SCOPING REVIEW PROTOCOL:

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

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Contents

1 General Information

1.1 Identifying Information

Date: 2020 February

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Review Title:

Heterogeneity and mixing in deterministic compartmental 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 Sub-Saharan Africa, and for what purposes (research questions) have HIV transmission models been used?
2. What parameterizations have been used to represent risk heterogeneity and mixing in compartmental HIV transmission models?
3. How are parameterizations of risk heterogeneity and mixing (2) in HIV transmission models associated with specific contexts and applications (1)?

2 Methods

2.1 Eligibility Criteria

Publication Details:

Include

- English language
- published before 2020
- non-review peer-reviewed journal article

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

- deterministic model
- compartmental model
- dynamical model
- between-host dynamics

Exclude

- stochastic (random) model
- individual-based model
- non-dynamical model
- within-host / sub-cellular dynamics only
- no mathematical modelling

HIV Infection:

Include

- HIV infection modelled

Exclude

- other infections modelled

2.2 Information Sources

Databases:

- MEDLINE
- EMBASE

2.3 Search Strategy

Search Terms:

Publication Details

TBD

Mathematical Model of Transmission

```
("Computer Simulation/" OR "Models, Biological/" OR "Mathematical Computing/") AND
("Disease Transmission, Infectious/")
```

HIV

```
("HIV Infections/" OR "HIV/")
```

Validation References:

- [24] (1994) Garnett and Anderson *"Balancing sexual partnership in an age and activity stratified model of HIV transmission in heterosexual populations"*
- [16] (2009) Granich et al. *"Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model"*
- [25] (2014) Eaton and Hallett *"Why the proportion of transmission during early-stage HIV infection does not predict the long-term impact of treatment on HIV incidence"*
- [26] (2015) Henry and Koopman *"Strong influence of behavioral dynamics on the ability of testing and treating HIV to stop transmission"*
- [27] (2017) Maheu-Giroux et al. *"Population-level impact of an accelerated HIV response plan to reach the UNAIDS 90-90-90 target in Côte d'Ivoire: Insights from mathematical modeling"*
- [28] (2018) Mukandavire et al. *"Estimating the contribution of key populations towards the spread of HIV in Dakar, Senegal"*

Results: February 20, 2020

MEDLINE: total (validation)

- 47 (0): `("Computer Simulation/" OR "Models, Biological/" OR "Mathematical Computing/") AND ("Disease Transmission, Infectious/") AND ("HIV Infections/" OR "HIV/")`
- 2523 (2): `("Computer Simulation/" OR "Models, Biological/" OR "Mathematical Computing/") AND ("HIV Infections/" OR "HIV/")`

2.4 Data Management

After performing an initial search in the named databases, 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 by multiple reviewers based on a set of user-defined criteria, tracking the results of review and highlighting conflicts.

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 A (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, two reviewers (JK, TBD) will screen the abstracts for inclusion using the Eligibility Criteria. Decision conflicts will be resolved by discussion, mediated by a third reviewer (SM) where necessary.

2.6 Data Extraction

Appendix A 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 .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 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

References

[1] Robert W. Eisinger, Carl W. Dieffenbach, and Anthony S. Fauci. *HIV viral load and transmissibility of HIV infection undetectable equals untransmittable*. 2019.

[2] Collins C. Iwuji et al. "Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial". In: *The Lancet HIV* 5.3 (2018), e116–e125. URL: http://www.ncbi.nlm.nih.gov/pubmed/29199100.

[3] D Havlir et al. "SEARCH community cluster randomized study of HIV "test and treat" using multi- disease approach and streamlined care in rural Uganda and Kenya". In: *International AIDS Conference 2018*. Amsterdam, Netherlands, 2018. URL: https://programme.aids2018.org/Abstract/Abstract/13469.

[4] Richard J. Hayes et al. "Effect of universal testing and treatment on HIV incidence - HPTN 071 (popart)". In: *New England Journal of Medicine* 381.3 (2019), pp. 207–218.

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[7] Elisa Mountain et al. "Antiretroviral therapy uptake, attrition, adherence and outcomes among hiv-infected female sex workers: A systematic review and meta-analysis". In: *PLoS ONE* 9.9 (2014), e105645. URL: https://dx.plos.org/10.1371/journal.pone.0105645.

[8] Ann E. Kurth et al. *Combination HIV prevention: Significance, challenges, and opportunities*. 2011.

[9] Audrey Pettifor et al. *Can money prevent the spread of HIV? A review of cash payments for HIV prevention*. 2012.

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[12] Seyed M. Moghadas et al. "Could condoms stop the AIDS epidemic?" In: *Journal of Theoretical Medicine* 5.3-4 (2003), pp. 171–181.

[13] Cliff C. Kerr et al. "Optima: A Model for HIV Epidemic Analysis, Program Prioritization, and Resource Optimization". In: *Journal of Acquired Immune Deficiency Syndromes* 69.3 (2015), pp. 365–376. URL: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{\&}an=00126334-201507010-00017.

[14] Jan A.C. C. Hontelez et al. "Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study". In: *PLoS Medicine* 10.10 (2013), e1001534. URL: http://dx.plos.org/10.1371/journal.pmed.1001534.

[15] R. M. Anderson et al. "A preliminary study of the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of AIDS". In: *Mathematical Medicine and Biology* 3.4 (1986), pp. 229–263. URL: https://academic.oup.com/imammb/article-lookup/doi/10.1093/imammb/3.4.229.

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A Data Extraction Form

Data Extraction Form

Heterogeneity in compartmental models of HIV transmission: a systematic review of parameterizations

Article Meta-Data

1. Year

   Year of publication

   _____

2. Authors

   e.g. First Last, First Last, ...

   _____

3. Journal

   _____

4. URL

   _____

5. Bib ID

   For cross-linking with reference management software

   _____

Context

6. Geography Scale

What geography is modelled?

Tick all that apply.

- [ ] Illustrative
- [ ] Regional
- [ ] National
- [ ] Province
- [ ] City

7. Geography Name

Name of the modelled geography

_____

8. t0

What year was the simulation started? For illustrative models, use "0"

_____

9. t1

What year was the simulation stopped? For illustrative models, use the duration of the simulation

_____

10. Key Populations

KP included in the model

Tick all that apply.

- [ ] FSW
- [ ] Clients
- [ ] AGYW
- [ ] GBMSM
- [ ] Trans
- [ ] PWID
- [ ] Infants

11. Research Questions

Tick all that apply.

- [ ] Project HIV Prevalence / Incidence
- [ ] Intervention Impact
- [ ] tPAF of Risk Groups
- [ ] Cohort / Trial Simulation
- [ ] Other: _____

Model: Approach

12. Model Type

Mark only one oval.

- ◯ Compartmental
- ◯ Individual

13. Model Stochasticity

Mark only one oval.

- ◯ Deterministic
- ◯ Stochastic

14. Language

Tick all that apply.

- [ ] R
- [ ] Python
- [ ] C
- [ ] Excel
- [ ] Java
- [ ] Matlab

15. Code

Open source URL, if available

_____

Model: Populations

16. Sex & Orientation

e.g. HSM, HSF, MSM, ... or NA if sex / orientation was not modelled

17. Age Groups

e.g. 15-20, 21-35, 35-55 or NA if age was not modelled

18. Risk Strata by

Tick all that apply.

- [ ] Number of Partners

Other: [ ]

19. Risk Strata Defined

e.g. female-low: 1 partner, female-medium: 5 partners, female-high: 25 partners, ...

20. Risk Strata Sizes

e.g. female-low: 0.35, female-medium: 0.125, female-high: 0.025, ...

21. Turnover

Individuals move between which strata

Tick all that apply.

- [ ] Age
- [ ] Risk

22. Interventions & Strata

Tick all that apply.

	Universal	by year	by CD4	FSW	Clients	AGYW	GBMSM	Trans	PWID	Infants
ART	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
PrEP	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
PEP	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
HIV Vaccine	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
PMTCT	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
STI Treatment	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
TB Treatment	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
VMMC	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Condoms	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Behaviour Change	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Needle Exchange	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Model: Biology

23. CD4 Strata

e.g. <100, 100-200, 200-350, >350 or NA if CD4 was not modelled

24. VL Strata

e.g. <10^6, <10^5, <10^4, <10^3, <10^2, <10^1 or NA if VL was not modelled

25. Treatment Strata

e.g. PrEP, PEP, uDx, Dx, ART, ART-fail or NA if Treatment was not stratified

_____

Model: Transmission

26. Transmission Resolution

Mark only one oval.

- ◯ Act
- ◯ Partnership

27. Transmission Modes

Tick all that apply.

- ☐ Heterosexual Sex
- ☐ Anal Sex
- ☐ Needle Sharing
- ☐ Mother to Child

28. Types of Partnerships

Tick all that apply.

- ☐ Generic
- ☐ Main
- ☐ Casual
- ☐ Commercial
- ☐ Transactional
- ☐ Needle Sharing

29. Associative Mixing by

Tick all that apply.

- ☐ Age
- ☐ Risk
- ☐ Serostatus

30. Transmission Modifiers

Tick all that apply.

- [ ] Condoms
- [ ] Male Circumcision
- [ ] STI Coinfection
- [ ] PrEP
- [ ] PEP
- [ ] Positioning

Data

31. Prevalence Targets

Tick all that apply.

- [ ] Overall
- [ ] by Sex
- [ ] by Age
- [ ] by Risk
- [ ] KP specific

32. Incidence Targets

Tick all that apply.

- [ ] Overall
- [ ] Sex
- [ ] Age
- [ ] Risk
- [ ] Key Populations