SCOPING REVIEW PROTOCOL:

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

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# 1 General Information

## 1.1 Identifying Information

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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 *Sub-Saharan Africa*, 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?
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 *Sub-Saharan Africa*?

## 2 Methods

### 2.1 Eligibility Criteria

We have different scopes for each of our research questions as follows:

1. any type of transmission model, in SSA context
2. deterministic compartmental transmission models, in any context
3. deterministic compartmental transmission models, in SSA context

Most of our eligibility criteria apply for all 3 questions, but regarding these three scopes, let: [c] = criteria for deterministic compartmental transmission models, and [s] = criteria for SSA context. 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 model
- between-host dynamics
- deterministic model[c]
- compartmental model[c]

*Exclude*

- no mathematical modelling
- non-dynamical model
- within-host/cellular/protein modelling
- mouse models
- stochastic (random) model[c]
- individual-based model[c]

**Epidemic Context:**

*Include*

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

*Exclude*

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

## 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, and 9 publications of HIV modelling applied elsewhere. We ensure that these 9+9 validation references (VR) are contained in our search results, as an indicator that the search is performing well.

SSA

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.

*other contexts*

1. [31] (1994) Garnett and Anderson
2. [12] (2003) Moghadas et al.
3. [32] (2007) Goodreau and Golden
4. [33] (2008) Deering et al.
5. [34] (2010) Vickerman et al.
6. [35] (2012) Goodreau et al.
7. [36] (2013) Alam et al.
8. [37] (2015) Henry and Koopman
9. [38] (2016) Punyacharoensin et al.

**Search Terms:**

We operationalize our inclusion & exclusion criteria using the following search terms, where `term/` denotes a MeSH term, `tw` searches all text fields, and `kf` searches all heading fields. 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. Additionally, we exclude the MeSH term `animal/`.

| Criteria | Search Terms |
|---|---|
| HIV | `exp HIV/ OR (HIV* OR "human immunodeficiency virus").tw,kf` |
| model | `model, theoretical/ OR model, biological/ OR computer simulation/ OR patient-specific modeling/ OR monte carlo method/ OR exp stochastic processes/ OR (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*)).tw,kf` |
| exclude | `animal/` |
| limits | `(year = 1860-2019) AND (english language)` |

**Results:**

The results from MEDLINE & EMBASE on 2020 March 15 were:

| | Total Hits | VR | Terms |
|---|---|---|---|
| 1 | 773,236 | 9+9 | `exp HIV/ OR (HIV* OR "human immunodeficiency virus").tw,kf` |
| 2 | 1,294,099 | 9+9 | `model, theoretical/ OR model, biological/ OR computer simulation/ OR patient-specific modeling/ OR monte carlo method/ OR exp stochastic processes/ OR (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*)).tw,kf` |
| 3 | 8,519,337 | 0+0 | `animal/` |
| 4 | 15,133 | 9+9 | `1 AND 2` |
| 5 | 13,948 | 9+9 | `1 AND 2 NOT 3` |
| 6 | 13,553 | 9+9 | `1 AND 2 NOT 3 (limits)` |

where VR = validation references hit. These results (6) 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. For each item, the data extraction form given in Appendix **??** (Google Forms) will be completed. Upon submission of the form, a row in the linked tabular database (Google Sheets) will be automatically populated with the results. Analysis of the tabular data will then be performed in Python, with the aim of generating statistics and figures to answer the Review Questions.

## 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

Appendix **??** gives the data extraction form to be used for each included reference. The form includes a combination of short text inputs and pre-defined categorical variables in the following sections:

- Article meta-data: authors, journal, title, etc.
- Model context: geography, time, research questions
- Model approach: model type, code
- Modelled populations: sex, age, risk, turnover, interventions
- Modelled biology: $CD4$, viral load, treatment
- Modelled transmission: modes, types of acts, partnership types, modifiers
- Data: calibration targets

Some short text inputs will capture semi-structured data, such as the relative sizes of population strata, like:

`HSF-low: 0.35, HSF-medium: 0.125, HSF-high: 0.025, ...`

corresponding to: heterosexual females in the low risk group representing 0.35 proportion of the total population, etc. Provided the input are structured in the suggested way, the text can later be parsed in Python, even though the population strata definitions may change from model to model.

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

## 2.7 Quality Assessment

N/A

## 2.8 Data Synthesis [TBD]

### 2.8.1 Question 1: Context

### 2.8.2 Question 2: Parameterizations

### 2.8.3 Question 3: Trends

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