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

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1 Introduction

Viral load suppression by antiretroviral therapy (ART) has undisputed individual-level health benefits. Partner-based trials have also clearly demonstrated prevention of HIV transmission via ART (undetectable = untransmittable).[1–3] Such demonstrations have complemented earlier model-based evidence of "treatment as prevention",[4,5] motivating several large-scale community-based trials of universal test-and-treat.[6–8]

Unfortunately, universal test-and-treat without combination prevention interventions did not significantly reduce HIV incidence in these trials.[6–8] Proposed explanations for non-significance include: participation bias; poor linkage to care, possibly associated with stigma and accessibility; concurrent cascade improvements in the control arm, including expanded testing and ART eligibility; mobility and sexual mixing outside study communities; and possible de-emphasis of primary prevention.[6–9] These explanations highlight the potential challenges of implementing ART as prevention at scale, particularly if the unique treatment and prevention needs of at-risk populations are not explicitly incorporated into ART scale-up; that is, if heterogeneities in risk and access to care are not sufficiently considered.[9]

Given the upstream and complementary role of transmission modelling to project the impact of ART as prevention,[4,5] we were motivated to critically appraise assumptions and representations of risk heterogeneity in earlier models assessing ART as prevention. This appraisal might help explain the differences between projected and observed ART prevention impacts. For the appraisal, we considered "factors of risk heterogeneity", meaning population stratifications and epidemiological phenomena which may/not be included in transmission models. We also defined the following 5 mechanisms by which factors of risk heterogeneity might influence ART prevention impact.

- **Biological Effects:** differential transmission risk within HIV disease course that coincide with differential ART coverage[10]
- **Network Effects:** differential transmission risk within sub-populations that increase the challenge of epidemic control through core group dynamics[11–13]
- **Coverage Effects:** differential transmission risk within sub-populations who also experience barriers to achieving viral suppression via ART, such as key populations[14–16]
- **Behavioural Effects:** differential transmission risk due to behavioural changes related to engagement in the ART cascade
- **Epidemic Effects:** changes in the relative prevalence of people in each ART cascade step within the sexually active population

We then compiled a list of key factors of risk heterogeneity, and their associated mechanisms of influence on ART prevention impact (Table 1). Based on this list, we reviewed the model-based evidence of ART prevention impact in order to answer the following research questions. Among dynamical compartmental models of 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?

2 Methods

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.

2.1 Inclusion/Exclusion Criteria

A first set of criteria identified any studies applying dynamical models of sexual HIV transmission to any research question and context within SSA. A dynamical transmission model projects the number of new HIV infections based on model inputs and previous model outputs, thereby capturing nonlinear population-level transmission dynamics, such as indirect benefits of prevention interventions. Models were only included if they considered sexual transmission of HIV, possibly alongside other routes of transmission, such as mother-to-child and parenteral, and possibly alongside transmission of other infectious diseases such as other STI, tuberculosis, or malaria. We excluded studies without primary modelling results, such as commentaries and reviews, as well as conference publications.

A second set of criteria was used to select studies using compartmental (vs individual-based) HIV transmission models, applied to assess the any outcome related to the prevention benefits of ART scale-up. These studies formed the basis of the analysis to answer our first and second research questions. A third set of criteria was used to select a subset of the above to answer our third research question. The subset were selected if they specifically examined scale-up of ART coverage alone (vs combination intervention), and reported incidence reduction or cumulative infections averted after X years, as compared to a base-case scenario reflecting reality. Complete inclusion/exclusion criteria are given in Appendix A.2.

2.2 Data Extraction

Most variables were extracted per-study, vs per-scenario within the study. We also noted whether studies used the same model, and whether identical analyses were con-

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

Factor	MP [a]	Definition	Possible mechanism(s) of influence on ART prevention impact
Acute Infection	β_i	Increased infectiousness immediately following infection[10]	**Biological**: transmissions during acute infection are unlikely to be prevented by ART
Late Stage Infection	β_i	Increased infectiousness during late stage infection	**Biological**: transmissions during late-stage are more likely to be prevented by ART
Drug Resistance	β_i	Transmitted factor that requires regimen switch to achieve viral suppression	**Biological**: transmissions during longer delay to achieving viral suppression will not be prevented by ART
HIV Mortality	μ	Increased HIV/AIDS-associated mortality during late-stage disease	**Epidemic**: reduced mortality via ART could increase the overall HIV prevalence[17]
Population Turnover	ν; μ	Individuals enter into and exit from the sexually active population reflecting sexual lifecourse	**Epidemic**: net replacement of exiting virally suppressed individuals with entering susceptible individuals could require greater ART initiation rates for the same coverage
Concurrent Interventions	varies	Any increase in prevention interventions reflecting observed or projected trends	**Epidemic**: Declining incidence due to prevention interventions could reduce the potential for ART prevention benefit
HIV Morbidity	c; η	Reduced sexual activity during late stage disease	**Behavioural**: reduced morbidity via ART could increase HIV prevalence among the sexually active population
HIV Counselling	c; κ	Reduced sexual activity and/or increased condom use after HIV diagnosis	**Behavioural**: increased HIV testing with ART scale up can contribute to prevention even before viral suppression is achieved
Risk Compensation	c; κ	Increased sexual activity and/or reduced condom use after ART initiation	**Behavioural**: increased risk behaviour before achieving viral suppression could increase transmission risk
Activity Groups	c; κ	Any stratification by rate of partnership formation	**Network**: higher transmission risk among higher activity
Key Populations	c; κ	Any epidemiologically defined higher risk groups, including: FSW, Clients, MSM, PWID, AGYW	**Network & Coverage** higher transmission risk and barriers to viral suppression among key populations
Age Groups	c; κ	Any stratification by age	**Network & Coverage**: higher transmission risk and barriers to viral suppression among youth
Internal Turnover	ϕ	Individuals move between activity groups and/or key populations reflecting sexual lifecourse	**Network & Coverage**: counteract effect of stratification due to shorter periods in higher risk; viral suppression may be achieved only after periods of higher risk
Assortative Mixing	m	Any degree of assortative mixing by age, activity, and/or key populations	**Network & Coverage**: assortative sexual networks compound effect of stratification
Partnership Types	η; κ	Different partnership types are simulated, with different volumes of sex and/or condom usage	**Network & Coverage**: generally shorter duration and higher condom use among higher risk partnerships
Anal Sex	β_s; η	Anal sex is simulated, with higher receptive transmission probability[18]	**Network & Coverage**: higher prevalence of anal sex among key populations[19]
STI Infection	β_i; β_s	Increased transmission probability due to STI infection	**Network & Coverage**: higher prevalence of STI coincides with higher sexual activity
ART Cascade Gaps	τ; α	Lower ART cascade coverage among higher risk groups or key populations	**Coverage**: ART prevention benefits may be allocated among lowest risk

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

ducted in multiple studies (for example, if a second study only added economic analysis to modelling results from an earlier study).

2.2.1 Epidemic Context

To answer our first research question, we extracted the following data. Studies were categorized by the geographic location (country and SSA region) and scale of the simulated population (city, sub-national, national, super-national), including whether multiple geographic contexts were considered. The epidemic phase was categorized based on the overall HIV prevalence and incidence at the time of intervention roll-out/scenario divergence, as well as the sign ($+/-/=$) of the first and second order derivatives of HIV prevalence and incidence, assessed visually from plots. Finally, we noted whether any key populations were simulated, in addition to the so-called general population.

2.2.2 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 variation 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 following *key populations* was included in the model: female sex workers (FSW); male clients of FSW (Cli); adolescent girls and young women (AGYW); men who have sex with men (MSM); and people who inject drugs (PWID). 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 which of the following characteristics were used to define different sexual *partnership types*: the risk groups involved; different volumes of sex (total number of coital acts per partnership, subsuming frequency and partnership duration); and different levels of condom use. We noted whether simulated partnerships represented any of the following identifiable types: main/spousal; casual/extramarital; commercial/sex work; and transactional (exchange of gifts/favours for sex, outside formal sex work). 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.

2.2.3 ART Prevention Impact

For our third research question, we examined the subset of studies reporting incidence reduction or infections averted due to ART scale-up alone (see 2.1). We then extracted

the following data for each ART scale-up scenario within each study. We noted: the years that ART scale-up started and stopped, corresponding to the time each scenario diverged from the base-case scenario; the time ART coverage or initiation rates stabilized following scale-up; the final overall ART coverage achieved and/or the final ART initiation rate (per person-year among PLHIV); the criteria for ART initiation (e.g. CD4 count); and the assumed relative reduction in transmission probability on ART . Then, we extracted two population-level ART prevention outcomes from in-text, tabular, and figure data: relative reduction in incidence (%) or proportion of infections averted (%) reported for different time horizons relative to the start of ART scale-up. 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, to quantify the potential influence of different factors of heterogeneity on projected incidence reduction and infections averted (outcomes), we fit a multivariate regression model for each outcome, and computed the partial correlation coefficients associated with each factor.

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

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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 2: 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 3: 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 4: 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 5: 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 6: Criteria for inclusion and exclusion

Include	Exclude
Publication information	
• English language • published before 2020 • peer-reviewed journal article	• non-English language • published in or after 2020 • non-peer-reviewed article • review article only [1] • textbook, grey literature • opinions, comments, correspondence • conference abstracts and proceedings
Mathematical Modelling of HIV Transmission	
• sexual HIV transmission (at least) • dynamical HIV transmission model [2] • population-level dynamics • compartmental model [3] *	• no heterosexual HIV transmission modelled • HIV transmission model is not dynamical • only within-host/cellular/protein modelling • individual-based model *
Context	
• any region in Sub-Saharan Africa (SSA)	• only regions outside SSA modelled • only theoretical context modelled
Research Question	
• assesses prevention benefits of ART scale-up [4] *	• only individual-level benefits of ART modelled • only prevention benefits of other interventions

[1] Review articles were included if they also presented new HIV transmission modelling results fitting our criteria, and all review article references were screened. [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] Studies whose stated objective was to assess reductions in HIV incidence / cumulative infections attributable to scale-up of ART intervention (under any initiation criteria). * Applied after initial identification of all HIV transmission models, including individual-based, applied to any research question in a SSA context.