HIV Screening via Fourth-Generation Antigen-Antibody or Nucleic Acid Amplification Test: A Cost-Effectiveness Analysis

Supporting Information

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This dynamic compartmental model captures HIV disease progression and HIV transmission via heterosexual contact, homosexual contact, and needle-sharing, under varying levels of HIV screening and treatment with antiretroviral therapy. The current model is an extension of the author's previously published HIV transmission model.[1, 2]

S.1 HIV Epidemic Model

S.1.1 Risk Groups

The adult population was subdivided into six risk groups (male IDU, male MSM, male IDU/MSM, male other, female IDU, female other). This particular set of risk groups was selected to capture variations in demographics (population sizes, initial HIV prevalence, mortality rate), behavior (number of sexual partners, condom use, injection drug use, needle-sharing), as well as known epidemiological factors (probability of disease transmission, effect of male circumcision).

S.1.2 Transmission Modes

The dynamic model captures HIV transmission via three modes: heterosexual contact, homosexual contact, and needle-sharing. Table S1 shows the possible modes of transmission between any two risk groups. In the model, men who have sex with men were allowed to have heterosexual contact with women.

S.1.3 Disease Transmission

The sufficient contact rate between uninfected and infected individuals is represented as a matrix, $\lambda = [\lambda_{i,j}]$, where $\lambda_{i,j}$ represents the sufficient contact rate between members of (uninfected) compartment i and members of (infected) compartment j. I calculated the total contact rate, $\lambda_{i,j}$, as the sum of the three transmission modes: needle-sharing ($\gamma_{i,j}$), opposite-sex (heterosexual) contact ($\beta^o_{i,j}$), and same-sex (homosexual) contact ($\beta^s_{i,j}$).

The sufficient contact rates due to needle-sharing, opposite-sex, and same-sex contact were modeled as binomial processes, where a "success" is defined as infection transmission. Uninfected individuals randomly select a partner n times; the probability of "success" is the probability of transmission per partnership.

$$\begin{aligned} P\{\mathrm{T}\} &= 1 - P\{\text{no T}\} \\ &= 1 - (P\{\text{no T per trial}\})^{\#\text{ trials}} \\ &= 1 - (1 - P\{\text{T per trial}\})^{\#\text{ trials}} \\ &= 1 - (1 - P\{\text{select person in } j\}\, P\{\text{T per trial} \mid \text{select person in } j\})^{\#\text{ trials}} \end{aligned}$$

where T refers to disease transmission and a trial is either a sexual partnership or shared needle.

Needle-sharing transmission The needle-sharing sufficient contact rate between uninfected individuals in compartment i and infected individuals in compartment j is:

$$\gamma_{i,j}(t) = 1 - \left(1 - \left[\frac{X_j(t) d_j s_j}{\sum_k X_k(t) d_k s_k}\right] \tau_{i,j}\right)^{d_i s_i} \tag{S.1}$$

where i, j, k correspond to compartments of IDUs. The term in brackets, $\left[\frac{X_j(t) d_j s_j}{\sum_k X_k(t) d_k s_k}\right]$, corresponds to the probability of selecting a needle-sharing partner in compartment j, based on a proportional mixing assumption (i.e., individuals with many partners are more likely to select a partner who also has many partners). The probability of needle-sharing transmission, $\tau_{i,j}$, between individuals in compartment i and j depends on the transmission probability per shared needle, π^k, and the reduction in infectivity due to ART, δ_h^d (if individuals in compartment j are receiving ART).

Heterosexual transmission The opposite-sex (heterosexual) sufficient contact rate between uninfected individuals in compartment i and infected individuals in compartment j

is:

$$\beta^o_{i,j}(t) = 1 - \left(1 - \left[\frac{X_j(t)n^o_j(1-u^o_j\kappa)}{\sum_k X_k(t)n^o_k(1-u^o_k\kappa)}\right]\sigma_{i,j}\right)^{n^o_i(1-u^o_i\kappa)} \tag{S.2}$$

where i is male and j, k are female, or i is female and j, k are male. The term in brackets, $\left[\frac{X_j(t)n^o_j(1-u^o_j\kappa)}{\sum_k X_k(t)n^o_k(1-u^o_k\kappa)}\right]$, corresponds to the probability of selecting a sexual partner in compartment j. The probability of heterosexual transmission, $\sigma_{i,j}$, between individuals in compartment i and j depends on the transmission probability per partnership, π^k_{mf} or π^k_{fm} (which reflects each partners' gender), and the reduction in infectivity due to ART, δ^s_h. For men, $\sigma_{i,j}$ was also adjusted by $1-\delta_c$ based on circumcision status. Additionally, the number of sexual partners for status-aware infected individuals in compartment j was adjusted by $1-\epsilon_k$.

Homosexual transmission The same-sex (homosexual) sufficient contact rate between uninfected individuals in compartment i and infected individuals in compartment j is:

$$\beta^s_{i,j}(t) = 1 - \left(1 - \left[\frac{X_j(t)n^s_j(1-u^s_j\kappa)}{\sum_k X_k(t)n^s_k(1-u^s_k\kappa)}\right]\sigma_{i,j}\right)^{n^s_i(1-u^s_i\kappa)} \tag{S.3}$$

where i, j, k correspond to compartments of MSM. The term in brackets, $\left[\frac{X_j(t)n^s_j(1-u^s_j\kappa)}{\sum_k X_k(t)n^s_k(1-u^s_k\kappa)}\right]$, again corresponds to the probability of selecting a sexual partner in compartment j. As with heterosexual transmission, the probability of homosexual transmission, $\sigma_{i,j}$, depends on the transmission probability per partnership, π^k_{mm}, and the reduction in infectivity due to ART, δ^s_h. In the model, male circumcision was assumed to have no effect on homosexual transmission, although this assumption can be updated as additional clinical data become available. Once again, status-aware infected individuals reduce their number of sexual partners by ϵ_k.

Total transmission I calculated the overall sufficient contact rate between uninfected individuals in compartment i and infected individuals in compartment j by first converting the annual transmission probability to a continuous rate, according to the formula $rate =$

$-ln(1-p)/t$. The total contact rate was calculated as the sum of the three modes of transmission: needle-sharing ($\gamma_{i,j}$), opposite-sex (heterosexual) contact ($\beta^o_{i,j}$), and same-sex (homosexual) contact ($\beta^s_{i,j}$). For small probability values, the approximation $p \approx -ln(1-p)$ was assumed. The total contact rate at time t between individuals in compartments i and j, $\lambda_{i,j}(t)$, is:

$$\begin{aligned} \lambda_{i,j}(t) &= -ln[1-\gamma_{i,j}(t)] + -ln[1-\beta^o_{i,j}(t)] + -ln[1-\beta^s_{i,j}(t)] \\ \lambda_{i,j}(t) &\approx \gamma_{i,j}(t) + \beta^o_{i,j}(t) + \beta^s_{i,j}(t) \end{aligned} \tag{S.4}$$

S.2 HIV Interventions

I compared alternative HIV screening strategies by varying the following attributes:

- Targeted risk group (everyone, MSM and IDUs, or MSM only)
- Screening frequency (annually, every six months, every three months)
- Tests offered (immunoassay only, or immunoassay followed by pooled NAAT if immunoassay-negative)

S.2.1 HIV Screening

It was assumed that voluntary HIV screening was accompanied by an effective counseling program may help reduce an individual's number of heterosexual partners (n^o_j) and homosexual partners (n^s_j), which subsequently reduces the sufficient contact rate (Equations S.2-S.3). The degree of behavior change (ε_k) was allowed to vary by HIV status, where k refers to acute HIV or chronic infection (asymptomatic, symptomatic, or AIDS).

Unidentified (i.e., status-unaware) individuals with *acute HIV infection* in compartment i transition to compartment $i+1$ at rate ψ_i, which depends on the rate of HIV screening via immunoassay (ψ_{ASSAY}) or NAAT (ψ_{NAAT}), as well as the test's sensitivity at detecting

infection:

$$\psi_i = f_{NAAT} \cdot sens_{NAAT} \left(\frac{\omega_{ASSAY}}{1/\theta_{ACUTE}} - \frac{\omega_{NAAT}}{1/\theta_{ACUTE}} \right) \psi_{ACUTE} + \left(1 - \frac{\omega_{ASSAY}}{1/\theta_{ACUTE}} \right) \psi_{ASSAY} \tag{S.5}$$

The terms ω_{ASSAY} (either ω_{3GEN} or ω_{4GEN}) and ω_{NAAT} are the window periods of detection for third- or fourth-generation immunoassay and NAAT, respectively, where $\omega_{ASSAY} > \omega_{NAAT}$ (Figure S1) The average duration of the acute infection period is $1/\theta_{acute}$. The term $\left(\frac{\omega_{ASSAY}}{1/\theta_{ACUTE}} - \frac{\omega_{NAAT}}{1/\theta_{ACUTE}} \right)$ refers to the fraction of individuals with acute infection who would receive a positive NAAT test but a negative immunoassay. The pooling algorithm sensitivity ($sens_{NAAT}$) for the NAAT test depends on the prevalence of acute infection and master pool size. The fraction of individuals who receive their NAAT test results (f_{NAAT}) reduces the overall flow of individuals to the identified compartment. Because all individuals were assumed to receive an immunoassay prior to a NAAT test, the term $\left(1 - \frac{\omega_{ASSAY}}{1/\theta_{ACUTE}} \right)$ refers to the fraction of individuals with acute infection who would receive a positive immunoassay test, and hence would not subsequently receive a NAAT test. The model also assumed that $\psi_{ASSAY} \geq \psi_{NAAT}$, which implies that individuals will always receive an immunoassay test prior to a NAAT test; however, I also consider an "fourth-generation immunoassay only" strategy, where screening via immunoassay was scaled up, but $\psi_{NAAT} = 0$.

Similarly, unidentified individuals with *chronic HIV infection* transition to an identified compartment at rate ψ_{ASSAY}. Finally, individuals with chronic infection may become identified through symptom-based case finding, at rate ν_i, which varies based on disease state (asymptomatic HIV, symptomatic HIV, or AIDS).

S.2.2 HIV Treatment

In the present study, individuals with symptomatic HIV or AIDS are eligible to begin ART regimens. A fraction (ϕ_i) begin ART immediately after identification (via screening or symptom-based case finding), or upon becoming eligible (i.e., advancing from asymptomatic

to symptomatic HIV). Additionally, individuals initiate ART at a continuous rate (α_i) after becoming eligible for treatment.

To model the effects of antiretroviral therapy on health and economic outcomes, I adjusted the appropriate model parameters to account for changes in disease progression rates (θ_i), mortality rates (μ_i), and quality-of-life factors (q_i). I assumed that suppressive antiretroviral therapy reduces an individual's viral load, which reduces the probability of HIV transmission via sexual contact ($\sigma_{i,j}$) and needle-sharing ($\tau_{i,j}$). The model accounted for the direct cost of antiretroviral therapy (c_H), as well as the indirect costs through reduced HIV-related healthcare costs (c_i).

S.3 Dynamic Compartmental Model

To estimate the projected HIV epidemic over time under various HIV screening and treatment scenarios, I created the following system of nonlinear differential equations for each of the six risk groups. Additionally, all male risk groups (male IDU, male MSM, male IDU/MSM, male other) are further subdivided to indicate circumcision status. The complete model comprises 120 equations (4 male groups $\times$ 24 compartments + 2 female groups $\times$ 12 compartments). For compactness, the equations for only one risk group are shown. The remaining five risk groups utilize similar equations, with modified indices. Note, HIV transmission can occur both within and across risk groups according to the appropriate rates of transmission (Equations S.1-S.3).

$$\frac{dX_1}{dt} = \rho_1 \sum_{\forall i} X_i - \psi_1 X_1 - \left(\sum_{j \geq 3} \lambda_{1,j}(t) \right) X_1 - \mu_1 X_1 \tag{S.6}$$

$$\frac{dX_2}{dt} = \psi_1 X_1 - \left(\sum_{j \geq 3} \lambda_{2,j}(t) \right) X_2 - \mu_2 X_2 \tag{S.7}$$

$$\frac{dX_3}{dt} = \left(\sum_{j \geq 3} \lambda_{1,j}(t) \right) X_1 + \left(\sum_{j \geq 3} \lambda_{2,j}(t) \right) X_2 - \psi_3 X_3 - \theta_3 X_3 - \mu_3 X_3 \tag{S.8}$$

$$\frac{dX_4}{dt} = \psi_3 X_3 - \theta_4 X_4 - \mu_4 X_4 \tag{S.9}$$

$$\frac{dX_5}{dt} = \theta_3 X_3 - \psi_5 X_5 - \theta_5 X_5 - \mu_5 X_5 \tag{S.10}$$

$$\frac{dX_6}{dt} = \theta_4 X_4 + \psi_5 X_5 - \theta_6 X_6 - \mu_6 X_6 \tag{S.11}$$

$$\frac{dX_7}{dt} = \theta_5 X_5 - (\psi_7 + \nu_7) X_5 - \theta_7 X_7 - \mu_7 X_7 \tag{S.12}$$

$$\frac{dX_8}{dt} = \theta_6 (1 - \phi_6) X_6 + (\psi_7 + \nu_7)(1 - \phi_7) X_7 - \alpha_8 X_8 - \mu_8 X_8 \tag{S.13}$$

$$\frac{dX_9}{dt} = \theta_6 \phi_6 X_6 + (\psi_7 + \nu_7) \phi_7 X_7 + \alpha_8 X_8 - \mu_9 X_9 \tag{S.14}$$

$$\frac{dX_{10}}{dt} = \theta_7 X_7 - (\psi_{10} + \nu_{10}) X_8 - \mu_{10} X_{10} \tag{S.15}$$

$$\frac{dX_{11}}{dt} = \theta_8 X_8 + (\psi_{10} + \nu_{10})(1 - \phi_{10}) X_{10} - \alpha_{11} X_{11} - \mu_{11} X_{11} \tag{S.16}$$

$$\frac{dX_{12}}{dt} = \theta_9 X_9 + (\psi_{10} + \nu_{10}) \phi_{10} X_{10} + \alpha_{11} X_{11} - \mu_{12} X_{12} \tag{S.17}$$

For ease of notation, let X_i denote $X_i(t)$. A summary of all model parameters is given in Table S2. Figure S2 shows a schematic representation of the model. In the top diagram, boxes represent cohorts of individuals, stratified by HIV status, identification (i.e., screening) status, and treatment status if infected. Arrows represent transitions between compartments. Individuals may also leave each compartment according to the mortality or maturation rate.

S.4 Model Instantiation

The system of nonlinear differential equations (S.6-S.17) was instantiated with initial conditions using 2008 data on population sizes and HIV prevalence levels among each risk group. I divided the HIV-infected population into the four health states (acute HIV, asymptomatic HIV, symptomatic HIV, AIDS) in proportion to the average time spent in each state. The fraction of individuals in each state was then adjusted to account for the increase in life expectancy among individuals with symptomatic HIV and AIDS who are receiving antiretroviral therapy. I also estimated the fraction of men who are circumcised and assumed this remained constant over the duration of the model's time horizon. The model was implemented in the mathematical programming language Matlab R2010b.

S.5 Model Outcomes

I numerically solved the system of nonlinear differential equations to calculate the number of individuals in each compartment over time. The following outcome measures were calculated: HIV prevalence, new HIV infections, discounted costs and health benefits (quality-adjusted life years experienced), and incremental cost-effectiveness ratios.

HIV prevalence was calculated for each of the six risk groups (male IDU, male MSM, male IDU/MSM, male other, female IDU, female other) as follows:

$$\text{HIV prevalence at time } t = \frac{\sum_{i \geq 3} X_i(t)}{\sum_{\forall i} X_i(t)}$$

I calculated the (undiscounted) number of new HIV infections that occur in the entire population over the time horizon, T.

$$\text{New HIV infections} = \int_0^T \sum_{i \leq 2} \sum_{j \geq 3} \lambda_{i,j}(t) X_i(t) dt$$

Total health benefits for the entire population were measured in discounted quality-adjusted life years (QALYs). I assumed an infinite time horizon to account for health benefits occurring after the intervention duration.

$$\text{QALYs} = \int_0^{\infty} e^{-rt} \sum_{\forall i} q_i X_i(t) dt$$

Total discounted costs for the entire population were calculated as the sum of annual healthcare costs for all individuals, including costs of antiretroviral treatment, and total screening and counseling costs over the intervention's duration.

$$\begin{aligned}
& \text{Costs} \\
= & \int_0^{\infty} e^{-rt} \sum_{\forall i} c_i X_i(t) dt + \int_0^{T} e^{-rt} \left[\left(e_{NAAT} c_{NAAT} \right) \psi_{ACUTE} + (c_{ASSAY} + c_{coun}) \psi_{ASSAY} \right] X_1(t) dt \\
+ & \int_0^{T} e^{-rt} \left[(e_{NAAT} c_{NAAT} + c_{WB} + c_{coun} + c_{viral}) sens_{NAAT} \left(\frac{\omega_{ASSAY} - \omega_{NAAT}}{1/\theta_{ACUTE}} \right) \psi_{ACUTE} \right] X_3(t) dt \\
& + \int_0^{T} e^{-rt} \left[(c_{ASSAY} + c_{WB} + c_{coun}) \left(1 - \frac{\omega_{ASSAY}}{1/\theta_{ACUTE}} \right) \psi_{ASSAY} \right] X_3(t) dt \\
& + \int_0^{T} e^{-rt} \left[(c_{ASSAY} + c_{WB} + c_{coun}) (\psi_{ASSAY} + \psi_5) \right] X_5(t) dt \\
& + \int_0^{T} e^{-rt} \left[(c_{ASSAY} + c_{WB} + c_{coun}) (\psi_{ASSAY} + \psi_7) \right] X_7(t) dt \\
& + \int_0^{T} e^{-rt} \left[(c_{ASSAY} + c_{WB} + c_{coun}) (\psi_{ASSAY} + \psi_{10}) \right] X_{10}(t) dt
\end{aligned}$$

Finally, I calculated the incremental cost-effectiveness ratio (ICER) of each HIV screening strategy, relative to the status quo.

$$\text{ICER} = \frac{Cost_{Intervention} - Cost_{StatusQuo}}{QALY_{Intervention} - QALY_{StatusQuo}}$$

I also calculated the ICER of one screening strategy relative to another, if appropriate.

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