**Improving the validity of mathematical policy models for HIV elimination by incorporating empirical estimates of progression through the HIV treatment cascade**

**Supplementary Appendix**

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Table of Contents

[S1. Definition of each health state and its associated activities 3](#_Toc523222564)

[S2. Model parameters related to the natural progression of and recovery from the disease 4](#_Toc523222565)

[S3. Cumulative number of secondary HIV infections and HIV infectiousness for each health stage 6](#_Toc523222566)

[S4. Methods for deriving transition probabilities for between cascade stages 8](#_Toc523222568)

[S5. Sensitivity analyses 10](#_Toc523222569)

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# S1. Definition of each health state and its associated activities

The following definitions of health states and the activities associated with each state are defined by the Africa Centre (18):

Diagnosed with HIV: We define individuals in this state as those who knows his/her positive HIV status after their first positive test.

Pre-ART care linkage and retention: Individuals are considered linked to pre-ART care if they have a recorded HIV clinic visit, registration at a clinic, CD4 test, viral load count, or initiated ART. At the initial HIV diagnosis, providers are expected to check their CD4 count on the same day, although in reality this is rarely done. They are then expected to return for a repeat CD4 count and WHO clinical staging every six months to see if they have become eligible for ART. We define individuals who are retained in pre-ART care as those who have an assessment every six months and were not ART eligible at the last assessment. They are considered lost to follow up if they do not return to receive pre-ART services within six months since their last visit.

ART initiation and adherence: Individuals are recorded as having initiated ART based on the records of the date of the first ART prescription. During the study period, South Africa’s ART eligibility criterion shifted from the initial CD4 count of 200 to 350 cells/mm3 in July 2011.

# S2. Model parameters related to the natural progression of and recovery from the disease

##### Table S1. Model parameters related to the natural progression of and recovery from the disease

|  |  |  |
| --- | --- | --- |
| Model parameter | Value | Data source |
| Monthly probability of progression to the next disease stage, without ART (month-1) | CD4 > 500: starting at 0.0114, increase to 0.0139 after ten years, then increase to 0.0159 after another ten yearsCD4 350-500: starting at 0.0176, increase to 0.0246 after ten years, then increase to 0.0339 after another ten yearsCD4 200-350: starting at 0.0419, increase to 0.0469 after ten years, then decrease to 0.0572 after another ten yearsCD4≤200: starting at 0.0502, increase to 0.0510 after ten years, then decrease to 0.0598 after another ten years | (31) |
| Monthly probability of CD4 recovery when under treatment (month-1) | CD4 350-500: 0.1823CD4 200-350: 0.1823CD4≤200: 0.1122 | (32)  |
| Monthly probability of mortality, without ART (month-1) | CD4 > 500: starting at 0.0003, increase to 0.0004 after ten yearsCD4 350-500: starting at 0.0008, increase to 0.0011 after ten yearsCD4 200-350: starting at 0.0040, increase to 0.0057 after ten years, then decrease to 0.0048 after another ten yearsCD4≤200: starting at 0.0649, increase to 0.1135 after ten years, then decrease to 0.0650 after another ten years | (31) |
| Monthly probability of mortality, with ART (month-1) | 0-6 months on treatment CD4 > 500: starting at 0.0003, increase to 0.0004 after ten yearsCD4 350-500: starting at 0.0008, increase to 0.0011 after ten yearsCD4 200-350: starting at 0.0040, increase to 0.0057 after ten years, then decrease to 0.0048 after another ten yearsCD4≤200: starting at 0.0649, increase to 0.1135 after ten years, then decrease to 0.0650 after another ten years7-12 months on treatment CD4 > 500: starting at 0.0003, increase to 0.0004 after ten yearsCD4 350-500: starting at 0.0008, increase to 0.0011 after ten yearsCD4 200-350: starting at 0.0029, increase to 0.0030 after ten years, then increase to 0.0034 after another ten yearsCD4≤200 : starting at 0.0061, decrease to 0.0056 after ten years, then increase to 0.0070 after another ten yearsGreater than 12 months on treatment CD4 > 500: starting at 0.0003, increase to 0.0004 after ten yearsCD4 350-500: starting at 0.0008, increase to 0.0011 after ten yearsCD4 200-350: starting at 0.0016, decrease to 0.0014 after ten years, then increase to 0.0017 after another ten yearsCD4≤200: starting at 0.0030, decrease to 0.0027 after ten years, then increase to 0.0033 after another ten years | (31) |
| Baseline mortality rate (month-1) | Varies by year | (33) |

# S3. Cumulative number of secondary HIV infections and HIV infectiousness for each health stage

*Cumulative number of secondary HIV infections*

In a serial monogamous population, the expected number of infections was computed based on an approximation formula developed by Hollingsworth et al. (21):

$R\_{0}=\sum\_{ij}^{} \frac{β\_{ij}cd\_{ij}}{β\_{ij}+c+\frac{1}{d\_{ij}}} $ (1)

where $β\_{ij}$ is the transmission hazard for health stages (i: cascade health states, j: CD4 levels), $c$ is partner change rate (set at 1.25 per year), and $d\_{ij}$ is the duration of the health stage. Hollingsworth et al. provide the hazard rates of HIV transmission by each infection stage (21). The contribution to the number of new infections in a fully susceptible population caused by this cohort, also known as the basic reproduction number $R\_{0}$, is therefore the probability of transmission $\frac{β\_{ij}cd\_{ij}}{β\_{ij}+c+\frac{1}{d\_{ij}}}$ , multiplied by the rate of partner change $c$, and the duration of the health state $d\_{ij}$.

Three possible outcomes may occur once a discordant partnership is formed: the partnership may discontinue with hazard c; the infected partner may progress to the next stage of disease with hazard 1/dij, where dij is the duration of the stage of infection; or transmission may occur with hazard βij. Thus, the probability of transmission to a partner in this stage of the infection may therefore be approximated by $\frac{β\_{ij}cd\_{ij}}{β\_{ij}+c+\frac{1}{d\_{ij}}}$.

In a random mixing population, the expected number of infections was computed as:

$R\_{0}=\sum\_{ij}^{} β\_{ij}d\_{ij}$ (2)

which is the transmission rate multiplied by the duration of each health stage.

*HIV infectiousness for each health stage*

Hollingsworth et al. provide the hazard rates of HIV transmission by each infection stage (Table S2) (21). We set the transmission hazard for patients with CD4 count greater than 200 cells/mm3 equal to the rate for the asymptomatic infection stage, and the rate for patients with CD4 count less than 200 cells/mm3 equal to the rate for the patients 10-19 months before death. Transmission hazard for those on ART are reduced by 96% (5).

##### Table S2. HIV infectiousness for each health stage

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment status | Health stage | Monthly HIV transmission hazard | Reference |
| Not on ART | CD4 500+ | 0.0088 | (21) |
| CD4 350-500 | 0.0088 |
| CD4 200-350 | 0.0088 |
| CD4 <200 | 0.0633 |
| On ART | CD4 350+ | 0.00035 | (5, 21)  |
| CD4 200-350 | 0.00035 |
| CD4 <200 | 0.00253 |

# S4. Methods for deriving transition probabilities for between cascade stages

Table S3. Methods for deriving transition probabilities for between cascade stages

|  |  |  |
| --- | --- | --- |
|  | Transition | Method |
| (1) | Undiagnosed to diagnosed | * Estimated the proportion of the full sample who were diagnosed within four years after their first positive HIV test
* Calculated the monthly transition probability required to achieve that proportion by first setting 86% of individuals with CD4 count less than 200 cells/μL to be diagnosed within four years and derived the monthly probability needed to meet this requirement. Conditioning on this probability, we then fixed 86% of individuals with CD4 count below 350 cells/μL to be diagnosed within four years, and continued the same approach for individuals with CD4 count 500 and above 500 cells/μL
 |
| (2) | Diagnosed to linked to pre-ART care | * Estimated monthly transition probability by applying Kaplan-Meier non-parametric survival analysis on the full dataset, pooled across CD4 levels
 |
| (3) | Retained in pre-ART care to LFU |
| (4) | LFU from pre-ART to returning |
| (5) | Pre-ART care to receiving ART | * Estimated monthly transition probability by applying Kaplan-Meier non-parametric survival analysis on the full dataset, stratified by CD4 cell count at time of linkage to pre-ART care
* Under the eligibility criterion of CD4 count below 200 cells/μL, we estimated the transition probability among people who were linked to pre-ART care before July 2011 and applied the non-parametric probabilities to each CD4 category
* Under the eligibility criterion of CD4 count below 350 cells/μL, we estimated the probabilities among people who were linked to pre-ART care after July 2011 for each CD4 group
* To approximate the rates of the higher CD4 groups under higher eligibility criteria, we calculated the hazard ratio of the Kaplan-Meier curves between the groups with CD4 count below 200 cells/μL and 200-350 cells/μL, and applied this hazard ratio to the rates of the group with 200-350 cells/μLto derive the rates for the CD4 group 350-500 cells/μL. We applied the same approach to derive the rates for the group with CD4 greater than 500 cells/μL
 |
| (6) | Retained in ART to LFU | * Estimated monthly transition probability by applying Kaplan-Meier non-parametric survival analysis on the full dataset, stratified by CD4 cell count at time of linkage to pre-ART care, under eligibility criteria of CD4 count below 200 and 350 cells/μL, respectively
* For higher eligibility scenarios, we assumed that people experienced the same rates under the CD4 count below 350 cells/μL eligibility criterion
 |
| (7) | LFU from ART to resuming ART |

# S5. Sensitivity analyses

*Transition probabilities*

We conducted one-way sensitivity analyses on all constant transition probabilities to examine the robustness of our results. The baseline values for each parameter were increased or decreased by 50 percent, and we noted variables for which the change in the parameter led to a change in the ratio of incremental benefits of greater than 20 percent. None of the parameter changes resulted in changes greater than our cutoff under the threshold expansion from CD4 200 to 350 and from 350 to 500 cells/mm3. Under the threshold expansion from CD4 500 cells/mm3 to everyone with HIV, the incremental benefits from this policy was sensitive to the probability of getting linked to care for people with CD4 count between 350 and 500 cells/mm3. A 50% increase in the linkage probability among this group led to an incremental benefit estimated in the conventional model to be 2.8 times greater than the empirical cascade model, which is 27% lower than the current estimate (3.8 times). A 50% decrease led to the incremental benefit in the conventional model to be 6.1 times (61% higher) greater than the empirical cascade model.

*Testing rates from published literature*

We applied a set of transition probabilities for the cascade progression from a published paper to test whether our findings are in a reasonable range (22). We created a third model, replacing the cascade progression probabilities with the parameters listed in Table S4. All other transition probabilities, including parameters related to the natural progression of and recovery from the disease, were kept the same as the empirical model to ensure comparability.

Table S4. Transition probabilities for the sensitivity analysis

|  |  |
| --- | --- |
| Transition stage | New value (from (22)) |
| Undiagnosed to diagnosed | CD4 > 500: 0.0193 (mean of the rates listed in Smith et al.)CD4 350-500: 0.0193CD4 200-350: 0.0193CD4≤200: 0.0287 (mean of the rates listed in Smith et al.)  |
| Diagnosed to linked to pre-ART care | CD4 > 500: 0.0180CD4 350-500: 0.0350CD4 200-350: 0.0430CD4≤200: 0.0690 |
| Pre-ART care to receiving ART | CD4 > 500: 0.0162CD4 350-500: 0.0325CD4 200-350: 0.0650CD4≤200: 0.0650 |
| Retained in ART to LFU | 0.0083 in first year0.0042 in later years  |

First, comparing to the conventional model, the results for the incremental benefits from eligibility changes from CD4 350 to 500 and from 500 to treatment for everyone from the sensitivity analysis are higher than the conventional model (the ratios are 2.63 and 3.53 for life expectancy and HIV transmission under random mixing, respectively). The ratios for the eligibility change from CD4 200 to 350 between the two models, however, are less 1 for both health outcomes. This means that the model for the sensitivity analysis predicts greater HIV transmission (worse health outcome) than the conventional model.

We present the comparison between the ratios in the main results and sensitivity analysis in Table S6. The main results presented in the manuscript are higher than the sensitivity analysis. The ratios for the eligibility change from CD4 200 to 350 are higher than others primary because, as shown in Table S5, the sensitivity analysis model yields a much lower health benefit, even lower than the conventional model. On the other hand, health benefits gained from reduction in HIV transmission for eligibility change from CD4 500 to treating everyone is much lower in the main result than the sensitivity analysis.

Table S5. Comparing results from the sensitivity analysis to the results from the conventional model

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  Incremental benefit of eligibility change from CD4 200 to 350, months  |  Ratio of incremental benefits, optimistic to cascade  |  Incremental benefit of eligibility change from CD4 350 to 500, months  |  Ratio of incremental benefits, optimistic to cascade  |  Incremental benefit of eligibility change from CD4 500 to treat all, months  |  Ratio of incremental benefits, optimistic to cascade  |
| Life expectancy (months) | Conventional | 49.5 | 0.65 | 138.8 | 2.63 | 32.9 | 3.53 |
| Sensitivity | 75.75 | 52.70 | 9.34 |
| HIV transmission (random mixing) (R0) | Conventional | 0.06 | 0.50 | 0.53 | 1.91 | 0.68 | 5.14 |
| Sensitivity | 0.12 | 0.28 | 0.13 |

Table S6. Comparison between main results and sensitivity analysis

|  |  |  |  |
| --- | --- | --- | --- |
| Comparison between main results and sensitivity analysis  | Ratio between two comparisons for eligibility change from CD4 200 to 350 | Ratio between two comparisons for eligibility change from CD4 350 to 500 | Ratio between two comparisons for eligibility change from CD4 500 to treat all |
| Life expectancy  |  1.65  |  1.37  |  1.07  |
| HIV transmission (random mixing) |  2.76  |  1.09  |  0.24  |