Scoping Review Protocol:

Heterogeneity and mixing in dynamical models of HIV transmission: a scoping review of parameterizations

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Contents

1 General Information

1.1 Identifying Information

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Heterogeneity and mixing in dynamical models of HIV transmission: a scoping review of parameterizations

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1.2 Background & Rationale

Different Populations need Different HIV Interventions

Advances in HIV antiretroviral treatment (ART) have produced highly effective drug regimens, whereby circulating levels of HIV virus in adherent patients are reduced to undetectable levels [**TBD**]. Viral suppression by ART has clear individual-level benefits for health and quality of life [**TBD**]. Moreover, recent trials have suggested that virally suppressed individuals cannot transmit HIV, a finding described as: "undetectable = untransmittable" (U=U) [1]. Inspired by U=U, researchers and policymakers have called for rapid scale-up of ART coverage as the main intervention by which to reduce HIV incidence ("treatment as prevention") in the widespread epidemics of Sub-Saharan Africa [**TBD**]. Global ambition to scale up ART coverage is further motivated by the UNAIDS 90-90-90 targets, defined as: 90% of people living with HIV are diagnosed; 90% of those diagnosed are on ART; and 90% of those on ART are virally suppressed.

Unfortunately, several large-scale trials aiming to demonstrate population-level impact of treatment as prevention in Sub-Saharan Africa have failed to show a significant reduction in new infections [2, 3, 4]. As suggested by Baral et al. [5] and others, these unexpected results might be attributable to implementation challenges at scale. Such challenges can emerge at several steps along the treatment cascade, including: testing for HIV, linkage to care after a positive test, starting ART after linkage to care, achieving viral suppression after starting ART [**TBD**]. Moreover, individuals who are most likely to experience challenges in HIV care are often at the highest risk of HIV acquisition and onward transmission [**TBD**]. Groups of vulnerable individuals in the epidemic are sometimes described as "key populations".

Several key populations have been identified, including: adolescent girls and young women; sex workers; men who have sex with men; transgender people; prisoners; and people who inject drugs [6]. Key populations often experience several risk factors for HIV transmission and barriers to care, such as: violence and coercion into unsafe sex; criminalization of lifestyle; stigma related to lifestyle or HIV status; housing and financial instability; and substance abuse [7, 6]. To meet the unique HIV prevention and treatment needs of key populations, specific interventions are needed which address known vulnerabilities [6]. For example, risk of HIV transmission can be reduced through needle exchange programs [8], increased access to condoms [**TBD**], and financial support to reduce transactional sex [9]. Similarly, outreach and support by community peers can increase engagement of key populations in HIV care [6].

Despite considerable evidence supporting the need for diversified HIV interventions, recent large-scale studies of treatment as prevention have not considered the unique needs of key populations [2, 3, 4]. Failure to deliver appropriate interventions to key populations has left these groups far behind global progress toward the 90-90-90 targets [10], threatening to undermine the expected benefits of treatment as prevention.

Mathematical Modelling of HIV Transmission

Population-level models of HIV transmission have long been used to project HIV epidemic trajectories (e.g. incidence over time) and predict intervention impacts (e.g. reduction in incidence after X years) [11]. In popular compartmental models, overall populations are stratified by disease state and risk group, while differential equations are used to govern movement of individuals between compartments. Many different compartmental model structures have been used, from a 3-compartment model, representing 3 disease states in a homogeneous population [12], to a 294-compartment model, representing 21 disease states and 14 risk groups [13].

Unfortunately, differences in model structure and assumptions have been shown to substantially influence projections of epidemic trajectory and intervention impact [11, 14]. Most importantly, failure to model heterogeneity in risk results in lower basic reproduction number R_0 [15], which could lead to overestimated ease of epidemic control through universal treatment as prevention [14]. And yet, several mathematical models that were used to support treatment as prevention did not consider heterogeneity in risk of HIV acquisition or transmission [**TBD**, 16, 11]. Even models that did consider risk heterogeneity rarely acknowledged known differences in the treatment cascade across risk groups [**TBD**, 11], such as among key populations [10]. Knight et al. [17] showed that the modelled impact of achieving 90-90-90 in a population overall was highly dependent on which risk groups were left behind in the remaining "10-10-10", emphasizing that differences in treatment cascade cannot be ignored. Finally, simulated sexual mixing between risk groups has generally been simpler than observed in reality [**TBD**], with potential implications for validity of modelling results. For example, Wang et al. [18] have shown that failure to model assortative mixing by HIV status among men who have sex with men may result in underestimated impact of pre-exposure prophylaxis.

One major reason why risk groups and mixing may be missing from HIV transmission models is lack of data. Despite best efforts, key populations are often not captured by large-scale demographic and health surveys, such as those by USAID [19], due to several barriers: household-based sampling methodologies, criminalization of lifestyle, social desirability bias, and stigma [20]. For example, in the 2006-07 Eswatini demographic and health survey [21] just 0.2% male respondents reported paying for sex, while estimates of commercial sex client populations in similar regions were as high as 8% [22]. In many cases, parallel surveys with specific sampling methodologies and community involvement can overcome these barriers, facilitating data collection on key populations [23]. Moreover, collection of key populations data can and should be integrated with modelling work and evaluation of tailored interventions.

Future Work

This review aims to identify parameterizations of risk heterogeneity and mixing used in previous transmission models of HIV in Sub-Saharan Africa. Identified parameterizations will then be considered in a systematic model comparison study, similar to that by Hontelez et al. [14]. For example, the projected impact of universal treatment as prevention will be compared in models with versus without female sex workers, or in models with versus without mixing by risk group. In comparing parameterizations, potential biases and uncertainties associated with simpler models can be estimated. Furthermore, considering the importance of data to inform complex models, the model comparison study will identify key pieces of information which are necessary to construct accurate models, so that these data may be prioritized for collection going forward.

1.3 Review Questions

1. In which contexts (geographies, populations, time periods) within SSA, and for what applications (research questions) have HIV transmission models been used?
2. What parameterizations have been used to represent risk heterogeneity and mixing in *deterministic compartmental* HIV transmission models applied to SSA?
3. How and why are particular parameterizations of risk heterogeneity and mixing in *deterministic compartmental* HIV transmission models associated with specific contexts and applications within SSA?

2 Methods

2.1 Eligibility Criteria

Note that for Question 1, our analysis is not limited to *deterministic compartmental* transmission models. So, let ^{c} denote criteria for *deterministic compartmental* transmission models applied only to Questions 2 and 3. Our criteria are:

Publication Details:

Include

- English language
- published before 2020
- peer-reviewed journal article (not review)

Exclude

- non-English language
- published in 2020 or later
- non-peer reviewed journal article
- review article (references will be screened)
- textbook, grey literature, opinions, comments, conference abstracts

Mathematical Model of Transmission:

Include

- dynamical transmission model[1]
- between-host dynamics
- deterministic model^c
- compartmental model^c

Exclude

- no transmission modelling
- transmission model is not dynamical
- within-host/cellular/protein modelling
- stochastic (random) model^c
- individual-based model^c

Epidemic Context:

Include

- HIV modelled (at least)
- any region in Sub-Saharan Africa (SSA)

Exclude

- only other infections modelled
- theoretical context or only region(s) outside of SSA modelled

[1]We define a *dynamical model* as one where the rates of change of system variables are a function of the current system state (e.g. a first-order ODE system), with fixed functional form.

2.2 Information Sources

We search the following databases: MEDLINE, EMBASE via Ovid.

2.3 Search Strategy

Our search strategy aims to identify any type of HIV transmission model applied in any context. We will later manually identify which models were deterministic and compartmental, and which works applied the model to SSA context.

Validation References:

Before performing the search, we identified 9 publications of HIV modelling applied to SSA. We ensure that these 9 validation references (VR) are contained in our search results, as an indicator that the search is performing well.

1. [16] (2009) Granich et al.
2. [24] (2013) Cremin et al.
3. [25] (2014) Eaton and Hallett
4. [26] (2014) Mishra et al.
5. [27] (2014) Anderson et al.
6. [13] (2015) Kerr et al.
7. [28] (2015) Boily et al.
8. [29] (2017) Maheu-Giroux et al.
9. [30] (2018) Mukandavire et al.

Search Terms:

We operationalize our inclusion & exclusion criteria using the search terms shown in Appendix A. We implement publication year and language criteria via Ovid "limits", but did not filter publication types (review, etc.), as we found such classifications to be unreliable.

Results:

The results from MEDLINE & EMBASE on 2020 March 20 were:

	Hits	Term
1	1,369,153	`[model]`
2	954,470	`[hiv]`
3	982,505	`[ssa]`
4	2190	`1 AND 2 AND 3`
5	1384	`4 NOT [exclude]`

These results (5) then form our initial database for screening.

2.4 Data Management

Based on the initial search, the bibliographic information (including abstract) of non-duplicate matching items will be exported from the search result in XML format, and uploaded to Covidence for abstract screening. Covidence provides tools for including and excluding items based on a set of user-defined criteria, tracking the results of review.

The full texts of included items will then be sought using institutional access and support.

2.5 Selection Process

Following upload of the initial search results to Covidence, one reviewer (JK) will screen the abstracts for inclusion using the Eligibility Criteria. Unclear edge cases will be resolved by discussion with SM.

2.6 Data Extraction

Data extraction and subsequent analysis will be completed by one reviewer (JK).

2.7 Quality Assessment

N/A

2.8 Data Synthesis

2.8.1 Question 1: Context

Geography: We will summarize the proportion of models representing each of the following scales of geography: *city, multiple cities, province, multiple provinces, country, multiple countries, regional*. Additionally, we will summarize the number of times each country has been modelled at the national level.

Epidemic Phase: Since the efficacy of various interventions may depend on the epidemic phase, we will approximate epidemic phase using (a) the trend of overall HIV incidence and prevalence at time of intervention roll-out (where applicable), using one of: *increasing, decreasing, flat (±5% relative per year), varies*; or (b) whether the time of intervention roll-out (where applicable) is: *before, after, or within 5 years of peak overall HIV prevalence*.

Key Populations: For each of the following key populations:

- adolescent girls and young women (AGYW)
- female sex workers (FSW)
- FSW clients
- men who have sex with men (MSM)
- people who inject drugs (PWID)

we will summarize the proportion of models that:

- specifically model the population
- use at least one population-specific behavioural data source for that country
- calibrate the model to reflect at least one population-specific HIV prevalence and/or incidence estimate

Interventions: For each of the following interventions:

- ART
- PrEP
- VMMC
- HIV vaccine
- TB treatment
- STI coinfection treatment

- condom use
- other behavioural interventions

we will summarize the proportion of models that:

- model the intervention to reflect historical events
- model future intervention as part of a research question
- model the intervention as applied to all model populations equally vs focused on specific populations

For those papers examining focused interventions, we will report the distribution of interventions and target populations.

Research Questions: We aim to categorize all research questions according to the following idea: *the impact of (X) on (Y)*, where X can be:

- epidemic context
- intervention type
- intervention targeting or scale
- model assumptions

and Y can be:

- projected epidemic
- projection accuracy
- intervention impact
- intervention cost effectiveness

Papers may have multiple X or Y.

2.8.2 Question 2: Parameterizations

Risk: First, we will summarize the *number* of risk groups employed by each model. Next, noting the proportionality between the basic reproduction number R_o and heterogeneity in partner change rates H_c:

$$R_o \geq \beta D \underbrace{\left(\mu_c + \frac{\sigma_c^2}{\mu_c}\right)}_{H_c} \tag{1}$$

we will estimate H_c using: (a) the relative sizes of each risk group (as a proportion of total population), and (b) the average contact rates of each risk group; We will also note: (c) the relative incidence rates experienced by each risk group (relative to the lowest risk group). We will also consider alternative measures of risk dispersion based on the same data, such as the *Gini coefficient*, and the *index of dispersion*. Where risk group sizes and/or contact rates and/or relative incidence rates vary across time and/or model fits, we will attempt to use any reported posterior means where available, else any reported prior means, else we will exclude that paper from this part of the analysis.

Transmission Modifiers: We will summarize the proportion of models which consider modification of the probability of transmission by each of the following factors:

- male circumcision
- condom use
- STI coinfection

Specifically, we will report proportions of models that consider:

- differences in the modifier by risk group

- changes to the modifier over time

We will also note the proportion of models which simulated transmission at the sex-act vs partnership level.

Age:

Health: The major health dimensions of interest are as follows:

- HIV viral load
- CD4 count
- STI coinfection

For each dimension, we will report:

- the proportion of papers which stratified by the dimension
- the distribution of how many strata were defined along the dimension across papers
- the proportion of papers that calibrated to country-specific data for this dimension

2.8.3 Question 3: Trends

In this research question, we are interested to know whether systemic biases have emerged in terms of which parameterizations

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A Full Search Terms & Results

Our search strategy and component 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.

Combined:

	Hits	Term
1	1,369,153	[model]
2	954,470	[hiv]
3	982,505	[ssa]
4	2190	1 AND 2 AND 3
5	1384	4 NOT [exclude]

Model:

	Hits	Term
1	238,076	model, theoretical/
2	334,921	model, biological/
3	302,802	computer simulation/
4	196,814	patient-specific modeling/
5	67,459	monte carlo method/
6	32,801	exp stochastic processes/
7	455,312	(model* ADJ3 (math* OR transmission OR dynamic* OR epidemi* OR compartmental OR deterministic OR individual OR agent OR network OR infectious disease* OR markov OR dynamic* OR simulat*)).mp.
8	1,369,153	OR/ 1-7

HIV:

	Hits	Term
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

Exclude:

	Hits	Term
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

SSA:

	Hits	Term
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