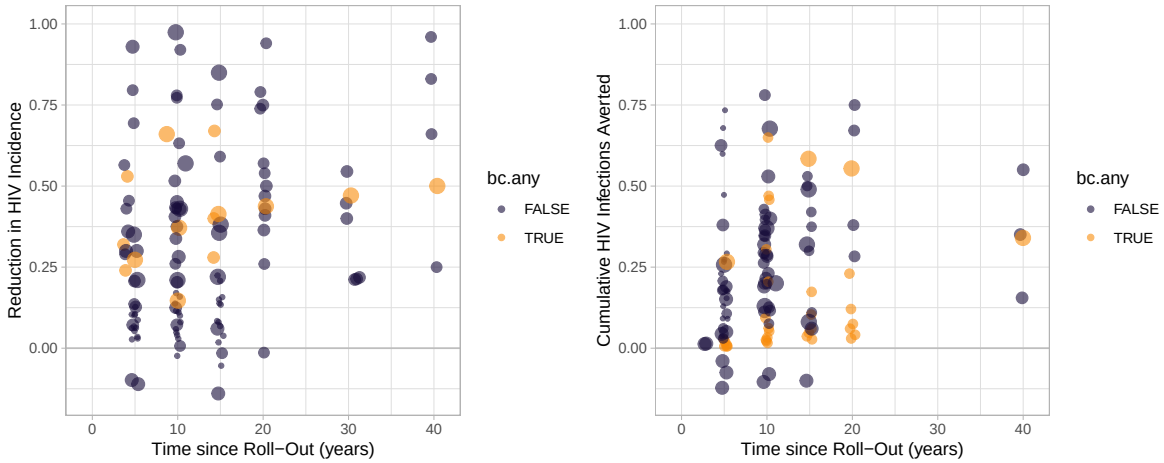


Figure C.27: any behaviour change associated with diagnosis or ART

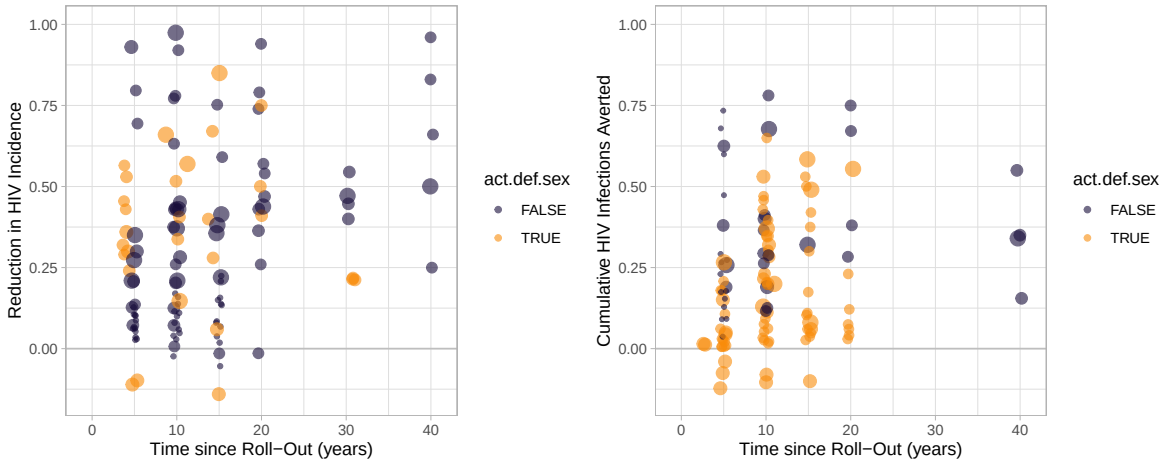


Figure C.28: stratified by sex

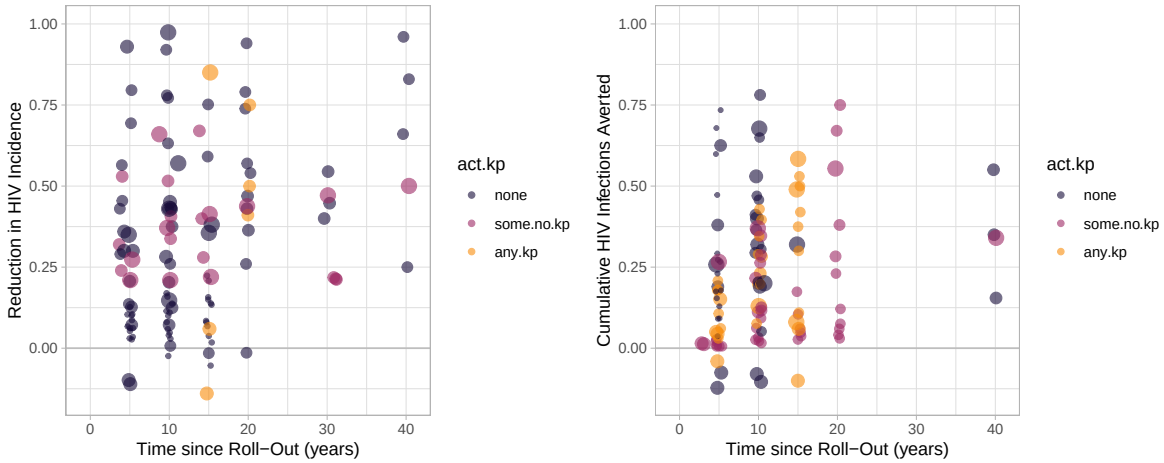


Figure C.29: activity groups & key populations

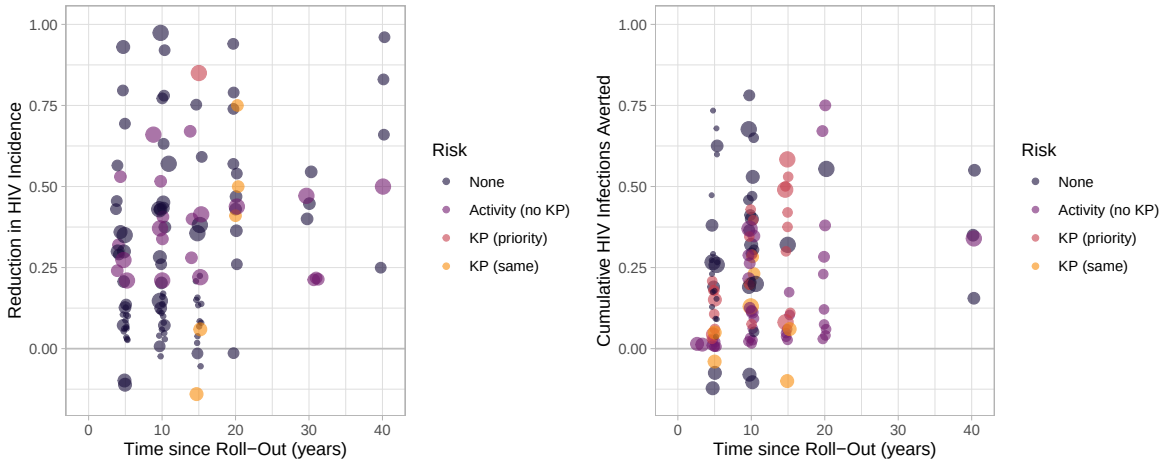


Figure C.30: summary of risk heterogeneity

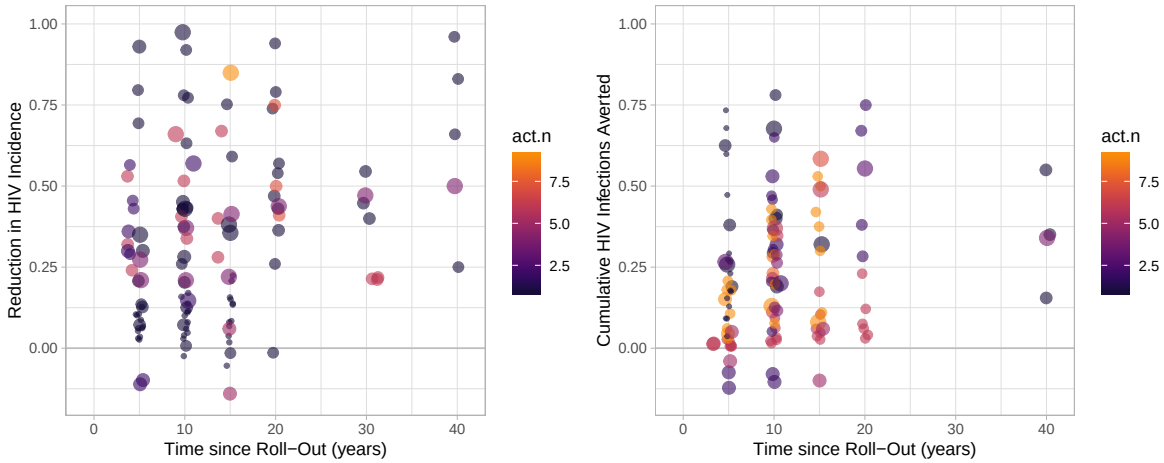


Figure C.31: number of activity groups

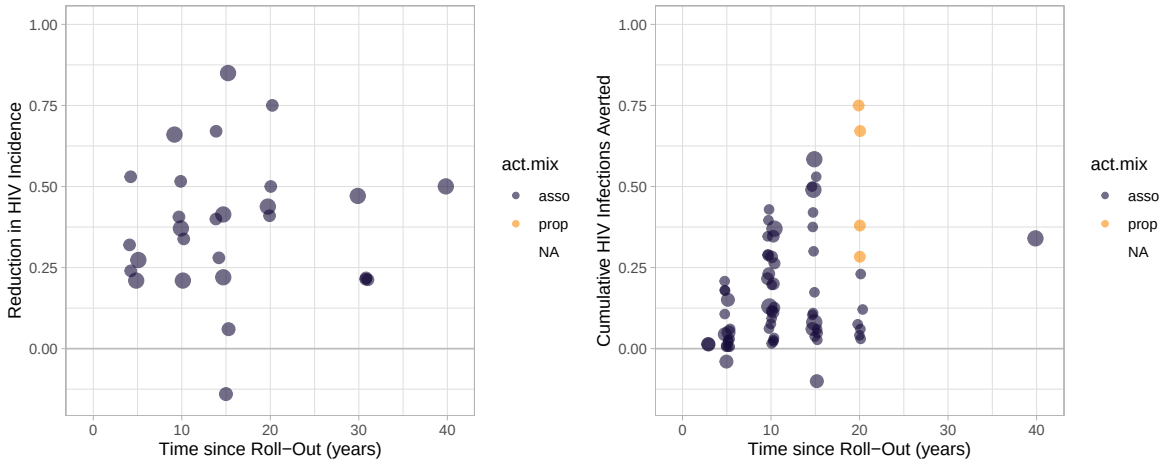


Figure C.32: type of activity mixing

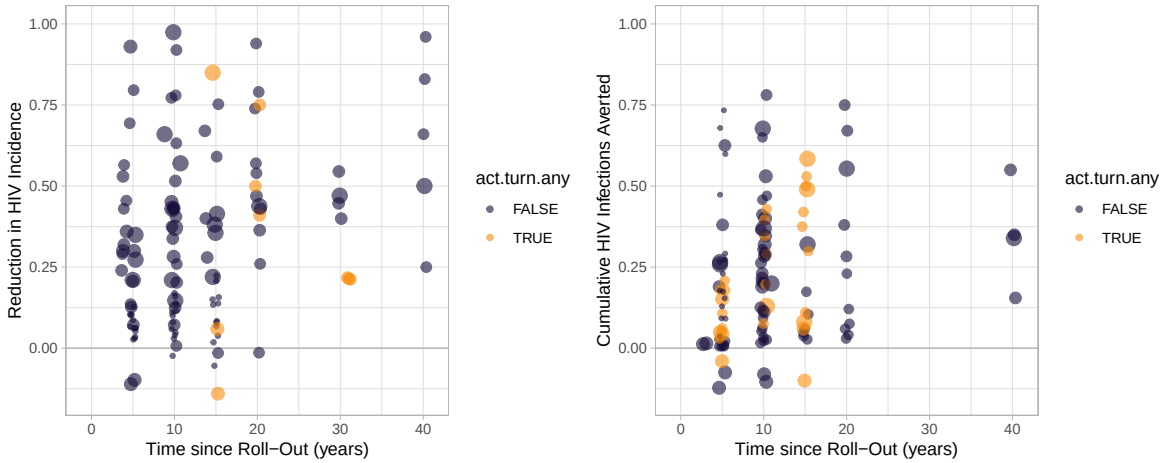


Figure C.33: any activity group turnover

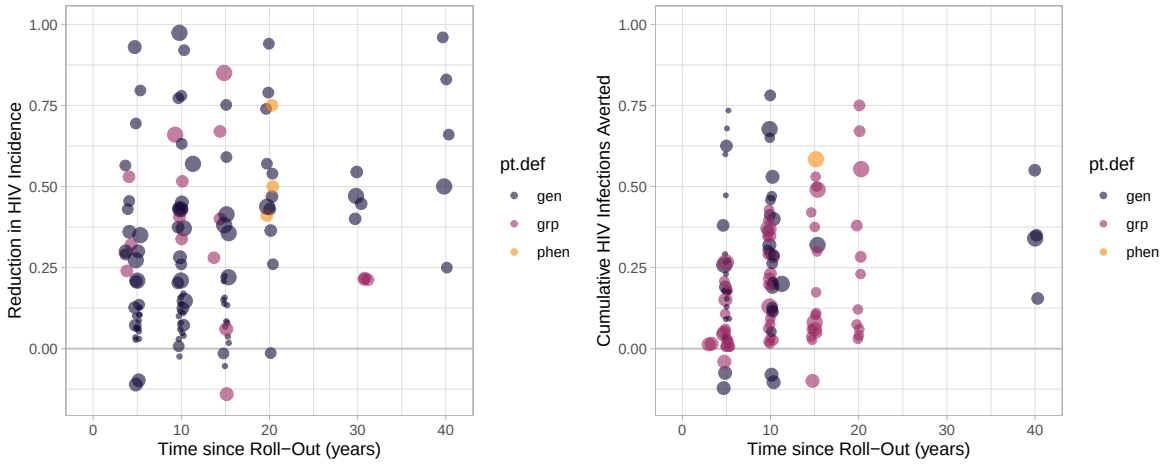


Figure C.34: type of partnership definition

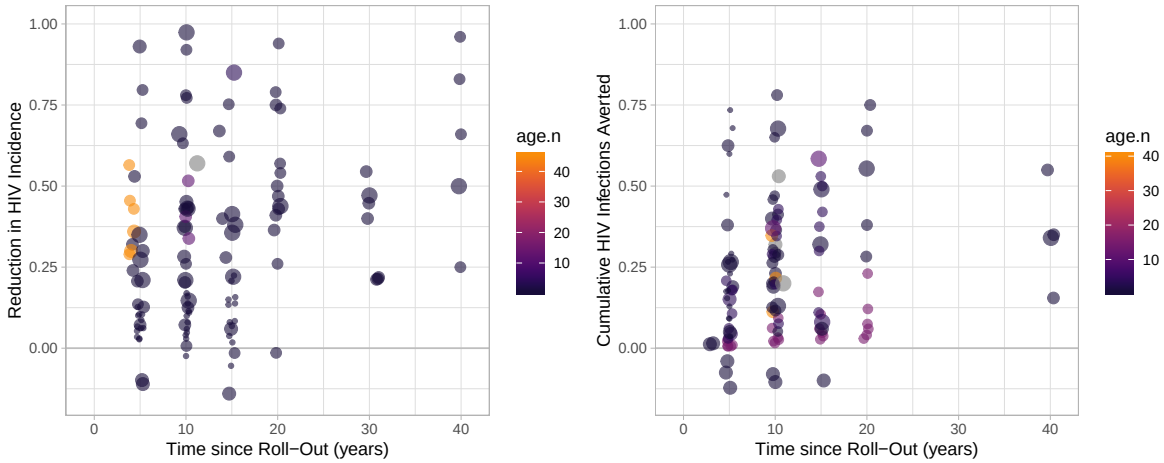


Figure C.35: number of age groups

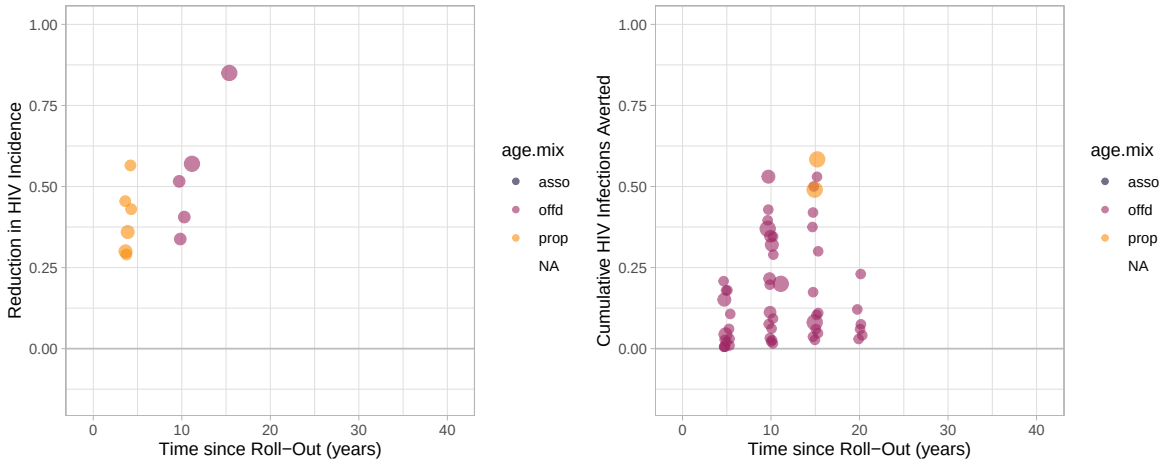


Figure C.36: type of age mixing

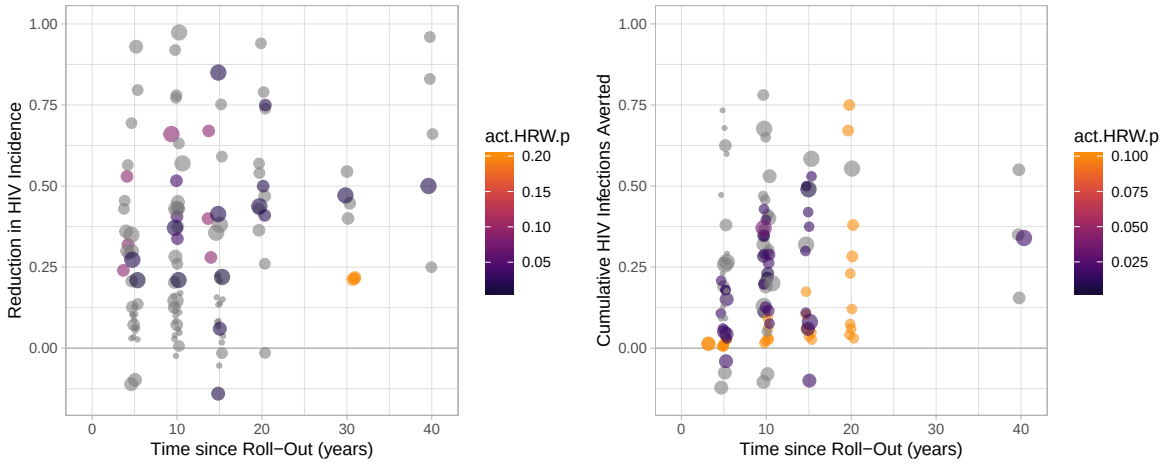


Figure C.37: proportion of women in the highest female activity group

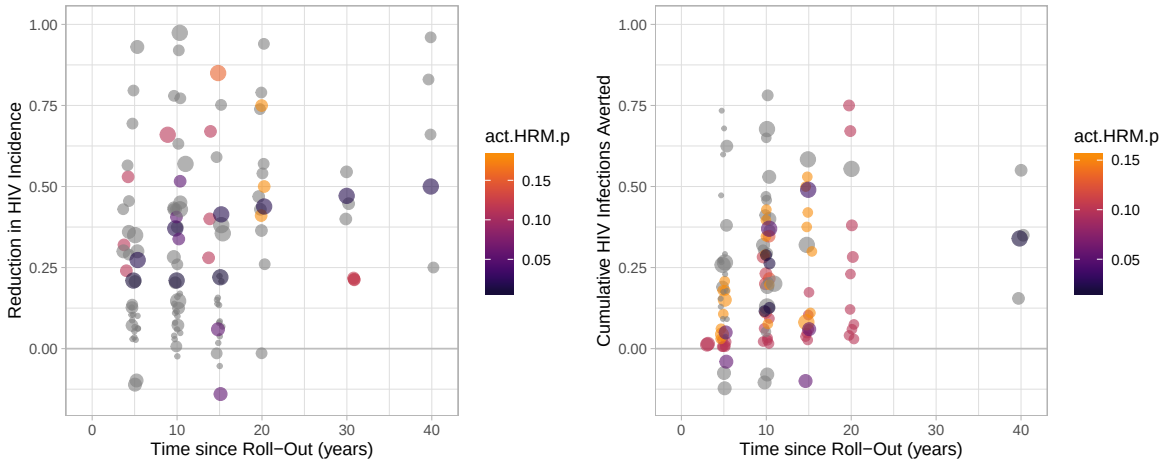


Figure C.38: proportion of men in the client or highest activity male group

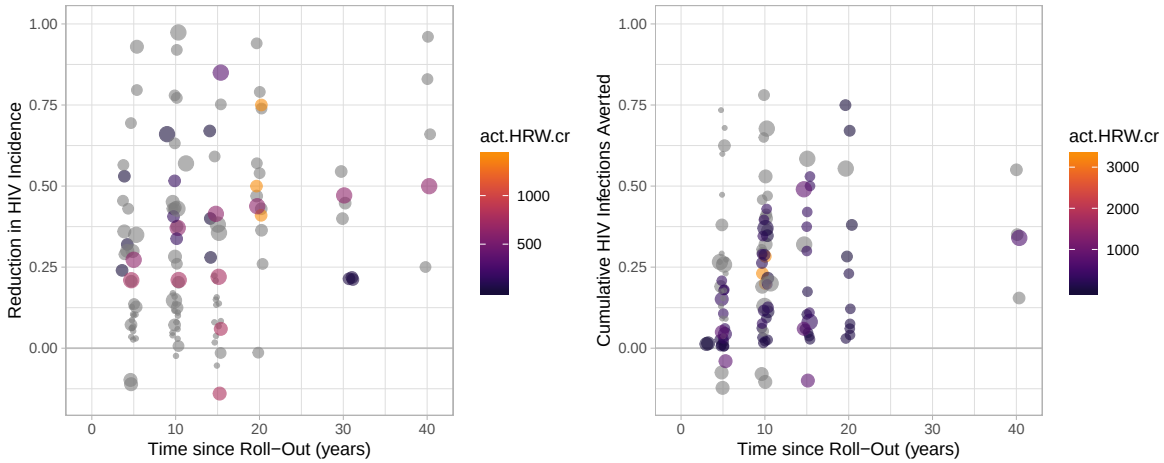


Figure C.39: ratio of partners per year in the highest vs lowest female activity groups

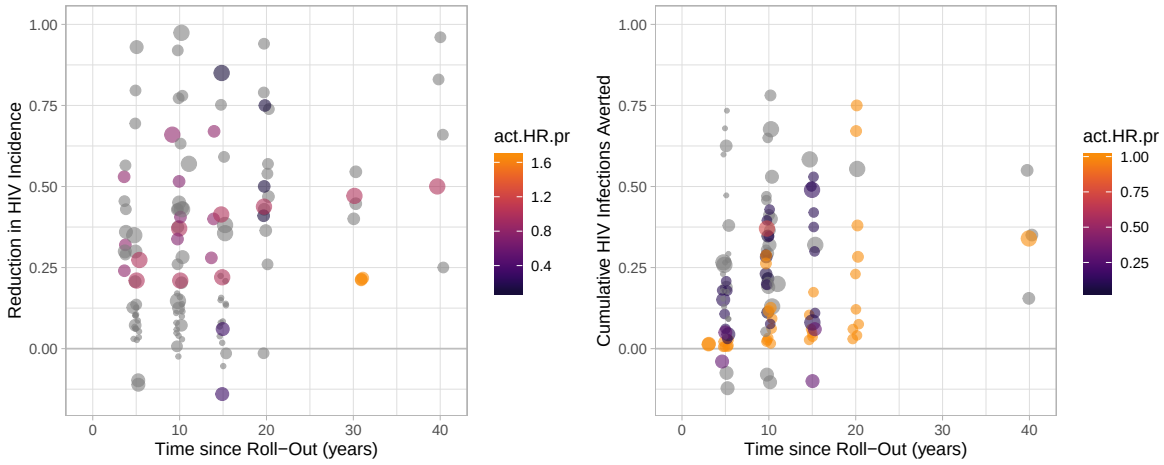
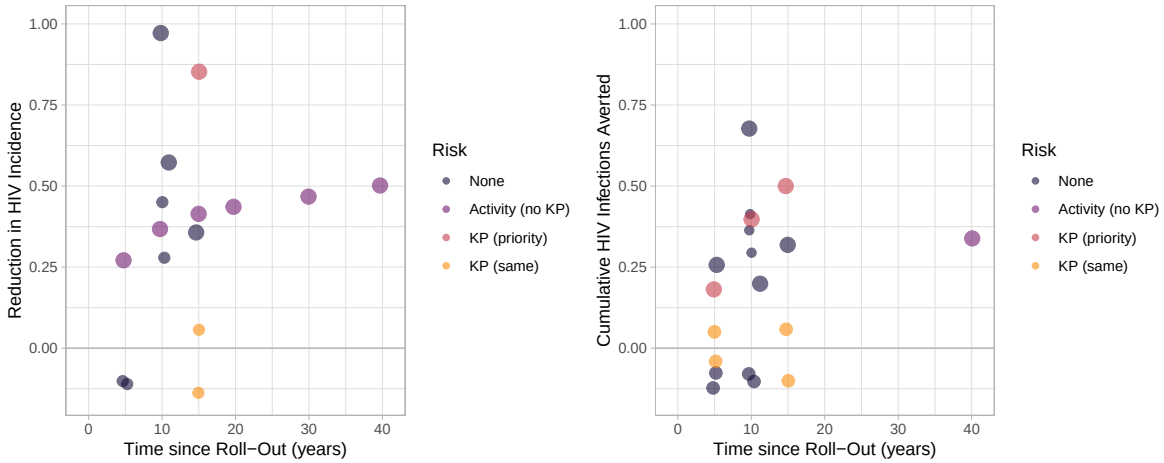


Figure C.40: ratio of highest female to highest male activity group sizes



(a) Reduction in HIV incidence (%)

(b) Cumulative HIV infections averted (%)

Figure C.41: 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.

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 conditions of ART scale-up

		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 (%)	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	
	Phenom.	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 was higher in KP vs overall due to prioritized programs; same: cascade was 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.	
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.	
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.	
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.	
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.	
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.	
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.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
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.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
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).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
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.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
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.	
Limitations	20	Discuss the limitations of the scoping review process.	
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.	
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.	

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.