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

immediate

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## Contents

# 1 Introduction

The HIV epidemic in Sub-Saharan Africa in 2019 included nearly one million new infections, and approximately two thirds (25.7 million) of all people living with HIV globally.[1] Combating the epidemic requires combination prevention, including HIV treatment, as recommended by the World Health Organization.[2] Effective HIV treatment with antiretroviral therapy (ART) leads to viral load suppression and has been shown to prevent HIV transmission between sex partners.[3–5]

Following empirical evidence of partnership-level efficacy of ART in preventing HIV,[3–5] and model-based evidence of "treatment as prevention",[6,7] several large-scale community-based trials of universal test-and-treat (UTT) have recently been completed.[8–10] 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.[8–10] Thus the population-level reductions in incidence anticipated from transmission modelling were not observed.

One theme in the proposed explanations for limited population-level ART effectiveness was heterogeneity in intervention coverage and transmission risks.[11,12] While viral suppression improved under UTT in all three trials, 21–54% of study participants remained unsuppressed.[8–10] Populations experiencing barriers to viral suppression under UTT may be at highest risk for onward transmission, such as individuals with acute infection, sex workers, and mobile populations.[13–15] Moreover, non-residents of study communities were excluded from interventions (including 17% of enumerated household adults in one trial[9]) and all three trials noted substantial migration into/out of study communities.[8–10] While widespread UTT scale-up may fill some of these coverage gaps, equitable access to ART for marginalized and mobile populations remains an open challenge.[13,16]

Given the upstream and complementary role of transmission modelling to project the impact of ART as prevention,[7,17] and the critical role of risk heterogeneity in epidemic dynamics, we sought to critically appraise assumptions and representations of risk heterogeneity in models assessing ART as prevention in Sub-Saharan Africa via scoping review. Our objectives were to answer the following research questions. Among dynamical compartmental models of sexual HIV transmission that have been used to simulate ART for prevention 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 framework to appraise 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 answer our research questions.

## 2.1 Appraisal Framework

For the appraisal, we considered "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 and social dimensions. We defined the following 4 domains through which these factors of risk heterogeneity might influence ART prevention impact.

- **Biological Effects:** differential transmission risk within HIV disease course that coincide with differential ART coverage[18]
- **Behaviour Change Effects:** differential transmission risk due to behavioural changes related to engagement in the ART cascade[19,20]
- **Network Effects:** differential transmission risk within sub-populations that increase the challenge of epidemic control through core group dynamics[21–24]
- **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[14,25–27]

We compiled a list of key factors of risk heterogeneity, and their associated mechanisms of influence on ART prevention impact (Table 1). We did not attempt to define the magnitude or direction of each factor's influence, since these can depend on the context, time horizon, and which if any parameters were fitted during model calibration.[28]

## 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). Duplicate studies were removed automatically and also manually. Potentially relevant studies were identified by title and abstract screening. Further selection of studies and subsequent data extraction used the full text and any available supplementary material. One reviewer (JK) conducted the search 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 | $\beta_i$ | Increased infectiousness immediately following infection[18] | **Biological**: transmissions during acute infection are unlikely to be prevented by ART |
| Late Stage Infection | $\beta_i$ | Increased infectiousness during late stage infection | **Biological**: transmissions during late-stage are more likely to be prevented by ART |
| Drug Resistance | $\beta_i$ | 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 | $c$; $\eta$ | Reduced sexual activity during late stage disease | **Behaviour Change**: reduced morbidity via ART could increase HIV prevalence among the sexually active population |
| HIV Counselling | $c$; $\eta$; $\kappa$ | 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 | $c$; $\eta$ | Increased sexual activity use after ART initiation | **Behaviour Change**: increased risk behaviour if viral suppression is not sustained could increase transmission risk |
| Activity Groups | $c$; $\kappa$ | Any stratification by rate of partnership formation | **Network**: higher transmission risk among higher activity |
| Age Groups | $c$; $\kappa$ | Any stratification by age | **Network & Coverage**: higher transmission risk and barriers to viral suppression among youth |
| Key Populations | $c$; $\kappa$ | Any epidemiologically defined higher risk groups | **Network & Coverage** higher transmission risk and barriers to viral suppression among key populations |
| Group Turnover | $\phi$ | 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 | $\eta$; $\kappa$ | 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 | $\tau$; $\alpha$ | 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 — $\beta_i$, $\beta_s$: transmission probability per act (infectiousness, susceptibility); $\eta$: number of sex acts of each type per partnership; $\kappa$: proportion of sex acts unprotected by a condom; $c$: partnership formation rate; $m$: mixing matrix (probability of partnership formation); $\mu$: mortality rate; $\nu$: entry rate; $\phi$: internal turnover between activity groups; $\tau$: testing rate; $\alpha$: ART initiation rate (and retention-related factors).

#### 2.2.1 Inclusion/Exclusion Criteria

We sought to identify studies applying dynamical models of sexual HIV transmission to project the prevention impacts of increases in ART coverage in SSA. Complete inclusion/exclusion criteria are given in Appendix A.2. Peer-reviewed English journal articles published up to Dec 31, 2019 were considered for inclusion. We excluded publications without primary modelling results, such as commentaries and reviews, as well as conference publications.

Articles were considered for inclusion if they used a dynamical compartmental model of sexual HIV transmission at the population level. 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 $t$. We define a *compartmental model* as one where the system variables represent the numbers of individuals in each state, rather than unique individuals. Statistical models, non-dynamical models, and individual-based models were excluded. Articles were further considered for inclusion if model parameters were chosen to reflect at least one context within SSA (see Table A.4 for full country list). Finally, articles were included if they simulated at least one scenario with increasing ART coverage, possibly alongside scale-up of other interventions. The included articles 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. Articles in Dataset B specifically examined scale-up of ART coverage alone (vs combination intervention) for the whole population (vs ART targeted to subgroups), and reported HIV incidence reduction or cumulative HIV infections averted after a number of years, as compared to a base-case scenario reflecting the status quo.

### 2.3 Data Extraction

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 our first research question, we extracted the following data. Articles were categorized by the geographic location (country and SSA region) and scale of the simulated population (city, sub-national, national, regional), including whether multiple geographic contexts were considered. The epidemic phase was categorized based on the overall HIV prevalence (low: $< 1\%$, medium: $1 - 10\%$, high: $> 10\%$), and the trend in incidence at the time that scenarios diverged (increasing, increasing but stabilizing, stable/equilibrium, decreasing but stabilizing, and decreasing). Finally, we noted whether the simulated population included any of 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). See key population definitions in Appendix B.2.1

### 2.3.2 Factors of Risk Heterogeneity

For our second research question, 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 noted 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. Similarly, we noted whether ART coverage was assumed to be equal across modelled risk groups, possibly ignoring historical gaps/future challenges in reaching higher risk groups.

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

Finally, we noted whether differences in rates of progression along the *ART cascade* were considered between age groups, sexes, activity groups, and/or key populations. Specifically, we noted differences in rates of diagnosis, ART initiation, and treatment discontinuation (due to either dropout or resistance).

### 2.3.3 ART Prevention Impact

For our third research question, 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. CD4 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 mod-

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

elled). We plotted impact magnitude vs time since $t_0$, stratified by factor levels, and tested whether the distribution of impact magnitudes was the same under all factor levels (non-parametric Kruskal-Wallis test).

# 3 Results

Database search identified 1384 publications, of which 94 articles met the inclusion criteria (Figure 1). Among 360 articles using dynamical HIV transmission models applied to SSA, 255 were compartmental models, of which 94 were applied simulate ART scale-up (Database A), of which 40 reported infections averted or incidence reduction due to population-wide ART scale-up, as compared to a base case reflecting status quo (Database B). Appendix A.3 lists the included papers, and Appendix C provides additional results.

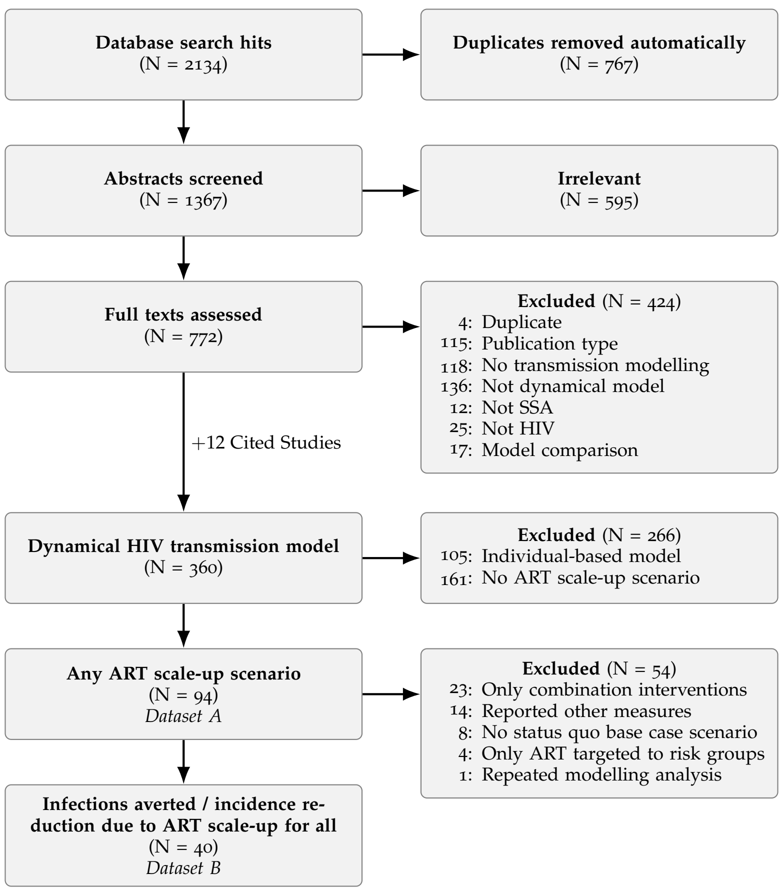



Figure 1: PRISMA flowchart of article identification

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

| Study Characteristic | | Articles |
|---|---|---|
| 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 articles: 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 articles 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.

## 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 articles modelled HIV transmission at the national level, including 51 single-country and 10 multi-country analyses. Articles also explored regional (1), sub-national (16), and city-level (16) epidemic scales. South Africa was the most common country simulated (52 articles), but was not disproportionately represented among SSA countries: the number of articles per million PLHIV as of 2019 in South Africa (7.22) was similar to the SSA median (6.27). Figure C.1 illustrates the number of articles by country.

ART prevention impacts were most often modelled in high-prevalence epidemics ($>10\%$ HIV prevalence, 41 articles) or medium-prevalence epidemics ($1-10\%$, 23 articles). No articles reported overall HIV prevalence of $< 1\%$ at time of ART scale-up, although for 30 articles, 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).

### 3.1.1 Key Populations

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

Among 31 articles 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 articles; 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], and 2 articles represented HIV along a continuous dimension using a partial differential equations model. Most HIV states were defined by CD4 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 articles, 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 articles, vs a "virally suppressed" state specifically in 15 articles. Treatment failure due to drug resistance was simulated in 30 articles, 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 articles.

### 3.2.2 Behavioural Effects

Reduced sexual activity due to late-stage HIV symptoms was simulated in 25 articles, including at least one state with: complete withdrawal from sexual activity (14); reduced rate of partnership formation (9); and/or reduced rate of coital frequency (6).

Separate states representing diagnosed HIV and on-treatment but not yet virally suppressed were simulated in 30 and 17 articles, respectively. Behaviour change by status-aware PLHIV associated with HIV testing and counselling was simulated in 22 articles, including: increased condom use (12); fewer partners per year (4); less sex per partnership (3); serosorting (1); and/or a generic reduction in transmission probability (8).

Dropout from treatment, was simulated in 30 articles, 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 dropout.

### 3.2.3 Network Effects

Representations of risk heterogeneity that might contribute to core group dynamics varied widely. Risk groups defined at least in part by activity (different rates and/or types of partnerships formed) were simulated in 59 articles, and at least in part by sex in 64 articles. 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 female and male activity groups (including FSW and clients, where applicable) comprised 2 [0, (2, 4), 23] and 9 [0, (2, 14), 35] % of female and male populations, respectively.

Natural turnover between activity groups and/or key populations was considered in 28 articles, of which 9 considered turnover of only one specific high-activity group or key population. Another 7 articles 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 articles 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 articles, including all articles without activity groups. Second, partnerships were defined by the activity groups involved (44 articles), which approximately represented main/spousal (40); casual (40); and sex work (33) partnerships. 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 articles). All models with phenomenological partnerships defined differential total sex volume and condom use between types.

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

#### 3.2.4 Coverage Effects

Differential progression along the ART cascade was considered in 21 articles, including differences between sexes in 15; age groups in 7; and key populations in 12. No articles considered differences among activity groups beyond key populations. Another 2 articles did not simulate differential progression but specifically justified that assumption 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. Likewise, differences between age groups affected rates of diagnosis (6); ART initiation (1); and retention (0). Among key populations, *lower* rates of diagnosis, ART initiation, and retention were simulated in 0, 2, and 4 articles respectively, while *higher* rates were simulated in 8, 2, and 1.

### 3.3 ART Prevention Impact

The 40 articles reporting prevention impacts of ART for all simulated 126 total ART scale-up scenarios, including 61 with reported HIV incidence reduction, and 73 with reported cumulative HIV infections averted. Projected impact on incidence ranged from 93% reduction over 10 years[6] to 14% *increase* over 15 years;[29] and impact on cumulative infections from 78% reduction over 10 years[30] to 12% *increase* over 5 years.[31]

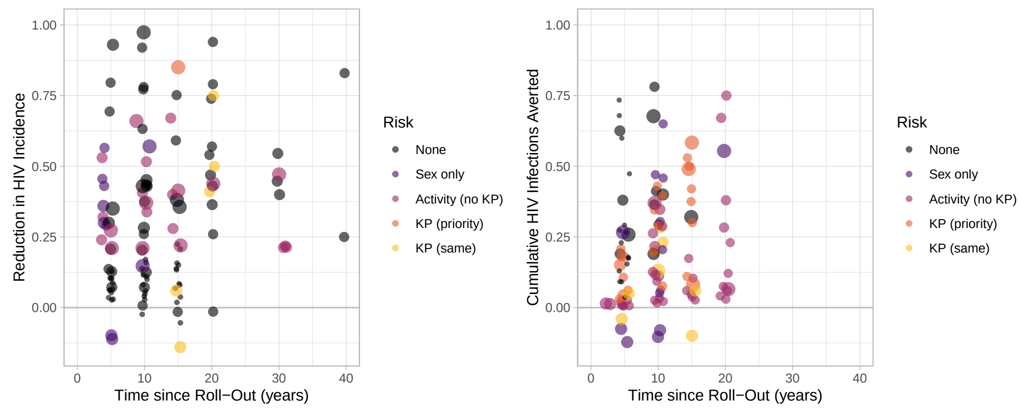
Table 3 summarizes the median [IQR] projected impacts of ART scale-up, stratified by factors of heterogeneity and with univariate test results. Projected impact increased with time horizon, CD4 initiation threshold, and ART coverage. Projected impact was also higher for medium-prevalence epidemics than high-prevalence. Curiously, impact was significantly higher when ART reduced transmission to 4-10% vs 0-4% or 10+%, and when transmitted drug resistance was considered. Also unexpected, modelling HTC-related behaviour change and sex stratification were each associated with larger incidence reduction, but fewer cumulative infections averted.

Figure 2 illustrates the projected ART projection impact vs time horizon, stratified by a composite metric of heterogeneity considering sex, activity, and key population risk groups, plus differential coverage in the key population cascade. Over a short time horizon (5-10 years), the models projecting highest impact do not consider any risk stratification. Models considering key populations but without higher (prioritized) KP cascade also project markedly lower cumulative infections averted, as compared to models without prioritized key populations cascade.

Table 3: Projected ART prevention benefits, stratified by factors of risk heterogeneity

| | | HIR (%) | | | | HCIA (%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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 | 0.072 |
| | 11-20 | 20 | ( 8, 42 ) | 63 | | 22 | ( 8, 38 ) | 57 | |
| | 21-30 | 47 | ( 39, 65 ) | 15 | | 18 | ( 6, 42 ) | 12 | |
| | 31+ | 46 | ( 24, 57 ) | 12 | | 34 | ( 29, 40 ) | 4 | |
| HIV Prevalence (%) | 0-1 | — | ( —, — ) | 0 | 0.002 | 49 | ( 49, 49 ) | 1 | 0.016 |
| | 1-10 | 44 | ( 40, 50 ) | 12 | | 27 | ( 13, 38 ) | 33 | |
| | 10+ | 21 | ( 7, 43 ) | 94 | | 12 | ( 3, 29 ) | 64 | |
| RR Transmission on ART | 0.0-0.039 | 22 | ( 14, 35 ) | 11 | $< 0.001$ | 6 | ( 2, 22 ) | 42 | $< 0.001$ |
| | 0.4-0.099 | 49 | ( 34, 67 ) | 42 | | 27 | ( 15, 38 ) | 60 | |
| | 0.1+ | 11 | ( 5, 26 ) | 70 | | 7 | ( 0, 24 ) | 8 | |
| CD4 Threshold for ART Initiation | 200 | 28 | ( 26, 32 ) | 3 | $< 0.001$ | 28 | ( 24, 30 ) | 4 | $< 0.001$ |
| | 350 | 29 | ( 21, 38 ) | 10 | | 18 | ( 12, 26 ) | 19 | |
| | 500 | 29 | ( 16, 43 ) | 15 | | 29 | ( 23, 35 ) | 13 | |
| | Any | 56 | ( 22, 75 ) | 41 | | 55 | ( 31, 65 ) | 19 | |
| ART Coverage (%) | 0-59 | 28 | ( 26, 31 ) | 3 | 0.018 | 28 | ( 11, 37 ) | 9 | 0.145 |
| | 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 | 39 | ( 26, 52 ) | 12 | 0.003 |
| | Yes | 26 | ( 9, 44 ) | 91 | | 16 | ( 5, 32 ) | 101 | |
| Late-Stage Infection | No | 39 | ( 13, 56 ) | 38 | 0.25 | 40 | ( 20, 47 ) | 9 | 0.029 |
| | Yes | 22 | ( 8, 43 ) | 88 | | 17 | ( 5, 34 ) | 104 | |
| Trans. Drug Resist. | No | 21 | ( 7, 43 ) | 114 | $< 0.001$ | 18 | ( 5, 36 ) | 99 | 0.211 |
| | Yes | 72 | ( 39, 85 ) | 12 | | 25 | ( 14, 30 ) | 14 | |
| HIV Morbidity | No | 21 | ( 7, 45 ) | 102 | 0.088 | 27 | ( 12, 41 ) | 71 | $< 0.001$ |
| | Any | 34 | ( 22, 46 ) | 24 | | 6 | ( 3, 23 ) | 42 | |
| HTC Behav. Change | No | 21 | ( 7, 45 ) | 112 | 0.031 | 23 | ( 11, 38 ) | 78 | 0.001 |
| | Any | 41 | ( 29, 49 ) | 14 | | 6 | ( 3, 22 ) | 35 | |
| Sex Stratification | No | 21 | ( 7, 44 ) | 97 | 0.076 | 29 | ( 18, 44 ) | 39 | $< 0.001$ |
| | Yes | 36 | ( 22, 52 ) | 29 | | 10 | ( 3, 28 ) | 74 | |
| Activity Groups & Key Populations | None | 19 | ( 7, 44 ) | 98 | 0.072 | 28 | ( 15, 46 ) | 40 | 0.002 |
| | Yes (no KP) | 35 | ( 22, 46 ) | 22 | | 7 | ( 3, 25 ) | 42 | |
| | Yes + KP | 46 | ( 15, 69 ) | 6 | | 20 | ( 8, 36 ) | 31 | |
| Activity Turnover | No | 26 | ( 8, 45 ) | 117 | 0.649 | 19 | ( 5, 35 ) | 85 | 0.742 |
| | Yes | 22 | ( 21, 50 ) | 9 | | 18 | ( 7, 38 ) | 28 | |
| Partnership Types | Generic | 21 | ( 8, 44 ) | 107 | 0.098 | 27 | ( 15, 41 ) | 45 | 0.002 |
| | by Groups | 33 | ( 22, 52 ) | 16 | | 11 | ( 4, 28 ) | 67 | |
| | Phenom. | 50 | ( 46, 62 ) | 3 | | 58 | ( 58, 58 ) | 1 | |
| Differential KP Cascade | Priority | 85 | ( 85, 85 ) | 1 | 0.114 | 21 | ( 11, 41 ) | 23 | 0.118 |
| | Same | 25 | ( 8, 45 ) | 125 | | 17 | ( 4, 34 ) | 90 | |
| | Gaps | — | ( —, — ) | 0 | | — | ( —, — ) | 0 | |

[a] N: number of scenarios. [b] P-values from non-parametric Kruskal-Wallis test for whether two or more independent samples originate from the same distribution. HIR: HIV incidence reduction; CHIA: cumulative HIV infections averted; RR: relative risk; HTC: HIV testing and counselling; KP: key populations. Factor definitions are given in Appendix B.




(a) Reduction in HIV incidence

(b) Cumulative HIV infections averted

Figure 2: Projected ART prevention benefits, stratified by factors of risk heterogeneity: whether models considered sex, sexual activity, key populations, and differences in ART cascade across key populations

The number of articles (scenarios) reporting incidence reduction, cumulative infections averted, both, or either was: 23 (61), 23 (73), 6 (10), and 41 (126), respectively (Dataset B). If any article 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 article. 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: modelled ART cascade was higher in KP due to prioritized programs; same: cascade was assumed the same in KP; no scenarios in Dataset B considered lower cascade among KP.

# 4 Discussion

We sought to critically appraise representations of risk heterogeneity in compartmental models of HIV transmission used to project the prevention impacts of ART scale-up in Sub-Saharan Africa (SSA). We conceptualized such representations as a set of factors, including stratifications and phenomena, which may be simulated in the model different ways or not at all. Via scoping review, we found that such representations varied widely, as did the projected population-level prevention impacts of ART scale-up.

**Modelled Factors of Heterogeneity:** Three areas for potential improvement emerged among modelled factors of heterogeneity. First, highest risk groups may not be modelled to reflect sufficiently disproportionate transmission risk so as to adequately capture core group effects. For example, the highest activity groups among women and men were still often relatively large (Figures C.7 and C.8), and even among models with key populations, heterogeneity *within* key populations was rarely considered. Many models also implicitly excluded the possibility of "main/spousal" partnerships (with more sex and lower condom use) forming between two higher activity individuals.

Second, representations of the ART cascade tended to overlook key steps such as diagnosis, linkage to care, and in some cases treatment failure/dropout;[32] some of these simplifications might result in overly optimistic rates of ART initiation and viral suppression. However, equally overlooked were potential prevention benefits due to behaviour change from HIV testing and counselling.

Third, intersectionality of transmission risks and cascade progression were rarely considered, such that rates of diagnosis, linkage, viral suppression, and retention were usually assumed equal across sexes, activity groups, age groups, and key populations. However, evidence of differential cascade engagement by sex and age is mounting.[27,33,34] In some contexts, reported cascade coverage among female sex workers may approach or surpass that of the wider population,[14,25] but the same is unlikely for men who have sex with men.[25,35] Moreover, key population cascade data are often obtained through prioritized research and programs that improve coverage, suggesting that unmeasured key population cascades could be lowest.[25]

**Significance:** The prevention impacts of ART will continue to grow under increasing adoption of universal test and treat. Maximizing these impacts will require continuous integration of context-specific data and assumptions into transmission models to understand challenges and opportunities. Priorities for such data could include detailed cascade data, stratified by sex, age, and key populations. In the absence of clear patterns relating modelled factors of risk heterogeneity to projected ART prevention benefits, questions also remain as to which factors are most influential, and in which contexts. Such questions should be explored in step-wise model structure comparison studies, such as in Andrews *et al.* [36], Hontelez *et al.* [37], and Eaton *et al.* [38].

**Limitations:** Our review has four main limitations. First, the key populations considered in our analysis did not include adolescent girls and young women, transgender people, or mobile populations, despite the fact that such populations may face similar risks of transmission and barriers to care as other key populations.[13,39] We also did not document representations of violence, coercion, or anal sex, which may similarly coincide with transmission risks and barriers to care.[40,41] 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 by Eaton *et al.* [38] and Knight *et al.* [42], 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. We were further discouraged from estimating effects after noting opposite trends in incidence reduction and cumulative infections averted for several factors, suggesting the potential for finding spurious patterns.

# References


1. UNAIDS. *AIDSinfo* 2020.
2. WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* Geneva, Switzerland, 2016.
3. Lundgren, J. D. *et al.* How achievable is immediate ART for all? *The Lancet HIV* **2,** 795–807 (2015).
4. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *New England Journal of Medicine* **373,** 808–822 (2015).
5. Cohen, M. S. *et al.* Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *New England Journal of Medicine* **375,** 830–839 (2016).
6. Granich, R. M., Gilks, C. F., Dye, C., De Cock, K. M. & Williams, B. G. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet* **373,** 48–57 (2009).
7. Eaton, J. W. *et al.* HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Medicine* **9** (ed Bartlett, J.) e1001245 (2012).
8. Iwuji, C. C. *et al.* Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. *The Lancet HIV* **5,** e116–e125 (2018).
9. Havlir, D. V. *et al.* HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa. *New England Journal of Medicine* **381,** 219–229 (2019).
10. Hayes, R. J. *et al.* Effect of universal testing and treatment on HIV incidence - HPTN 071 (popart). *New England Journal of Medicine* **381,** 207–218 (2019).
11. Abdool Karim, S. S. HIV-1 Epidemic Control — Insights from Test-and-Treat Trials. *New England Journal of Medicine* **381,** 286–288 (2019).
12. Baral, S. *et al.* The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment. *The Lancet HIV* **6,** e632–638 (2019).
13. Tanser, F., Bärnighausen, T., Vandormael, A. & Dobra, A. HIV treatment cascade in migrants and mobile populations. *Current Opinion in HIV and AIDS* **10,** 430–438 (2015).
14. Hakim, A. J. *et al.* Gaps and opportunities: measuring the key population cascade through surveys and services to guide the HIV response. *Journal of the International AIDS Society* **21,** e25119 (2018).
15. Nyato, D. *et al.* Facilitators and barriers to linkage to HIV care and treatment among female sex workers in a community-based HIV prevention intervention in Tanzania: A qualitative study. *PLoS ONE* **14** (ed Madiba, S.) e0219032 (2019).
16. De Gruchy, T. & Vearey, J. "Left behind": why implementing migration-aware responses to HIV for migrant farm workers is a priority for South Africa. *African Journal of AIDS Research* **19,** 57–68 (2020).
17. Delva, W. *et al.* HIV treatment as prevention: Principles of good HIV epidemiology modelling for public health decision-making in all modes of prevention and evaluation. *PLoS Medicine* **9** (ed Bartlett, J.) e1001239 (2012).
18. Pilcher, C. D. *et al.* Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *Journal of Infectious Diseases* **189,** 1785–1792 (2004).
19. Ramachandran, S., Mishra, S., Condie, N. & Pickles, M. *How do HIV-negative individuals in sub-Saharan Africa change their sexual risk behaviour upon learning their serostatus? A systematic review* 2016.
20. Tiwari, R. *et al. Sexual behaviour change following HIV testing services: a systematic review and meta-analysis* 2020.
21. Anderson, R. M., Medley, G. F., May, R. M. & Johnson, A. M. A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS. *Mathematical Medicine and Biology* **3,** 229–263 (1986).
22. Boily, M. C. & Mâsse, B. Mathematical models of disease transmission: A precious tool for the study of sexually transmitted diseases. *Canadian Journal of Public Health* **88,** 255–265 (1997).
23. Watts, C. *et al.* Remodelling core group theory: the role of sustaining populations in HIV transmission. *Sexually Transmitted Infections* **86,** iii85–iii92 (2010).

24. Dodd, P. J., Garnett, G. P. & Hallett, T. B. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. *AIDS* **24,** 729–735 (2010).

25. Mountain, E. *et al.* Antiretroviral therapy uptake, attrition, adherence and outcomes among hiv-infected female sex workers: A systematic review and meta-analysis. *PLoS ONE* **9** (ed Sluis-Cremer, N.) e105645 (2014).

26. Lancaster, K. E., Cernigliaro, D., Zulliger, R. & Fleming, P. F. HIV care and treatment experiences among female sex workers living with HIV in sub-Saharan Africa: A systematic review. *African Journal of AIDS Research* **15,** 377–386 (2016).

27. Green, D. *et al. Evidence of sociodemographic heterogeneity across the HIV treatment cascade and progress towards 90-90-90 in sub-Saharan Africa – a systematic review and meta-analysis* 2020.

28. Eaton, J. W. & Hallett, T. B. Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence. *Proceedings of the National Academy of Sciences* **111,** 16202–16207 (2014).

29. Salomon, A. *et al.* Integrating HIV prevention and treatment: From slogans to impact. *PLoS Medicine* **2,** 0050–0056 (2005).

30. Abbas, U. L., Anderson, R. M. & Mellors, J. W. Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings. *Journal of acquired immune deficiency syndromes (1999)* **41,** 632–41 (2006).

31. Barnighausen, T., Bloom, E. & Humair, S. Human resources for treating HIV/AIDS: Are the preventive effects of antiretroviral treatment a game changer? *PLoS ONE* **11,** e0163960 (2016).

32. Mountain, E. *et al. The HIV care cascade and antiretroviral therapy in female sex workers: Implications for HIV prevention* 2014.

33. Witzel, T. C., Lora, W., Lees, S. & Desmond, N. Uptake contexts and perceived impacts of HIV testing and counselling among adults in East and Southern Africa: A meta-ethnographic review. *PLoS ONE* **12** (ed Fox, M. P.) e0170588 (2017).

34. Mayanja, Y. *et al.* 'Test and Treat' Among Women at High Risk for HIV-infection in Kampala, Uganda: Antiretroviral Therapy Initiation and Associated Factors. *AIDS and Behavior* **22,** 1053–1061 (2018).

35. Stannah, J. *et al.* HIV testing and engagement with the HIV treatment cascade among men who have sex with men in Africa: a systematic review and meta-analysis. *The Lancet HIV* **6,** e769–e787 (2019).

36. Andrews, J. R., Wood, R., Bekker, L.-G., Middelkoop, K. & Walensky, R. P. Projecting the benefits of antiretroviral therapy for HIV prevention: the impact of population mobility and linkage to care. *The Journal of infectious diseases* **206,** 543–51 (2012).

37. Hontelez, J. A. C. *et al.* Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study. *PLoS Medicine* **10** (ed Ford, N.) e1001534 (2013).

38. Eaton, J. W. *et al.* Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: A combined analysis of 12 mathematical models. *The Lancet Global Health* **2,** e23–e34 (2014).

39. Dellar, R. C., Dlamini, S. & Karim, Q. A. *Adolescent girls and young women: Key populations for HIV epidemic control* 2015.

40. Silverman, J. G. *Adolescent female sex workers: Invisibility, violence and HIV* 2011.

41. Baggaley, R. F. *et al.* Heterosexual Anal Intercourse: A Neglected Risk Factor for HIV? *American Journal of Reproductive Immunology* **69,** 95–105 (2013).

42. Knight, J. *et al.* Contribution of high risk groups' unmet needs may be underestimated in epidemic models without risk turnover: A mechanistic modelling analysis. *Infectious Disease Modelling* **5,** 549–562 (2020).

43. Hallett, T. *et al.* The role of testing and counselling for HIV prevention and care in the era of scaling-up antiretroviral therapy. *Epidemics* **1,** 77–82 (2009).

44. Bacaer, N., Pretorius, C. & Auvert, B. An Age-Structured Model for the Potential Impact of Generalized Access to Antiretrovirals on the South African HIV Epidemic. *Bulletin of Mathematical Biology* **72,** 2180–2198 (2010).

45. Pretorius, C., Stover, J., Bollinger, L., Bacaer, N. & Williams, B. Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa. *PLoS ONE* **5,** e13646 (2010).

46. Metzger, T., Lloyd-Smith, O. & Weinberger, S. Autonomous targeting of infectious superspreaders using engineered transmissible therapies. *PLoS Computational Biology* **7,** e1002015 (2011).

47. Yusuf, T. & Benyah, F. Optimal strategy for controlling the spread of HIV/AIDS disease: A case study of South Africa. *Journal of Biological Dynamics* **6,** 475–494 (2012).

48. Granich, R. *et al.* Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050. *PLoS one* **7,** e30216 (2012).

49. Wagner, G. & Blower, S. Universal Access to HIV Treatment versus Universal 'Test and Treat': Transmission, Drug Resistance & Treatment Costs. *PLoS ONE* **7,** e41212 (2012).

50. Abbas, L., Glaubius, R., Mubayi, A., Hood, G. & Mellors, W. Antiretroviral therapy and pre-exposure prophylaxis: Combined impact on HIV transmission and drug resistance in South Africa. *Journal of Infectious Diseases* **208,** 224–234 (2013).

51. Long, F. & Stavert, R. Portfolios of biomedical HIV interventions in South Africa: A cost-effectiveness analysis. *Journal of General Internal Medicine* **28,** 1294–1301 (2013).

52. Cremin, I. *et al.* The new role of antiretrovirals in combination HIV prevention: A mathematical modelling analysis. *AIDS* **27,** 447–458 (2013).

53. Alsallaq, R., Buttolph, J., Cleland, C., Hallett, T. & Kurth, A. Estimating the impact of combined prevention interventions targeting 15-24 years-old men and women in Nyanza, Kenya. *Sexually Transmitted Infections* **89** (2013).

54. Nichols, E. *et al.* Cost-effectiveness of PrEP in HIV/AIDS control in Zambia: A stochastic league approach. *Journal of Acquired Immune Deficiency Syndromes* **66,** 221–228 (2014).

55. Nichols, E. *et al.* Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: A modeling study. *AIDS* **28,** 73–83 (2014).

56. Alistar, S., Grant, M. & Bendavid, E. Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa. *BMC Medicine* **12,** 46 (2014).

57. Ying, R. *et al.* Cost-effectiveness of preexposure prophylaxis for high-risk HIV-discordant couples. *Topics in Antiviral Medicine* **23,** 511 (2015).

58. Low, A. *et al.* Potential impact of existing interventions and of antiretroviral use in female sex workers on transmission of HIV in Burkina Faso: A modeling study. *Journal of Acquired Immune Deficiency Syndromes* **68,** S180–S188 (2015).

59. Khademi, A. & Moody, A. R. *Multiscale partial volume estimation for segmentation of white matter lesions using flair MRI* in *Proceedings - International Symposium on Biomedical Imaging* **2015-July** (IEEE, 2015), 568–571.

60. Gilbert, A. *et al.* Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa. *PLoS ONE* **10,** e0126267 (2015).

61. Heaton, M. *et al.* Estimating the impact of the US President's Emergency Plan for AIDS Relief on HIV treatment and prevention programmes in Africa. *Sexually Transmitted Infections* **91,** 615–620 (2015).

62. Rahman, A., Vaidya, K. & Zou, X. Impact of early treatment programs on HIV epidemics: An immunity-based mathematical model. *Mathematical Biosciences* **280,** 38–49 (2016).

63. Gilbert, A. *et al.* Cost-effectiveness of community-based TB/HIV screening and linkage to care in rural South Africa. *PLoS ONE* **11,** e0165614 (2016).

64. Blaizot, S. *et al.* Potential impact of multiple interventions on HIV incidence in a hyperendemic region in Western Kenya: A modelling study. *BMC Infectious Diseases* **16,** 189 (2016).

65. Ying, R. *et al.* Home testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modelling analysis. *The Lancet HIV* **3,** e275–e282 (2016).

66. Heffernan, A. *et al.* Impact and cost-effectiveness of point-of-care CD4 testing on the HIV epidemic in South Africa. *PLoS ONE* **11,** e0158303 (2016).

67. Maheu-Giroux, M. *et al.* Changing Dynamics of HIV Transmission in Cote d'Ivoire: Modeling Who Acquired and Transmitted Infections and Estimating the Impact of Past HIV Interventions (1976-2015). *Journal of Acquired Immune Deficiency Syndromes* **75,** 517–527 (2017).

68. Maheu-Giroux, M. *et al.* Changing Dynamics of HIV Transmission in Côte d'Ivoire: Modeling Who Acquired and Transmitted Infections and Estimating the Impact of Past HIV Interventions (1976-2015). *Journal of Acquired Immune Deficiency Syndromes* **75,** 517–527 (2017).

69. Volz, M. *et al.* Phylodynamic analysis to inform prevention efforts in mixed HIV epidemics. *Virus Evolution* **3,** vex014 (2017).

70. Blaizot, S. *et al.* Combined interventions to reduce HIV incidence in KwaZulu-Natal: A modelling study. *BMC Infectious Diseases* **17,** 522 (2017).

71. Mukandavire, C. *et al.* Estimating the contribution of key populations towards the spread of HIV in Dakar, Senegal. *Journal of the International AIDS Society* **21,** e25126 (2018).

72. Guillon, M. Success factors for universal access to antiretroviral treatments in South Africa. *The International journal of health planning and management* **33,** e1160–e1178 (2018).

73. Akudibillah, G., Pandey, A. & Medlock, J. Optimal control for HIV treatment. *Mathematical biosciences and engineering : MBE* **16,** 373–396 (2018).

74. Stuart, M. *et al.* The City of Johannesburg can end AIDS by 2030: Modelling the impact of achieving the Fast-Track targets and what it will take to get there: Modelling. *Journal of the International AIDS Society* **21,** e25068 (2018).

75. De Montigny, S., Boily, C., Masse, R., Mitchell, M. & Dimitrov, T. Assessing the utility of the tipping point ratio to monitor HIV treatment programmes in the era of universal access to ART. *Infectious Disease Modelling* **3,** 85–96 (2018).

76. Hauser, A. *et al.* Bridging the gap between hiv epidemiology and antiretroviral resistance evolution: Modelling the spread of resistance in south africa. *PLoS Computational Biology* **15,** e1007083 (2019).

77. Johnson, L. F. & Dorrington, R. E. Modelling the demographic impact of HIV/AIDS in South Africa and the likely impact of interventions. *Demographic Research* **14,** 541–574 (2006).

78. Baggaley, R. F., Garnett, G. P. & Ferguson, N. M. Modelling the Impact of Antiretroviral Use in Resource-Poor Settings. *PLoS medicine* **3,** 493–504 (2006).

79. Wilson, D. P., Kahn, J. & Blower, S. M. Predicting the epidemiological impact of antiretroviral allocation strategies in KwaZulu-Natal: the effect of the urban-rural divide. *Proceedings of the National Academy of Sciences of the United States of America* **103,** 14228–33 (2006).

80. Bacaer, N., Ouifki, R., Pretorius, C., Wood, R. & Williams, B. Modeling the joint epidemics of TB and HIV in a South African township. *Journal of Mathematical Biology* **57,** 557–593 (2008).

81. Chigidi, E. & Lungu, M. Hiv model incorporating differential progression for treatment-naive and treatment-experienced infectives. *Mathematical Biosciences and Engineering* **6,** 427–450 (2009).

82. Williams, H. *et al.* HIV and hepatocellular and esophageal carcinomas related to consumption of mycotoxin-prone foods in sub-Saharan Africa. *American Journal of Clinical Nutrition* **92,** 154–160 (2010).

83. Nyabadza, F. & Mukandavire, Z. Modelling HIV/AIDS in the presence of an HIV testing and screening campaign. *Journal of Theoretical Biology* **280,** 167–179 (2011).

84. Barnighausen, T., Bloom, D. E. & Humair, S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. *Proceedings of the National Academy of Sciences* **109,** 21271–21276 (2012).

85. Wagner, G., Coburn, J. & Blower, S. Increasing survival time decreases the cost-effectiveness of using "test & treat" to eliminate HIV epidemics. *Mathematical Biosciences and Engineering* **10,** 1673–1686 (2013).

86. Decker, M. R. *et al.* Estimating the impact of reducing violence against female sex workers on HIV epidemics in Kenya and Ukraine: a policy modeling exercise. *American journal of reproductive immunology (New York, N.Y. : 1989)* **69 Suppl 1,** 122–32 (2013).

87. Wirtz, L. *et al.* Modelling the impact of HIV prevention and treatment for men who have sex with men on HIV epidemic trajectories in low- and middle-income countries. *International Journal of STD and AIDS* **24,** 18–30 (2013).

88. Shafer, A. *et al.* The dual impact of antiretroviral therapy and sexual behaviour changes on HIV epidemiologic trends in Uganda: A modelling study. *Sexually Transmitted Infections* **90,** 423–429 (2014).

89. Hove-Musekwa, S. D., Nyabadza, F., Mambili-Mamboundou, H., Chiyaka, C. & Mukandavire, Z. Cost-Effectiveness Analysis of Hospitalization and Home-Based Care Strategies for People Living with HIV/AIDS: The Case of Zimbabwe. *International scholarly research notices* **2014,** 836439 (2014).

90. Braithwaite, S. *et al.* Howinexpensive does an alcohol intervention in kenya need to be to deliver favorable value by reducing HIV-related morbidity andmortality? *Alcoholism: Clinical and Experimental Research* **38,** 71A (2014).

91. Nichols, E. *et al.* Increasing the use of second-line therapy is a cost-effective approach to prevent the spread of drug-resistant HIV: a mathematical modelling study. *Journal of the International AIDS Society* **17,** 19164 (2014).

92. Abu-Raddad, J. & Awa, F. How does population viral load vary with the evolution of a large HIV epidemic in sub-Saharan Africa? *AIDS* **28,** 927–929 (2014).

93. Anderson, S. J. *et al.* Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study. *The Lancet* **384,** 249–256 (2014).

94. Alistar, S., Long, F., Brandeau, L. & Beck, J. HIV epidemic control-a model for optimal allocation of prevention and treatment resources. *Health care management science* **17,** 162–181 (2014).

95. Cori, A. *et al.* HPTN 071 (PopART): A cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: Mathematical model. *PLoS ONE* **9** (ed Polis, M. A.) e84511 (2014).

96. Stover, J. *et al.* How Can We Get Close to Zero? The Potential Contribution of Biomedical Prevention and the Investment Framework towards an Effective Response to HIV. *PLoS one* **9,** e111956 (2014).

97. Wirtz, L. *et al.* Epidemic impacts of a community empowerment intervention for HIV prevention among female sex workers in generalized and concentrated epidemics. *PLoS ONE* **9,** e88047 (2014).

98. Korenromp, L. *et al.* Impact and cost of the HIV/AIDS national strategic plan for Mozambique, 2015-2019-projections with the spectrum/goals model. *PLoS ONE* **10,** e0142908 (2015).

99. Knight, G. *et al.* Tuberculosis Prevention in South Africa. *PLoS ONE* **10,** e0122514 (2015).

100. Kerr, C. C. *et al.* Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization. *Journal of Acquired Immune Deficiency Syndromes* **69,** 365–376 (2015).

101. Fraser, N. *et al.* Reorienting the HIV response in Niger toward sex work interventions: From better evidence to targeted and expanded practice. *Journal of Acquired Immune Deficiency Syndromes* **68,** S213–S220 (2015).

102. Kassa, M. & Ouhinou, A. The impact of self-protective measures in the optimal interventions for controlling infectious diseases of human population. *Journal of mathematical biology* **70,** 213–236 (2015).

103. Bekker, L. G. *et al. Combination HIV prevention for female sex workers: What is the evidence?* 2015.

104. Shannon, K. *et al. Global epidemiology of HIV among female sex workers: Influence of structural determinants* 2015.

105. Blaizot, S. *et al.* Estimation and short-term prediction of the course of the HIV epidemic using demographic and health survey methodology-like data. *PLoS ONE* **10,** e0130387 (2015).

106. Smith, A. *et al.* Maximising HIV prevention by balancing the opportunities of today with the promises of tomorrow: a modelling study. *The Lancet HIV* **3,** e289–e296 (2016).

107. Atun, R. *et al.* Long-term financing needs for HIV control in sub-Saharan Africa in 2015-2050: a modelling study. *BMJ open* **6,** e009656 (2016).

108. Shattock, J. *et al.* In the interests of time: Improving HIV allocative efficiency modelling via optimal time-varying allocations. *Journal of the International AIDS Society* **19,** 20627 (2016).

109. McGillen, J., Anderson, J. & Hallett, T. Optimizing resource allocation to reduce HIV incidence across sub-Saharan Africa. *Topics in Antiviral Medicine* **24,** 454–455 (2016).

110. Johnson, L. F. & Geffen, N. A Comparison of two mathematical modeling frameworks for evaluating sexually transmitted infection epidemiology. *Sexually Transmitted Diseases* **43,** 139–146 (2016).

111. Sharma, M. *et al.* Modeling the cost-effectiveness of homebased HIV testing and education (HOPE) for pregnant women and their male partners in Nyanza Province, Kenya. *AIDS Research and Human Retroviruses* **32,** 300 (2016).

112. Akudibillah, G., Pandey, A. & Medlock, J. Maximizing the benefits of ART and PrEP in resource-limited settings. *Epidemiology and Infection* **145,** 942–956 (2017).

113. Alsallaq, A. *et al.* The potential impact and cost of focusing HIV prevention on young women and men: A modeling analysis in western Kenya. *PLoS ONE* **12,** e0175447 (2017).

114. Anderson, J., Ghys, D., Ombam, R. & Hallett, B. HIV prevention where it is needed most: Comparison of strategies for the geographical allocation of interventions: Comparison. *Journal of the International AIDS Society* **20,** e25020 (2017).

115. Chiu, C., Johnson, F., Jamieson, L., Larson, A. & Meyer-Rath, G. Designing an optimal HIV programme for South Africa: Does the optimal package change when diminishing returns are considered? *BMC public health* **17,** 143 (2017).

116. Johnson, F. *et al.* Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. *PLoS Medicine* **14,** e1002468 (2017).

117. Stuart, M. *et al.* Getting it right when budgets are tight: Using optimal expansion pathways to prioritize responses to concentrated and mixed HIV epidemics. *PLoS ONE* **12,** e0185077 (2017).

118. McGillen, B. *et al.* Consequences of a changing US strategy in the global HIV investment landscape. *AIDS* **31,** F19–F23 (2017).

119. Cremin, I. *et al.* PrEP for key populations in combination HIV prevention in Nairobi: a mathematical modelling study. *The Lancet HIV* **4,** e214–e222 (2017).

120. Ross, J. M. *et al.* Modeling HIV disease progression and transmission at population-level: The potential impact of modifying disease progression in HIV treatment programs. *Epidemics* **23,** 34–41 (2018).

121. Anderson, J., Ghys, D., Ombam, R. & Hallett, B. Frontloading HIV financing maximizes the achievable impact of hiv prevention. *Journal of the International AIDS Society* **21,** e25087 (2018).

122. Anderson, J., Garnett, P., Enstone, J. & Hallett, B. The importance of local epidemic conditions in monitoring progress towards HIV epidemic control in Kenya: a modelling study. *Journal of the International AIDS Society* **21,** e25203 (2018).

123. Omondi, E., Mbogo, R. & Luboobi, L. Mathematical analysis of sex-structured population model of HIV infection in Kenya. *Letters in Biomathematics* **5,** 174–194 (2018).

124. Woods, B. *et al.* Appraising the value of evidence generation activities: an HIV modelling study. *BMJ global health* **3,** e000488 (2018).

125. Stevens, R. *et al.* Cost-effectiveness of a combination strategy to enhance the HIV care continuum in Swaziland: Link4health. *PLoS ONE* **13,** e0204245 (2018).

126. Stopard, J., McGillen, B., Hauck, K. & Hallett, B. The influence of constraints on the efficient allocation of resources for HIV prevention. *AIDS* **33,** 1241–1246 (2019).

127. Beacroft, L. & Hallett, T. B. The potential impact of a ”curative intervention” for HIV: a modelling study. *Global health research and policy* **4,** 2 (2019).

128. Reidy, M. *et al.* Evaluating the potential impact and cost-effectiveness of dapivirine vaginal ring pre-exposure prophylaxis for HIV prevention. *PLoS ONE* **14,** e0218710 (2019).

129. Omondi, O., Mbogo, W. & Luboobi, S. A mathematical modelling study of HIV infection in two heterosexual age groups in Kenya. *Infectious Disease Modelling* **4,** 83–98 (2019).

130. Maheu-Giroux, M. *et al.* Cost-Effectiveness of Accelerated HIV Response Scenarios in Cote d’Ivoire. *Journal of Acquired Immune Deficiency Syndromes* **80,** 503–512 (2019).

# A Search Strategy

## 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

| | 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

| | 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

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

## A.3 Included Papers

### A.3.1 Dataset B

[29] 2005 Salomon *et al.*
[30] 2006 Abbas *et al.*
[6] 2009 Granich *et al.*
[43] 2009 Hallett *et al.*
[44] 2010 Bacaer *et al.*
[45] 2010 Pretorius *et al.*
[46] 2011 Metzger *et al.*
[47] 2012 Yusuf & Benyah
[36] 2012 Andrews *et al.*
[48] 2012 Granich *et al.*
[49] 2012 Wagner & Blower
[50] 2013 Abbas *et al.*
[51] 2013 Long & Stavert
[52] 2013 Cremin *et al.*
[53] 2013 Alsallaq *et al.*
[54] 2014 Nichols *et al.*
[55] 2014 Nichols *et al.*
[56] 2014 Alistar *et al.*
[38] 2014 Eaton *et al.*
[57] 2015 Ying *et al.*
[58] 2015 Low *et al.*
[59] 2015 Khademi & Moody
[60] 2015 Gilbert *et al.*
[61] 2015 Heaton *et al.*
[62] 2016 Rahman *et al.*
[63] 2016 Gilbert *et al.*
[64] 2016 Blaizot *et al.*
[65] 2016 Ying *et al.*
[31] 2016 Barnighausen *et al.*
[66] 2016 Heffernan *et al.*
[67] 2017 Maheu-Giroux *et al.*
[68] 2017 Maheu-Giroux *et al.*
[69] 2017 Volz *et al.*
[70] 2017 Blaizot *et al.*
[71] 2018 Mukandavire *et al.*
[72] 2018 Guillon
[73] 2018 Akudibillah *et al.*
[74] 2018 Stuart *et al.*
[75] 2018 de Montigny *et al.*
[76] 2019 Hauser *et al.*

### A.3.2 Dataset A less B

[77] 2006 Johnson & Dorrington
[78] 2006 Baggaley *et al.*
[79] 2006 Wilson *et al.*
[80] 2008 Bacaer *et al.*
[81] 2009 Chigidi & Lungu
[82] 2010 Williams *et al.*
[83] 2011 Nyabadza & Mukandavire
[84] 2012 Barnighausen *et al.*
[85] 2013 Wagner *et al.*
[86] 2013 Decker *et al.*
[87] 2013 Wirtz *et al.*
[88] 2014 Shafer *et al.*
[89] 2014 Hove-Musekwa *et al.*
[90] 2014 Braithwaite *et al.*
[91] 2014 Nichols *et al.*
[92] 2014 Abu-Raddad & Awa
[93] 2014 Anderson *et al.*
[94] 2014 Alistar *et al.*
[95] 2014 Cori *et al.*
[96] 2014 Stover *et al.*
[97] 2014 Wirtz *et al.*
[98] 2015 Korenromp *et al.*
[99] 2015 Knight *et al.*
[100] 2015 Kerr *et al.*
[101] 2015 Fraser *et al.*
[102] 2015 Kassa & Ouhinou
[103] 2015 Bekker *et al.*
[104] 2015 Shannon *et al.*
[105] 2015 Blaizot *et al.*
[106] 2016 Smith *et al.*
[107] 2016 Atun *et al.*
[108] 2016 Shattock *et al.*
[109] 2016 McGillen *et al.*
[110] 2016 Johnson & Geffen
[111] 2016 Sharma *et al.*
[112] 2017 Akudibillah *et al.*
[113] 2017 Alsallaq *et al.*
[114] 2017 Anderson *et al.*
[115] 2017 Chiu *et al.*
[116] 2017 Johnson *et al.*
[117] 2017 Stuart *et al.*
[118] 2017 McGillen *et al.*
[119] 2017 Cremin *et al.*
[120] 2018 Ross *et al.*
[121] 2018 Anderson *et al.*
[122] 2018 Anderson *et al.*
[123] 2018 Omondi *et al.*
[124] 2018 Woods *et al.*
[125] 2018 Stevens *et al.*
[126] 2019 Stopard *et al.*
[127] 2019 Beacroft & Hallett
[128] 2019 Reidy *et al.*
[129] 2019 Omondi *et al.*
[130] 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 Context

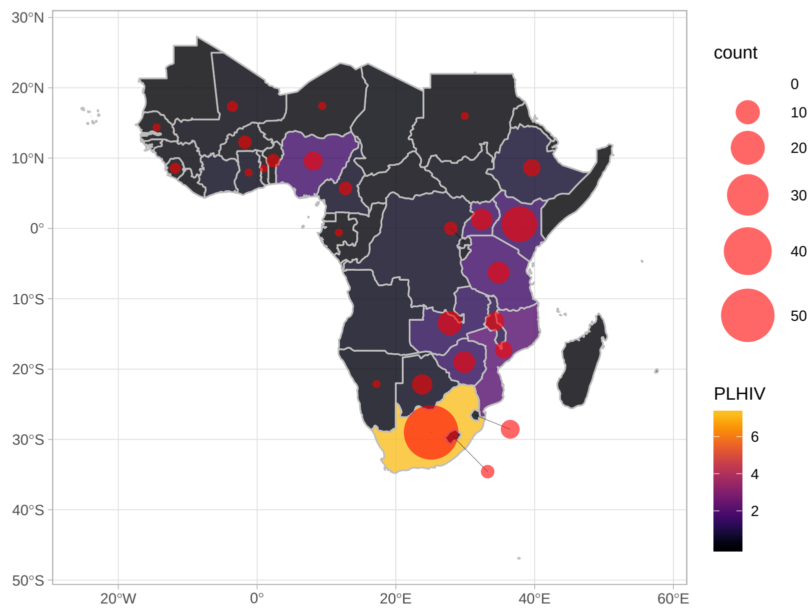



Figure C.1: Map showing number of articles (of 94 total) applying HIV transmission modelling in each country vs the number of people living with HIV (PLHIV, millions)

## C.2 Risk Heterogeneity

### C.2.1 Distributions

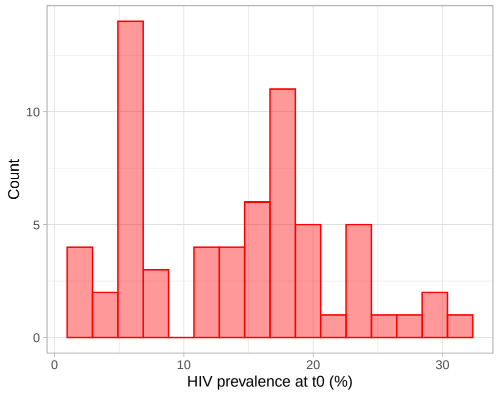



Figure C.2: HIV prevalence at $t_0$ (%)

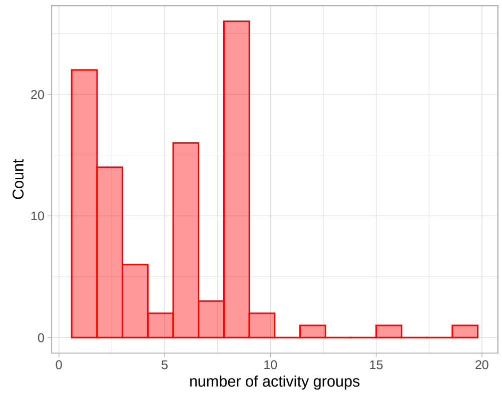



Figure C.5: number of activity groups

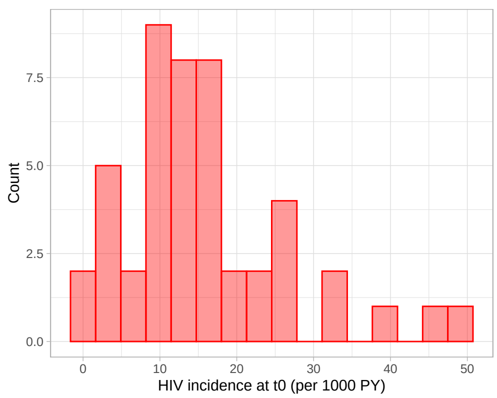



Figure C.3: HIV incidence at $t_0$ (per 1000 PY)

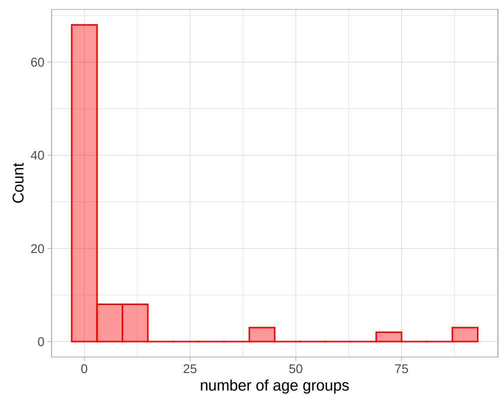



Figure C.6: number of age groups

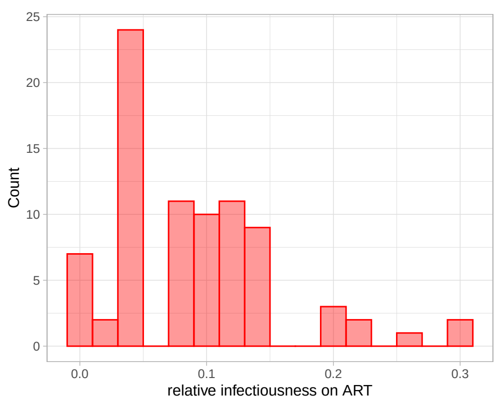



Figure C.4: relative infectiousness on ART

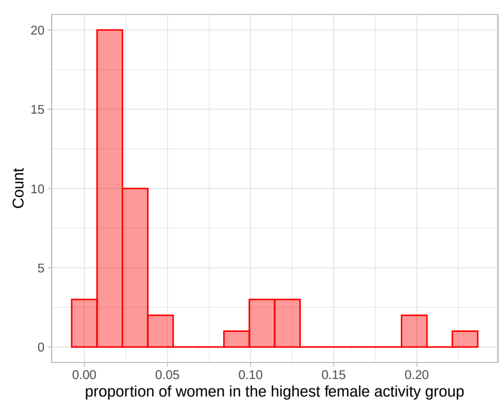



Figure C.7: proportion of women in the highest female activity group


Figure C.8: proportion of men in the client or highest activity male group

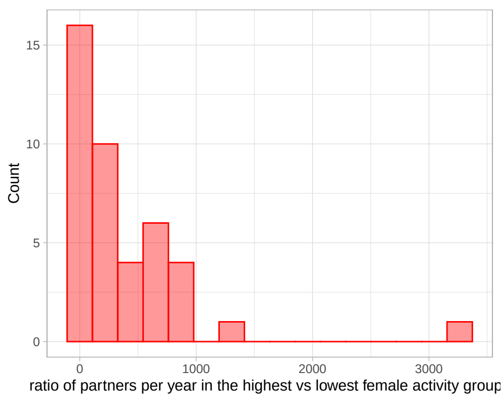



Figure C.9: ratio of partners per year in the highest vs lowest female activity groups


Figure C.10: ratio of highest female to highest male activity group sizes

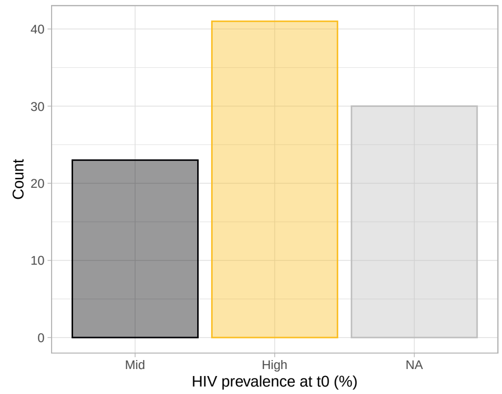



Figure C.11: HIV prevalence at $t_0$ (%)

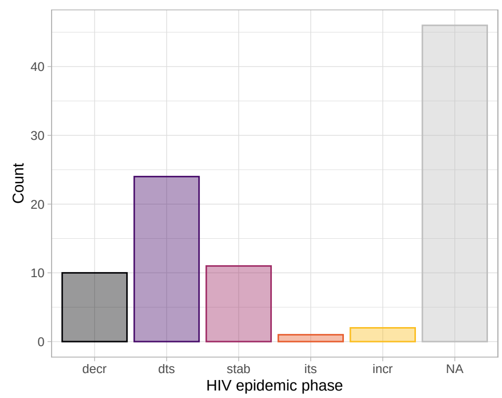



Figure C.12: HIV epidemic phase

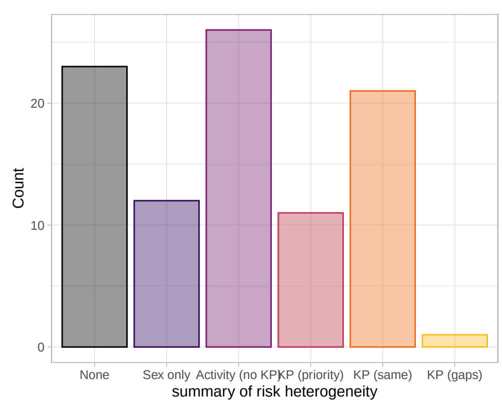



Figure C.13: summary of risk heterogeneity

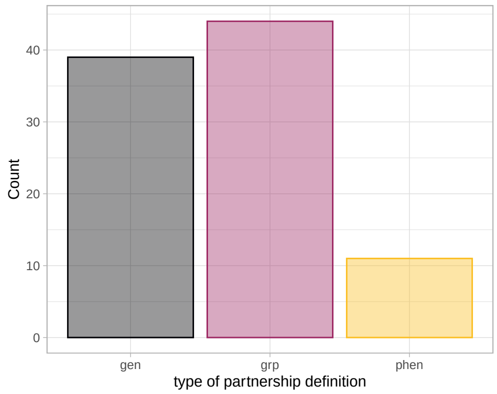



Figure C.14: type of partnership definition

## C.3 ART Prevention Impact

The following figures show the projected ART prevention impact (Dataset B), stratified by various factors of heterogeneity (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 articles (scenarios) reporting incidence reduction, cumulative infections averted, both, or either was: 23 (61), 23 (73), 6 (10), and 41 (126), respectively. If any article 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 articles 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.

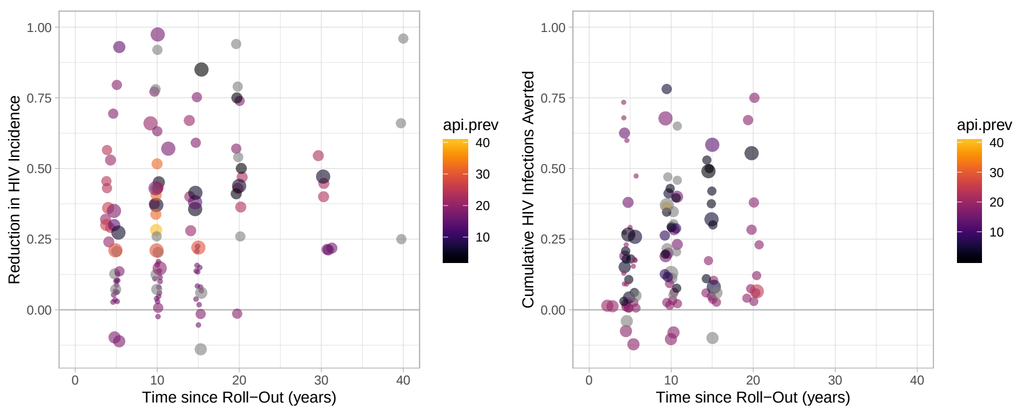



Figure C.15: HIV prevalence at $t_0$ (%)

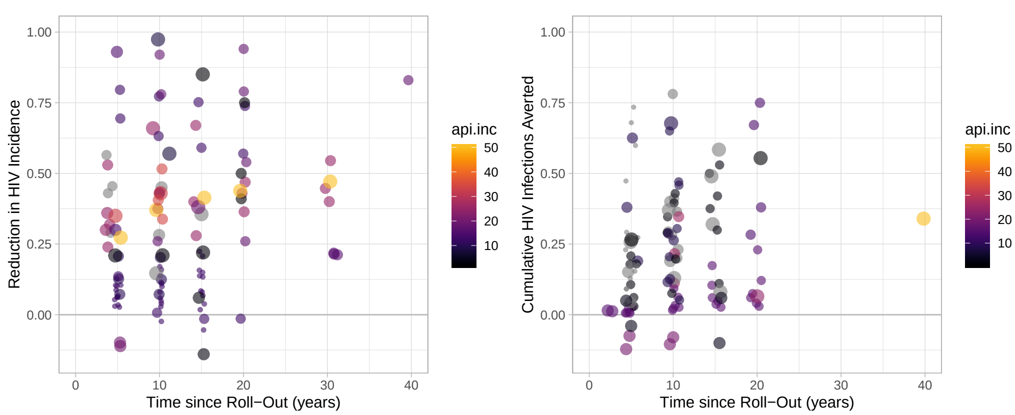



Figure C.16: HIV incidence at $t_0$ (per 1000 PY)

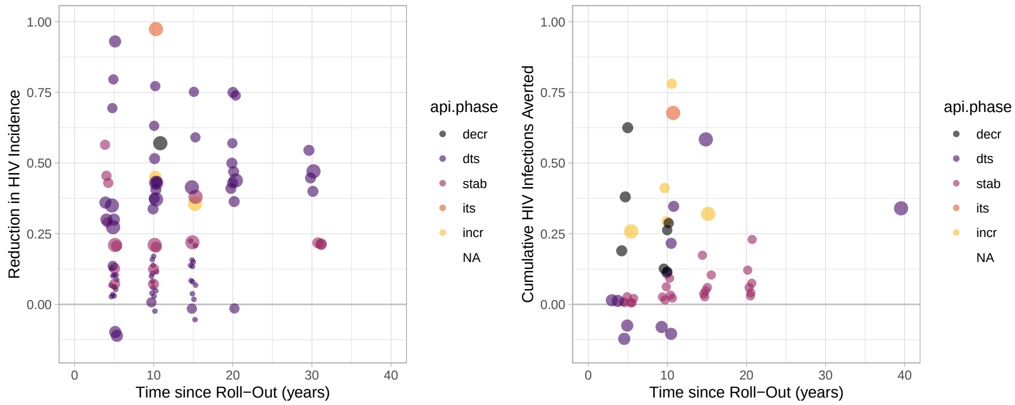



Figure C.17: HIV epidemic phase

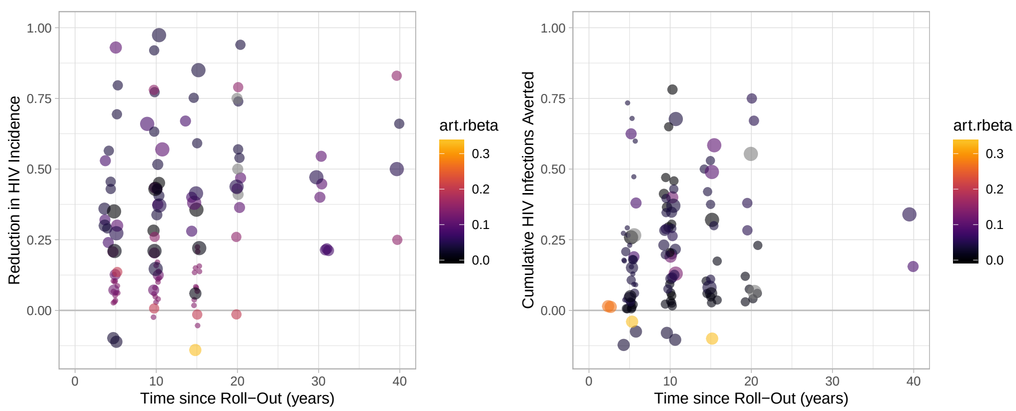



Figure C.18: relative infectiousness on ART

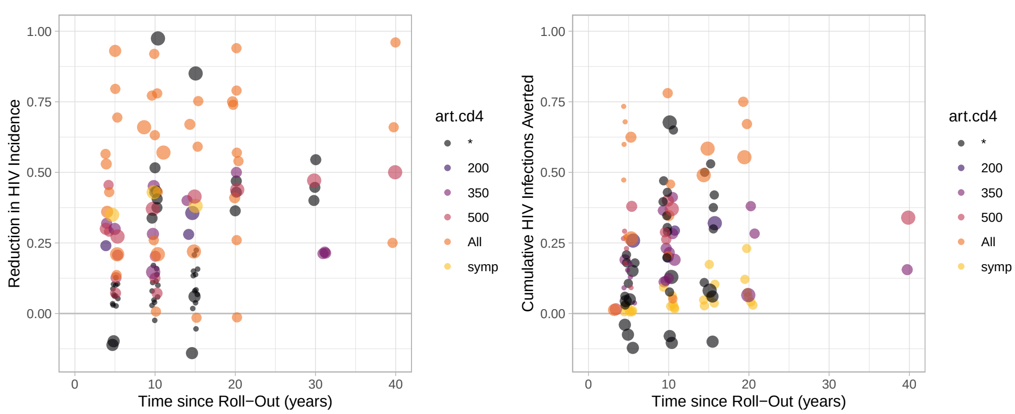



Figure C.19: CD4 initiation criteria (less than shown count)

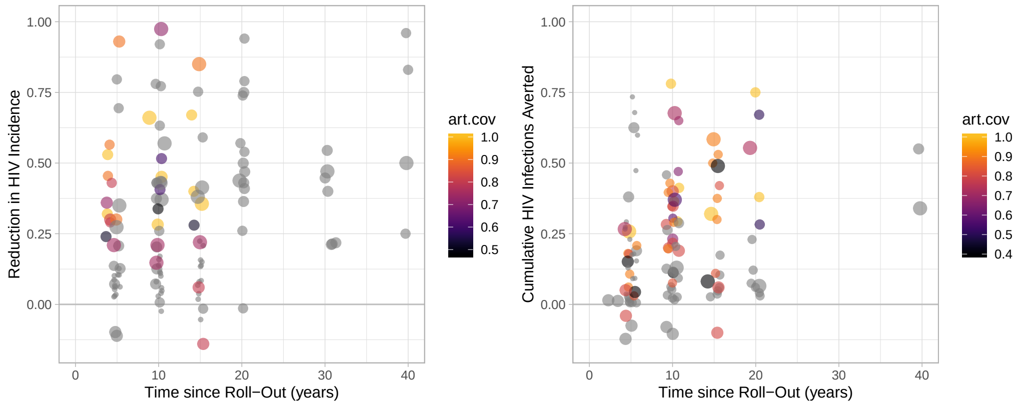


Figure C.20: ART coverage target

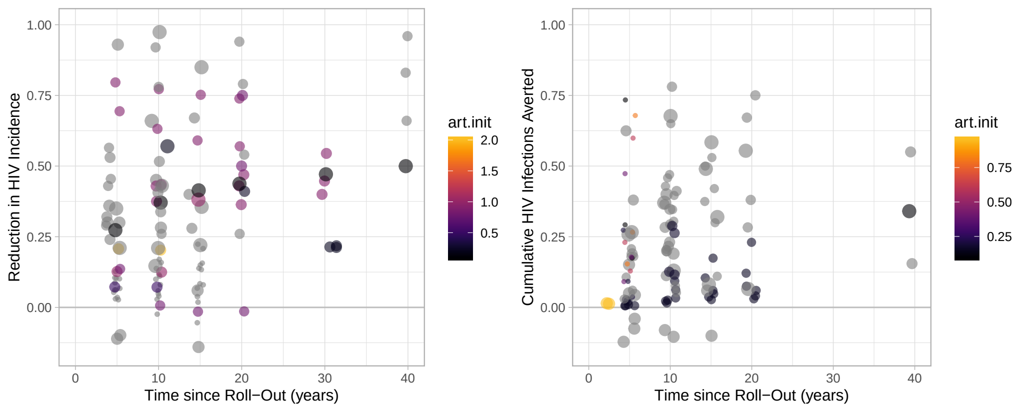


Figure C.21: ART initiation rate (per PY)

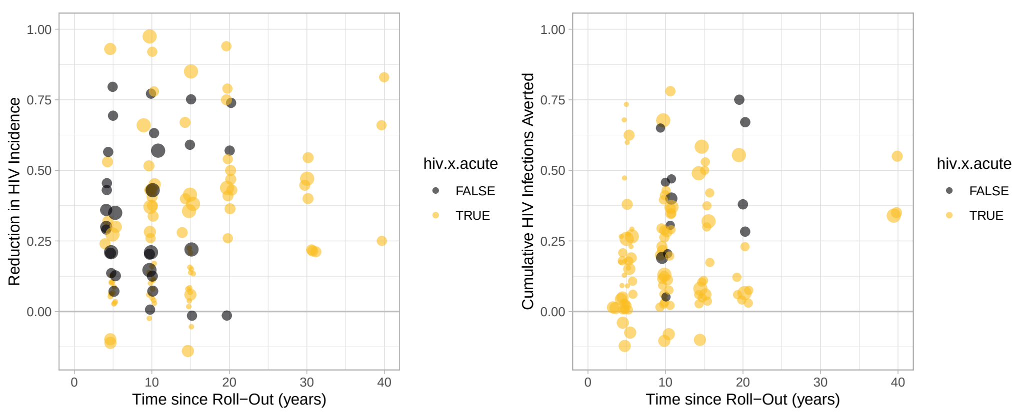


Figure C.22: increased infectiousness during acute infection

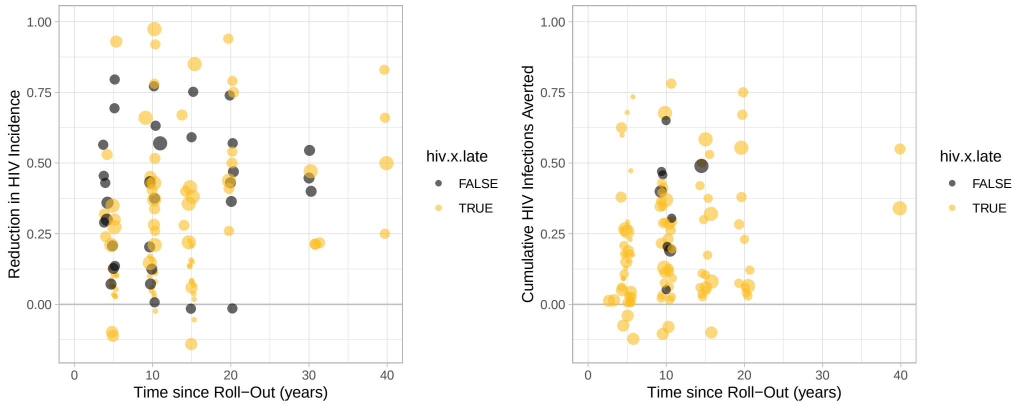



Figure C.23: increased infectiousness during late-stage infection

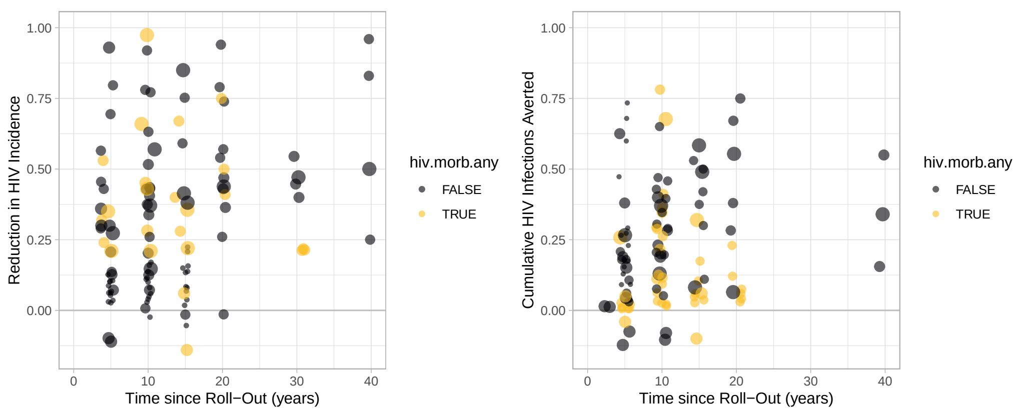



Figure C.24: decreased sexual activity during late-stage infection

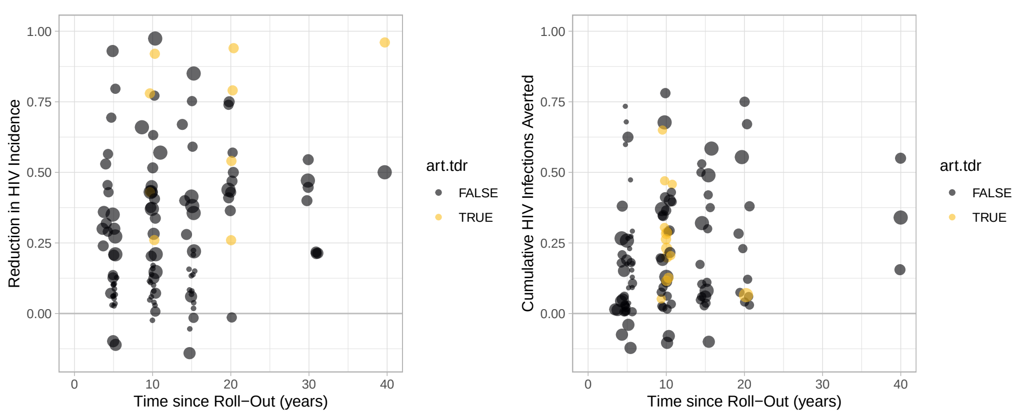



Figure C.25: any transmitted drug resistance

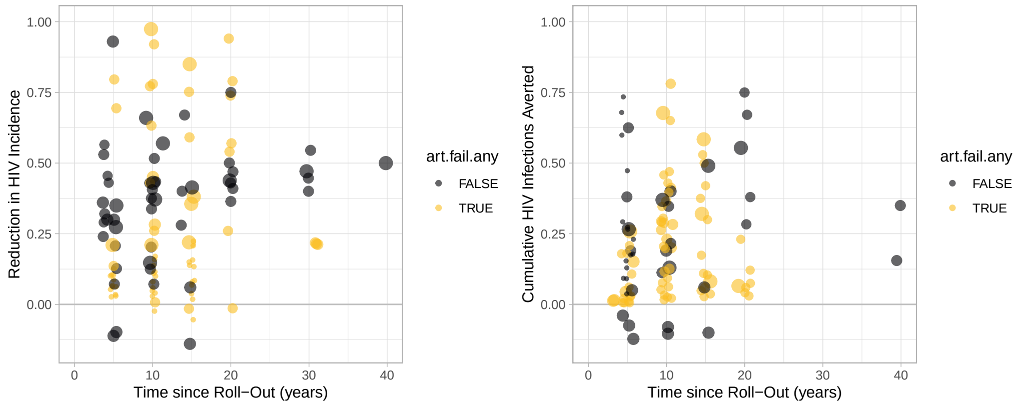



Figure C.26: any rate or state of ART failure

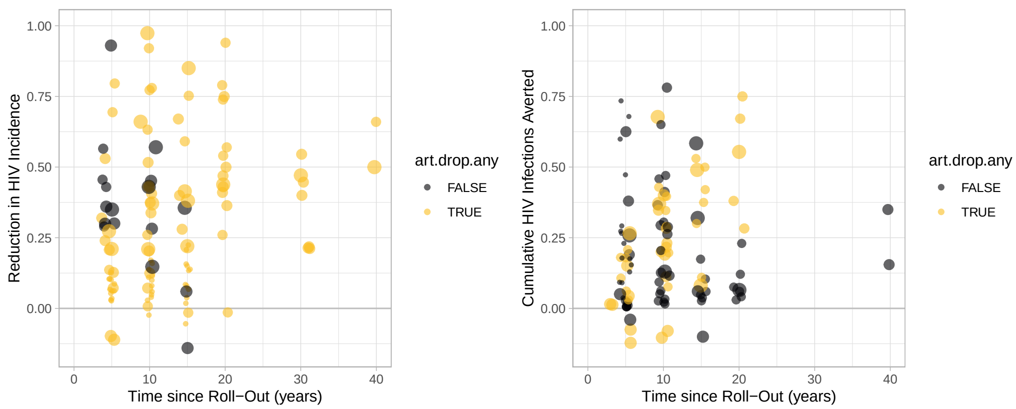



Figure C.27: any rate or state of ART dropout

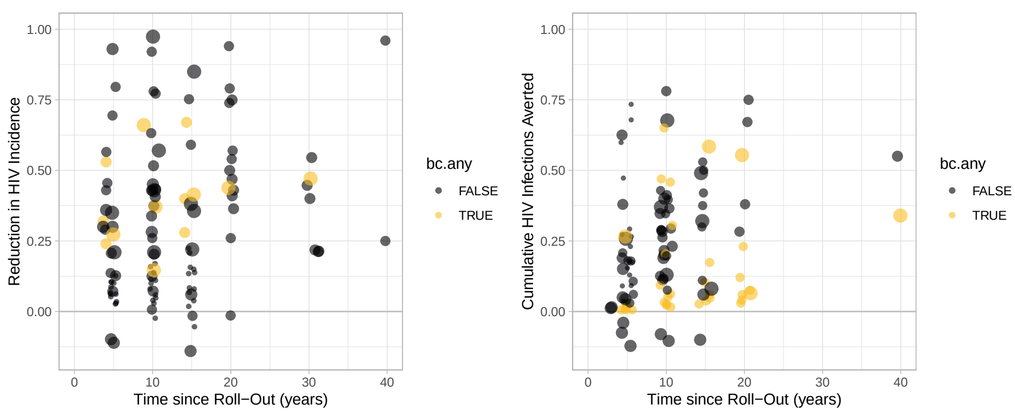



Figure C.28: any behaviour change associated with diagnosis or ART

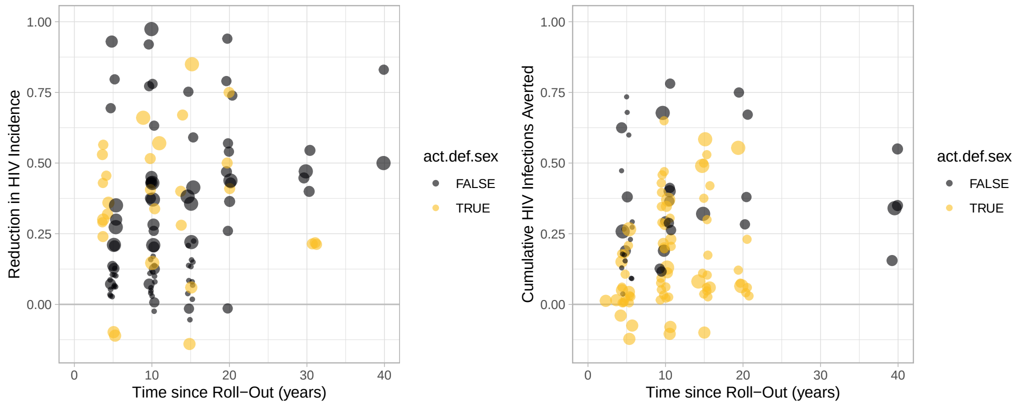



Figure C.29: stratified by sex

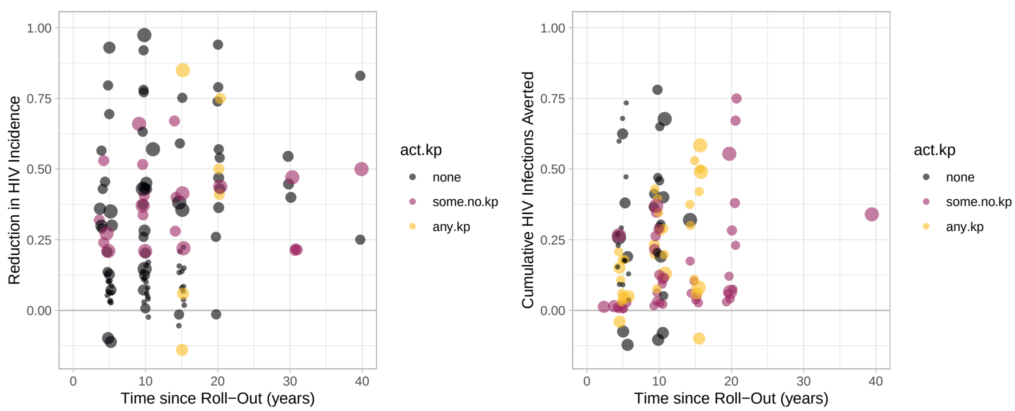



Figure C.30: activity groups & key populations

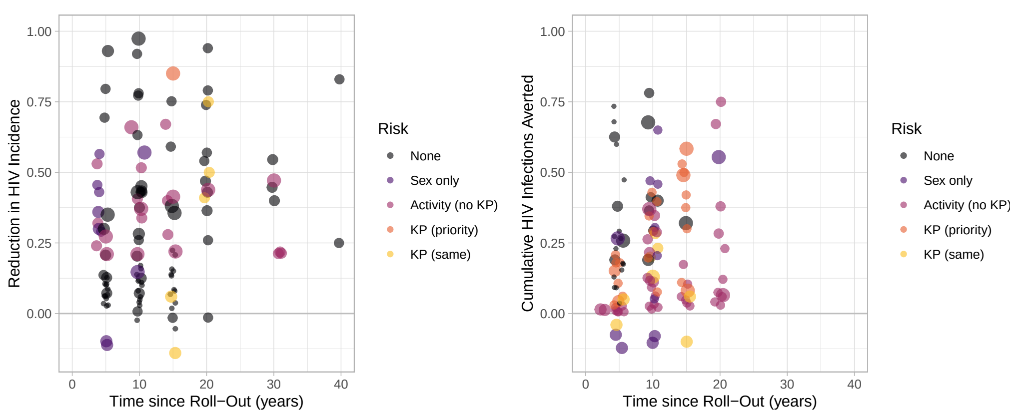



Figure C.31: summary of risk heterogeneity

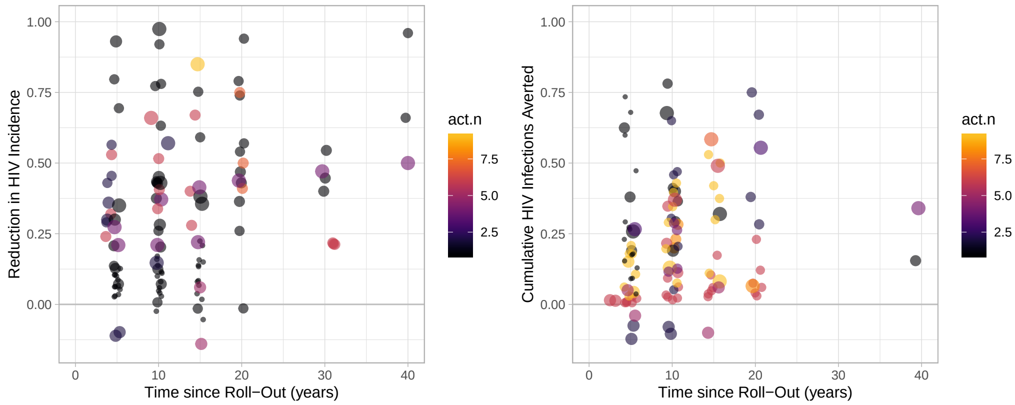



Figure C.32: number of activity groups

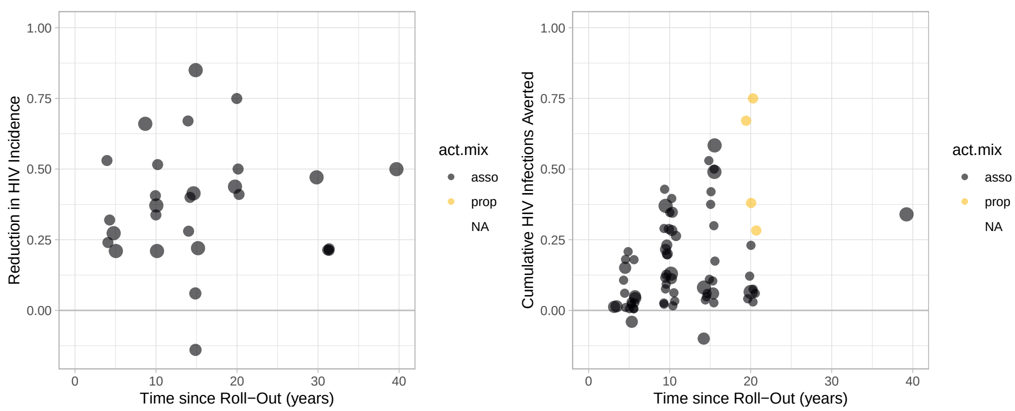



Figure C.33: type of activity mixing

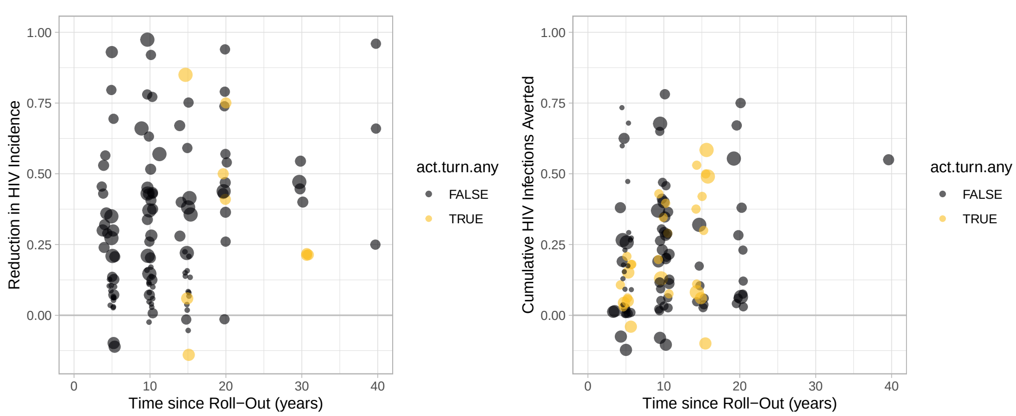



Figure C.34: any activity group turnover

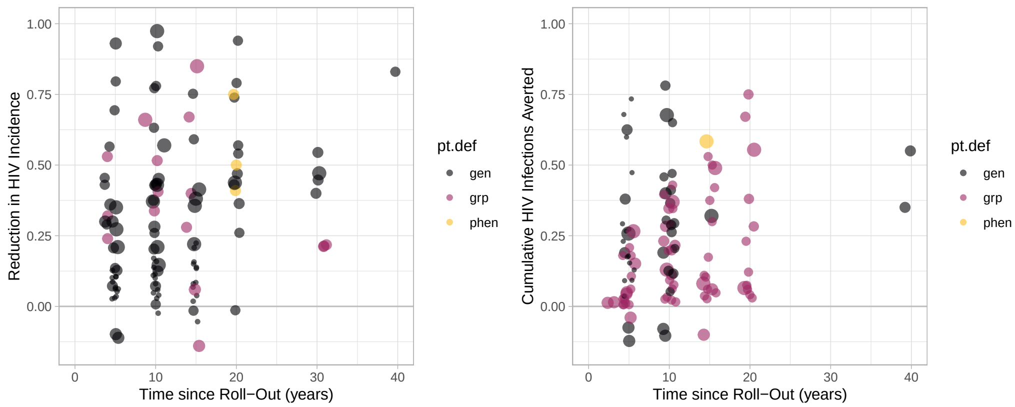



Figure C.35: type of partnership definition

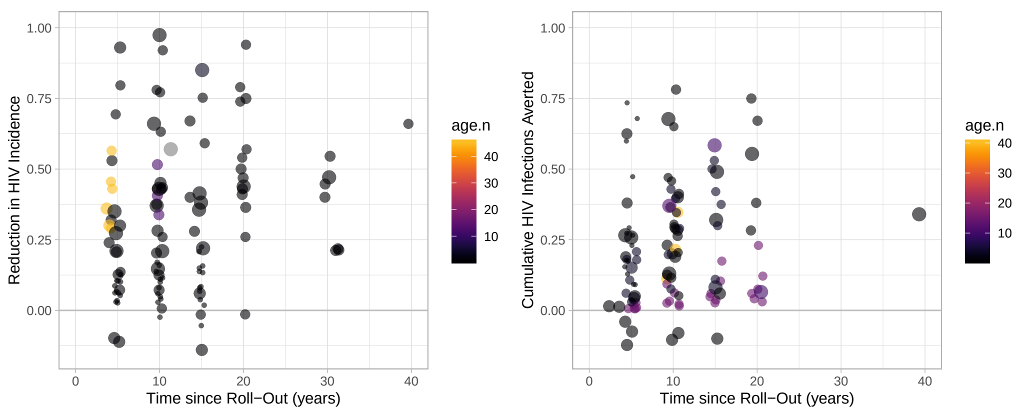



Figure C.36: number of age groups

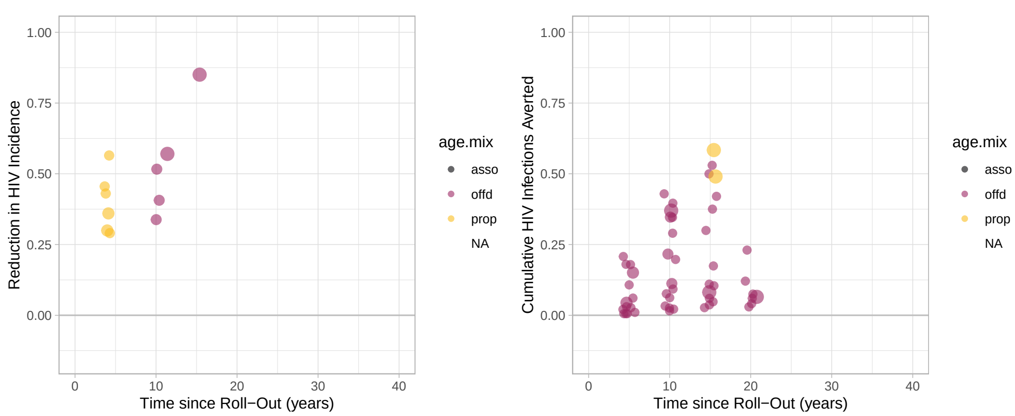



Figure C.37: type of age mixing

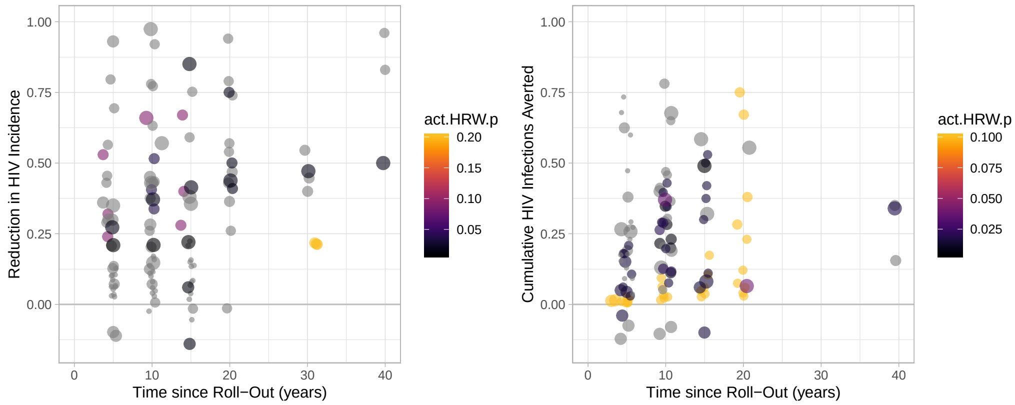


Figure C.38: proportion of women in the highest female activity group

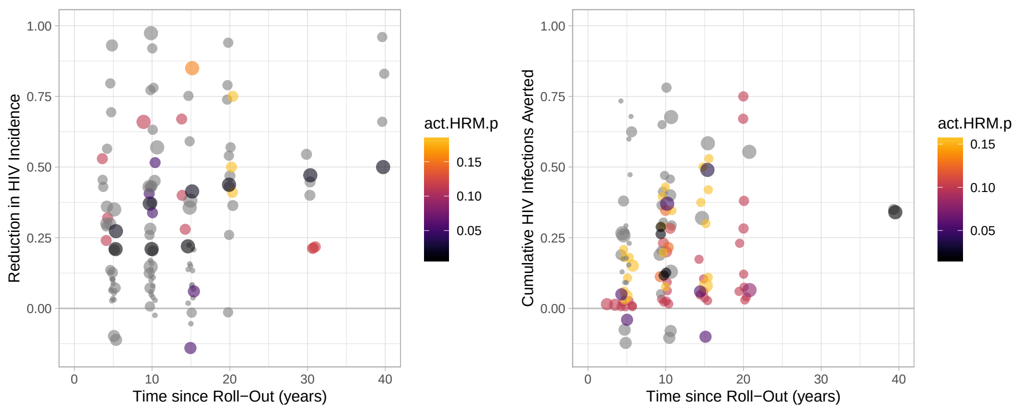


Figure C.39: proportion of men in the client or highest activity male group

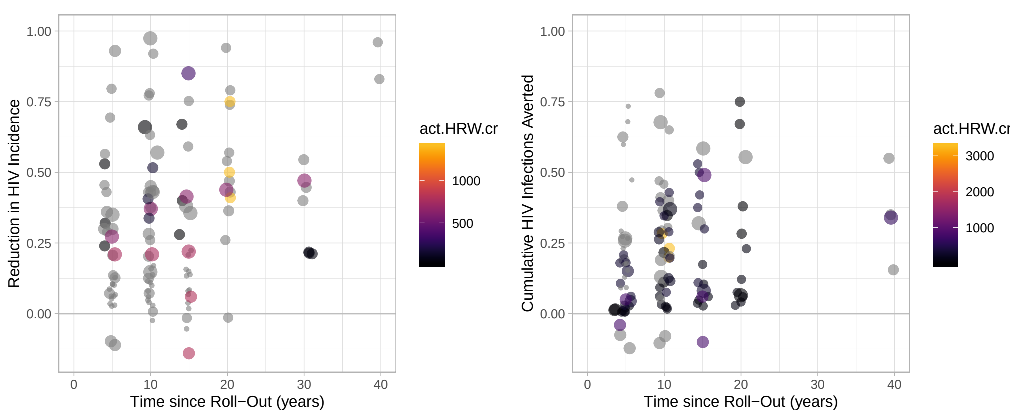


Figure C.40: ratio of partners per year in the highest vs lowest female activity groups

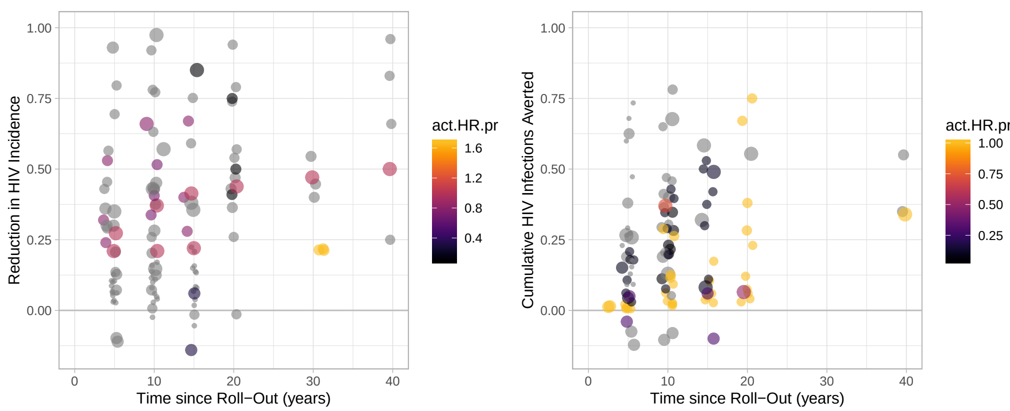



Figure C.41: ratio of highest female to highest male activity group sizes

# 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. | |

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| 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.