Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ying R, Sharma M, Celum C, et al. Home testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modelling analysis. Lancet HIV 2016; published online May 11. http://dx.doi.org/10.1016/S2352-3018(16)30009-1.
Supplementary appendix to

Home HIV testing and counseling for reducing HIV incidence in a generalized epidemic setting: a mathematical modeling analysis

I. Technical Specifications
II. Interventions
III. Epidemiological Parameters
IV. References
V. Additional Model Outputs
General Overview:

The purpose of this mathematical model is to study the impact of antiretroviral therapy (ART) provision to HIV-positive persons in a generalized HIV epidemic setting. We created a model that simulates heterosexual HIV transmission and is parameterized to a study of home-based testing and counseling for HIV in KwaZulu-Natal, South Africa (KZN), a region with HIV prevalence estimated to be 18%. The model reproduces population-level dynamics and stratifies the population by age, gender, and sexual risk. We structure the model to examine using home-based HIV testing and counseling campaigns to scale-up ART targeted to HIV-positive persons by CD4+ T-cell (CD4) count and HIV RNA concentration (viral load).

The model begins with an entirely HIV-negative population at time \( t = 0 \) with a size and distribution reflecting KZN in 1985. In the first iteration \( (t = 1985) \), two HIV-positive persons are placed in the population, while subsequent iterations evaluate the demography, enrollment, and aging of the population using 4th-order Runge-Kutta methods. The population dynamics are governed by a system of ordinary differential equations (ODEs) that are solved in MATLAB. The model iterates in three-month intervals from 1985 to 2045.

I. Technical Specifications

Model Development and Selection:
The structure and complexity of the model was developed to explore HIV testing strategies that identify high-risk individuals by gender, age, CD4 count, and viral load, and initiating those individuals on ART and PrEP. Furthermore, the model utilizes epidemiologic and behavioral data collected from an observational study of home-based HIV testing and counseling.

HIV Natural History:
The natural history of HIV infection is modeled in stages defined by CD4 count and viral load as shown in Figure S1.

![Figure S1. Model transition diagram](image)

A diagram of the natural history of HIV infection. All movement is in one direction except for enrollment in and dropout from interventions from ART.
When a person becomes HIV-infected, s/he enters the acute stage characterized by a short duration and high probability of HIV transmission. The person then progresses through stages of CD4 count and viral load at rates $\nu^d$ and $\omega^v$, respectively, where $d$ represents the current CD4 count and $v$ represents the current viral load. The parameters $\nu^d$ and $\omega^v$ are based on an analysis of disease progression using data from the Partners HSV/HIV\textsuperscript{4} and Partners PrEP\textsuperscript{5} studies, with the average life expectancy from infection to death for untreated persons being 10.7 years. The values are estimated in Table S1:

**Table S1. Duration of HIV infection in each CD4 and viral load stage by gender.** Values are based on estimates from previous longitudinal studies of ART-naïve participants.

| (a) Gender | Time (years) CD4 Stage | Life Expectancy |
|------------|------------------------|-----------------|
|            | Acute | >500 | 500 to 350 | 350 to 200 | $\leq$200 |
| Female     | 0.25  | 1.94 | 1.35       | 6.71       | 1.96       | 11.58     |
| Male       | 0.25  | 1.71 | 1.05       | 4.71       | 1.96       | 9.23      |
| Both       | 0.25\textsuperscript{a} | 1.88 | 1.22       | 5.90       | 1.96\textsuperscript{a} | 10.66     |

| (b) Gender | Time (years) Viral Load Stage | Life Expectancy |
|------------|-----------------------------|-----------------|
|            | Acute | $\leq$1,000 | 1,000 – 10,000 | 10,000 – 50,000 | $>50,000$ (est) |
| Female     | 0.25 | 3.06 | 2.27       | 5.45       | 1.18       | 11.58     |
| Male       | 0.25 | 3.44 | 1.45       | 3.04       | 1.50       | 9.23      |
| Both       | 0.25\textsuperscript{a} | 3.13 | 1.99       | 4.40       | 1.44       | 10.66     |

The population distribution of CD4 count and viral load as modeled with these estimates matches well with population data from KwaZulu-Natal (Figure S2).

**Figure S2. Model output for CD4 count and viral load distributions.** The population distribution for CD4 count and viral load as estimated in the model compared to distributions measured in the population.\textsuperscript{9}

**Ordinary Differential Equations:**
The model simulates a population from ages 0 to 59 in five-year age-groups, capturing vertical transmission and aging. The system of ODE’s describes the states $X_{a,r}^{g,d,v}(t)$ with the following indices:

- $g$ refers to gender
  - $g = 0$ for males; $g = 1$ for females
- $d$ refers to disease state defined by CD4 cell count, and treatment and circumcision status
  - $d = 0$ for HIV-negative; $d = 1$ for acute infection; $d = 2$ for CD4 >500 cells/μL; $d = 3$ for CD4 500-350 cells/μL; $d = 4$ for CD4 350-200 cells/μL; $d = 5$ for CD4 <200 cells/μL; $d = 6$ for HIV-negative, circumcised, and no PrEP; $d = 7$ for HIV-negative, circumcised, and on PrEP; $d = 8$ for HIV-negative, uncircumcised, and on PrEP; $d = 9$ for HIV-positive on ART
- $v$ refers to disease state defined by viral load
  - $v = 0$ for HIV-negative; $v = 1$ for acute infection; $v = 2$ for VL<1,000 copies/mL; $v = 3$ for VL 1,000-10,000 copies/mL; $v = 4$ for VL 10,000-50,000 copies/mL; $v = 5$ for VL>50,000 copies/mL;
  - $v = 6$ for HIV-positive and on ART
- $a$ refers to age group
  - $a = 0$ for ages 0 to 4; $a = 1$ for ages 5 to 9; ...; $a = 11$ for ages 55 to 59
- $r$ refers to sexual risk group defined by number of sexual partnerships per year
  - $r = 0$ for low risk; $r = 1$ for medium risk; $r = 2$ for high risk

The ODEs for the nine disease states are:

\[
\frac{dX_{a,r}^{g,0,0}(t)}{dt} = b_{g,0,r}^{0,0}(t) + \sigma_{a,r}^{g,0}X_{a,r}^{g,0,0}(t) - \left(\mu_{a}^{g} + \lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)\right)X_{a,r}^{g,0,0}(t)
\]

\[
\frac{dX_{a,r}^{g,1,v}(t)}{dt} = b_{g,1,r}^{0,1}(t) + \lambda_{a,r}^{g,0}X_{a,r}^{g,0,0}(t) + \psi_{0}\lambda_{a,r}^{1,0}(t)X_{a,r}^{1,6,v}(t) + \psi_{1}\lambda_{a,r}^{1,1}(t)X_{a,r}^{1,7,v}(t) + \psi_{2}\lambda_{a,r}^{1,2}(t)X_{a,r}^{1,8,v}(t) + \psi_{3}\lambda_{a,r}^{1,3}(t)X_{a,r}^{1,9,v}(t) + \psi_{4}\lambda_{a,r}^{1,4}(t)X_{a,r}^{1,5,v}(t)
\]

\[
\frac{dX_{a,r}^{g,2,v}(t)}{dt} = (v_{1} + \omega_{v-1})X_{a,r}^{g,1,v}(t) + \sigma_{a,r}^{g,2}X_{a,r}^{g,9,6}(t) - \left(\mu_{a}^{g} + \alpha_{a}^{g,2} + \nu_{2} + \omega_{v} + \pi_{a,r}^{g,2,v}(t)\right)X_{a,r}^{g,2,v}(t)
\]

\[
\frac{dX_{a,r}^{g,3,v}(t)}{dt} = (v_{2} + \omega_{v-1})X_{a,r}^{g,2,v}(t) + \sigma_{a,r}^{g,3}X_{a,r}^{g,9,6}(t) - \left(\mu_{a}^{g} + \alpha_{a}^{g,3} + \nu_{3} + \omega_{v} + \pi_{a,r}^{g,3,v}(t)\right)X_{a,r}^{g,3,v}(t)
\]

\[
\frac{dX_{a,r}^{g,4,v}(t)}{dt} = (v_{3} + \omega_{v-1})X_{a,r}^{g,3,v}(t) + \sigma_{a,r}^{g,4}X_{a,r}^{g,9,6}(t) - \left(\mu_{a}^{g} + \alpha_{a}^{g,4} + \nu_{4} + \omega_{v} + \pi_{a,r}^{g,4,v}(t)\right)X_{a,r}^{g,4,v}(t)
\]

\[
\frac{dX_{a,r}^{g,5,v}(t)}{dt} = (v_{4} + \omega_{v-1})X_{a,r}^{g,4,v}(t) + \sigma_{a,r}^{g,5}X_{a,r}^{g,9,6}(t) - \left(\mu_{a}^{g} + \alpha_{a}^{g,5} + \nu_{5} + \omega_{v} + \pi_{a,r}^{g,5,v}(t)\right)X_{a,r}^{g,5,v}(t)
\]

\[
\frac{dX_{a,r}^{g,6,0}(t)}{dt} = b_{g,6,1}(t) + \sigma_{a,r}^{g,6}X_{a,r}^{g,6,0}(t) - \left(\mu_{a}^{g} + \psi_{0}\lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)\right)X_{a,r}^{g,6,0}(t)
\]

\[
\frac{dX_{a,r}^{g,7,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t)X_{a,r}^{g,5,0}(t) - \left(\sigma_{a,r}^{g,0} + \mu_{a}^{g} + \psi_{0}\lambda_{a,r}^{g,0,0}(t)\right)X_{a,r}^{g,7,0}(t)
\]

\[
\frac{dX_{a,r}^{g,8,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t)X_{a,r}^{g,8,0}(t) - \left(\sigma_{a,r}^{g,0} + \mu_{a}^{g} + \psi_{1}\lambda_{a,r}^{g,1,0}(t)\right)X_{a,r}^{g,8,0}(t)
\]

\[
\frac{dX_{a,r}^{g,9,6}(t)}{dt} = \sum_{v=1}^{5} \sum_{d=1}^{5} \left[\pi_{a,r}^{g,d,v}(t)X_{a,r}^{g,d,v}(t) - \left(\sigma_{a,r}^{g,d} + \mu_{a}^{g}\right)X_{a,r}^{g,9,6}(t)\right]
\]

The equation variables are:

- $b_{g,0,r}^{0,0}(t)$ — The number of births that are HIV-negative ($d = 0$), HIV-positive ($d = 1$), uncircumcised ($c = 0$), or circumcised ($c = 1$)
- $\sigma_{a,r}^{g,d}(t)$ — The dropout rate from PrEP ($d = 0$) or ART ($d = 1, ..., 5$)
- $\mu_{a}^{g}$ — The background mortality
- $\lambda_{a,r}^{g,0}(t)$ — The force of infection for HIV-negative persons on PrEP ($d = 1$) or off PrEP ($d = 0$)
The equation variables are:

| \( \phi_{a,r}^{g,d} \) | The proportion of individuals in age \( a \), gender \( g \), and treatment status \( d \) \((d = 0, \text{no treatment}; d = 1, \text{PrEP}; d = 2, \text{ART}) \) that is born into sexual risk group \( r \) |
| \( \eta(t) \) | The proportion of births from HIV-positive females that result in vertical transmission |
| \( \pi_{0,r}^{1.5}(t) \) | The proportion of HIV-negative males that is circumcised at birth |
| \( \gamma_{d}^{g} \) | The annual fertility rate for females by age and disease state |

Each birth is multiplied by 0.5 given an assumed gender ratio at birth of 1:1. The proportion of births from HIV-positive mothers that result in infection, \( \eta(t) \), decreases linearly from 34% in 2004 to 20.2% in 2005, then to 7.1% in 2008.\(^{10,11}\) The proportion of circumcised HIV-negative males, \( \pi_{0,r}^{1.5}(t) \), remains at 10% from 1990 to 2013.\(^{10}\)
Mortality:
People leave the population due to death or aging past age 59. Mortality is represented by mortality caused by HIV, \(a\), and all other background mortality, \(\rho\). Mortality caused by HIV varies by stage of disease and age (individuals 0 to 4 years old and 50 to 59 years old are assumed to have elevated risks of death), and individuals on ART are assumed to have no disease-induced mortality.\(^{15,16}\) The background mortality rate is estimated to be the population mortality rate in 1990, prior to the generalized HIV epidemic.

Disease Transmission:
Disease transmission is governed by the force of infection, \(\lambda_{a,r}(t)\), which determines the number of people who are infected at each time-step.

\[
\lambda_{a,r}(t) = \sum_{a'=0}^{11} \sum_{r'=0}^{2} c_{a,a',r'}(t) \rho_{a,a',r'}(t) \beta_{a,r,r'}(t) \frac{\psi_{a}X_{a,r'}^{\delta_{a},d_{a'},v}(t) \beta_{a,r,r'}(t) \beta_{a,r,r'}(t)}{\sum_{v'=0}^{6} X_{a',r'}^{\delta_{a},d_{a'},v'}(t)}
\]

The equation variables are:

| Variable | Description |
|----------|-------------|
| \(c_{a,a',r'}(t)\) | The number of partners from age \(a'\) and sexual risk group \(r'\) that an individual has per year |
| \(\rho_{a,a',r'}(t)\) | The mixing matrix which describes the distribution of partners from each age and sexual risk group |
| \(\beta_{a,r,r'}\) | The probability of HIV transmission per partnership between an HIV-positive person of stage \(r'\) and HIV-negative person of risk group \(r\) |

The overall force of infection for a specific age-group is the sum of the risk of acquiring HIV from all possible partners.

Mixing Matrix:
Using methods similar to other models, the mixing matrix, \(\rho_{a,a',r'}(t)\), describes patterns of sexual contact by calculating the proportion of one’s sexual partners that come from a specific age and sexual-risk group.\(^{17}\)

\[
\rho_{a,a',r'}(t) = \left[ \sum_{r'=0}^{2} c_{a',r'}(t) \sum_{d'=0}^{6} X_{a',r'}^{\delta_{a},d_{a'},v}(t) \right] + (1 - \epsilon) \delta_{a}
\]

where

\[
\delta_{a} = \begin{cases} 
1.0 & \text{If } r = r' \\
0.0 & \text{If } r \neq r'
\end{cases}
\]

Before 2005:
\[
\delta_{a} = \begin{cases} 
0.3 & \text{If } a = a' \\
0.7 & \text{If } a = a' + 1 \text{ (for males)} \\
0.0 & \text{If } a = a' - 1 \text{ (for males)} \\
0.0 & \text{Otherwise}
\end{cases}
\]

After 2005:
\[
\delta_{a} = \begin{cases} 
0.7 & \text{If } a = a' \\
0.3 & \text{If } a = a' + 1 \text{ (for males)} \\
0.0 & \text{If } a = a' - 1 \text{ (for males)} \\
0.0 & \text{Otherwise}
\end{cases}
\]

Mixing patterns vary between random and assortative, as determined by the parameter \(\epsilon\). Random mixing (\(\epsilon = 1\)) is mixing proportional to the relative sizes of all compartments and this method is consistent for both random mixing
by risk and by age. However, assortative mixing ($e = 0$) is among groups with similar characteristics and differs for mixing by risk and age. Assortative mixing by risk ($e_r = 0$) is defined by the identity matrix $\delta_r^0$, whereas assortative mixing by age ($e_a = 0$) is defined by an off-diagonal matrix $\delta_a^d$. The off-diagonal pattern results in females of age $a$ being more likely to form partnerships with males of age $a = a' - 1$, which is consistent with reports of such age discrepancies in KZN. Although this off-diagonal method results in some age groups having fewer than 100% of their partnerships, those age-groups are adjusted against risky sexual behavior.20

**Per-Partnership Probability of Transmission:**

The per-partnership probability of transmission, $\beta_{0,r,a,d'}$, depends on the sexual risk group of the HIV-negative partner and the disease state of the HIV-positive partner. The probabilities of transmission per partnership are:

$$\beta_{0,r,a} = 1 - (1 - \chi_{0,r,a})^A$$

For male HIV-negative partners

$$\beta_{1,r,a} = (1 - (1 - \chi_{1,r,a})^A)$$

For female HIV-negative partners

$\chi_{0,r,a}$ is the per-act probability of transmission for an HIV-positive partner of HIV stage $d'$, and the exponent, $A_{0,r}$, is the number of coital acts based on the HIV-negative partner’s sexual risk group and gender.

**Rate of Partner Change:**

Data on sexual behavior and specifically, sexual contact rates, $c_{0,a,r}$, are often subject to biases leading to contact rate data that, when assuming solely heterosexual contact, are inconsistent between males and females. We account for this variability by using an adjusted contact rate, $c_{a,r,d'}(t)$, which equilibrates the reported number of sexual partners by males and females. The adjusted contact rate can be male- or female-driven, as determined by the parameter $\theta$, where $\theta = 1$ for male-driven, $\theta = 0$ for female-driven, and $\theta = 0.5$ when compromised equally. We assume $\theta = 0.5$ given the lack of data to assume otherwise. The adjusted contact rate for females is:

$$c_{1,a,r}(t) = c_{a,r}B_{a,r}(t)^{(1-\theta)}$$

For males, the adjusted contact rate is:

$$c_{0,a,r}(t) = c_{0,a}B_{a,r}(t)$$

The discrepancy between the two populations, $B_{a,r}(t)$, is defined as:

$$B_{a,r}(t) = \frac{c_{0,a,r}B_{0,a,r}(t) + \sum_{a=0}^{6} \sum_{a=0}^{6} \chi_{0,d} \chi_{a,r}(t)}{c_{1,a,r}B_{1,a,r}(t) + \sum_{a=0}^{6} \sum_{a=0}^{6} \chi_{1,d} \chi_{a,r}(t)}$$

**Model Calibration:**

The model was calibrated to fit HIV prevalence data from South Africa (1990 to 2000) and KwaZulu-Natal (2001 to 2012). The parameters for HIV transmission probability, sexual partnership duration, and sexual mixing were varied individually and final values were chosen by least-squares regression in the HIV prevalence output. HIV transmission probability was varied from 0.00053 to 0.00097 assuming a normal distribution, the rate of sexual partnership change was based on a previous study and varied by a factor from 0.5 to 1.5 assuming a normal distribution, and the degree of sexual mixing was varied from 0.1 to 1 assuming a normal distribution.

**Population Aging:**

To age the population, one-fifth of each compartment enters the next age group of corresponding gender, sexual risk, and disease state. When individuals age, they also change sexual risk; therefore, they redistribute to a set sexual-risk profile, $q_{a,r}$, that varies by age, gender, and treatment status. All compartments, except for the youngest and oldest age-groups, experience influx from the prior age and efflux into the next age. The 0 to 4 age-group only
receives influx through births while the 55 to 59 age-group exits the population rather than entering the next age. Therefore, each state has a second ODE that occurs at each time step:

\[
\frac{dX_{a,r}^{g,d}(t)}{dt} = - \frac{1}{5} X_{a,r}^{g,d}(t) \quad \text{for } a = 0
\]

\[
\frac{dX_{a,r}^{g,d}(t)}{dt} = - \frac{1}{5} X_{a,r}^{g,d}(t) + \frac{1}{5} \sum_{r=0}^{2} X_{a-1,r}^{g,d}(t) \phi_{a-1,r}^{g,d} \quad \text{for } a \neq 0
\]

II. Interventions

Community-based counseling and testing for HIV has been shown to increase HIV testing and linkage to care, detect early, asymptomatic cases of HIV that are eligible for treatment (CD4 ≤500 cells/µL), and initiate high-risk HIV-negative persons on PrEP. Therefore, we model PrEP and treatment enrollment frequencies as community-wide initiatives that occur every five years. Enrollment is represented by \( \pi_{a,r}^{g,d,v}(t) \), while dropout is represented by \( \sigma_{a,r}^{g,d} \).

**ART Treatment Enrollment:**
Coverage of ART treatment for HIV-positive persons increases from 0% in 2004 to 35% for persons with CD4 ≤200 cells/µL in 2006 as previously observed in KZN then to 36% coverage for all HIV-positive persons in 2014 as observed in the Home HTC study. ART coverage is modeled to reach the expected ART coverages in 2000, 2006, and 2014, and to reach a steady-state in approximately 2025. The steady-state ART coverage depends on the scenario being simulated. ART treatment is assumed to reduce the likelihood of HIV transmission by 96% as suggested by recent studies. We assume that 6% of individuals drop out from PrEP per year, which is equally likely for all individuals. We ignore the impact of ART-resistant HIV strains and combine all treatment failure into PrEP dropout. The ODE for HIV-negative persons on PrEP is:

\[
\frac{dX_{a,r}^{g,8,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t) X_{a,r}^{g,8,0}(t) - \left( \sigma_{a,r}^{g,0} + \mu_{a}^{0} + (1 - \psi_{1}) \lambda_{a,r}^{0,1}(t) \right) X_{a,r}^{g,7,0}(t)
\]

Furthermore, circumcised males can also use PrEP, resulting in an even greater reduction in HIV acquisition probability:

\[
\frac{dX_{a,r}^{g,7,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t) X_{a,r}^{g,7,0}(t) - \left( \sigma_{a,r}^{g,0} + \mu_{a}^{0} + (1 - \psi_{1})(1 - \psi_{0}) \lambda_{a,r}^{0,1}(t) \right) X_{a,r}^{g,6,0}(t)
\]

**Circumcision:**
This model includes a background level of circumcision of 10% as currently observed in KZN (Figure S3). Several studies show that circumcised males have a 60% (\( \psi_{0} = 0.6 \)) lower risk of acquiring HIV, but are not at a reduced risk of transmitting HIV. Therefore, the model does not track the circumcision status of HIV-positive persons. The ODE for HIV-negative circumcised males is:

\[
\frac{dX_{a,r}^{g,6,0}(t)}{dt} = b_{r,1}^{0,0}(t) + \sigma_{a,r}^{g,0} X_{a,r}^{g,7,0}(t) - \left( \mu_{a}^{0} + (1 - \psi_{0}) \lambda_{a,r}^{0,1}(t) - \pi_{a,r}^{g,6,0}(t) \right) X_{a,r}^{g,6,0}(t)
\]
Other models have studied the impact of circumcision in-depth to include wound healing periods and sexual activity. However, this model assumes that circumcision is instantaneous.

### III. Epidemiological Parameters

**Table S2. Initial population size.** Age distribution is based on SA 1985 census and scaled to fit KZN’s population growth and size profile.

| Age Cohort | Initial Population Size | Reference |
|------------|-------------------------|-----------|
|            | Male                    | Female    |           |
| 0 – 4      | 418,189                 | 417,311   | US Census, Stats South Africa |
| 5 – 9      | 361,938                 | 361,594   |           |
| 10 – 14    | 327,171                 | 329,333   |           |
| 15 – 19    | 289,627                 | 296,947   |           |
| 20 – 24    | 262,704                 | 273,204   |           |
| 25 – 29    | 235,673                 | 249,396   |           |
| 30 – 39    | 197,816                 | 211,839   |           |
| 35 – 39    | 160,952                 | 176,470   |           |
| 40 – 44    | 132,311                 | 143,351   |           |
| 45 – 49    | 110,849                 | 123,441   |           |
| 50 – 54    | 89,027                  | 98,355    |           |
| 55 – 59    | 70,487                  | 82,330    |           |

**Table S3. Sexual risk distribution by age and sex.** Values are calibrated to fit age-specific HIV incidence and prevalence data.

| Age Cohort | Male Risk Distribution | Female Risk Distribution | Reference |
|------------|------------------------|--------------------------|-----------|
|            | Low-Risk | Moderate-Risk | High-Risk | Low-Risk | Moderate-Risk | High-Risk | Calibrated to fit data |
| 0 – 4      | 0.999     | 0.0005       | 0.0005    | 0.999     | 0.0005       | 0.0005    |           |
| 5 – 9      | 0.999     | 0.0005       | 0.0005    | 0.999     | 0.0005       | 0.0005    |           |
| 10 – 14    | 0.98      | 0.015        | 0.005     | 0.98      | 0.015        | 0.005     |           |
| 15 – 19    | 0.80      | 0.17         | 0.03      | 0.85      | 0.13         | 0.02      |           |
| 20 – 24    | 0.78      | 0.20         | 0.02      | 0.75      | 0.22         | 0.03      |           |
| 25 – 29    | 0.65      | 0.28         | 0.07      | 0.68      | 0.27         | 0.05      |           |
| 30 – 34    | 0.55      | 0.35         | 0.10      | 0.72      | 0.23         | 0.05      |           |
| 35 – 39    | 0.65      | 0.28         | 0.07      | 0.75      | 0.20         | 0.05      |           |
| 40 – 44    | 0.71      | 0.23         | 0.06      | 0.79      | 0.16         | 0.05      |           |
| 45 – 49    | 0.78      | 0.17         | 0.05      | 0.80      | 0.16         | 0.04      |           |

**Figure S3. Circumcision prevalence in males.** Proportion of males circumcised over time. Note that circumcision among 15 to 59-year-old males surpasses the overall rate because uncircumcised males are less likely to acquire HIV, and thus have lower mortality.
### Table S4. Annual number of sexual partnerships by age, gender, and sexual risk.
Values are based on a previous study and calibrated to fit age-specific HIV incidence and prevalence data.

| Age Cohort | Male Partnerships per Year | Female Partnerships per Year | Reference |
|------------|---------------------------|-------------------------------|-----------|
|            | Low-Risk                  | Moderate-Risk                | High-Risk | Low-Risk | Moderate-Risk | High-Risk |
| 0 – 4      | 0.0001                    | 0.0001                       | 0.0001    | 0.0001   | 0.0001        | 0.0001   |
| 5 – 9      | 0.0012                    | 0.012                        | 0.12      | 0.0012   | 0.012         | 0.12     |
| 10 – 14    | 0.012                     | 0.0130                       | 1.2       | 0.012    | 0.12          | 1.2      |
| 15 – 19    | 0.14                      | 3.6                          | 84        | 0.24     | 3.6           | 67.2     |
| 20 – 24    | 0.42                      | 4.8                          | 96        | 0.6      | 4.8           | 103.2    |
| 25 – 29    | 1.14                      | 8.4                          | 120       | 0.78     | 8.4           | 120      |
| 30 – 34    | 1.32                      | 9.6                          | 126       | 0.74     | 7.2           | 122.4    |
| 35 – 39    | 1.12                      | 8.4                          | 108       | 0.71     | 7.2           | 111.6    |
| 40 – 44    | 1.08                      | 7.2                          | 102       | 0.66     | 6.0           | 102      |
| 45 – 49    | 0.96                      | 4.8                          | 90        | 0.56     | 6.0           | 90       |
| 50 – 54    | 1.02                      | 6.0                          | 96        | 0.40     | 4.8           | 62.4     |
| 55 – 59    | 0.84                      | 3.6                          | 72        | 0.12     | 0.6           | 12       |

### Table S5. Background mortality.
Values are estimated to be SA’s age-specific mortality in 1990, prior to the generalized HIV epidemic.

| Age Cohort | Background Mortality | Reference |
|------------|----------------------|-----------|
|            | Male                 | Female    |
| 0 – 4      | .06                  | .06       | UNICEF66 |
| 5 – 9      | .00053               | .00040    |          |
| 10 – 14    | .00056               |           |          |
| 15 – 19    | .00083               | .00076    |          |
| 20 – 24    | .00098               | .00130    |          |
| 25 – 29    | .00514               | .00183    |          |
| 30 – 34    | .00606               | .00252    | WHO97    |
| 35 – 39    | .00715               | .00315    |          |
| 40 – 44    | .00952               | .00448    |          |
| 45 – 49    | .01178               | .00576    |          |
| 50 – 54    | .01711               | .00964    |          |
| 55 – 59    | .02081               | .01293    |          |

### Table S6. Fertility rate by age and HIV status.
Females on ART are assumed to have equal fertility to HIV-negative females.

| Age Cohort | Fertility Rate (per year) | Reference |
|------------|---------------------------|-----------|
|            | Uninfected RR=1 | Acute RR=1 | >350 RR=0.42 | 200-350 RR=0.42 | <200 RR=0.59 |
| 0 – 4      | 0                       | 0          | 0             | 0                 | 0             |
| 5 – 9      | 0                       | 0          | 0             | 0                 | 0             |
| 10 – 14    | 0                       | 0          | 0             | 0                 | 0             |
| 15 – 19    | 0.175                   | 0.175      | 0.0788        | 0.0473            | 0.0332        |
| 20 – 24    | 0.313                   | 0.313      | 0.1409        | 0.0845            | 0.0595        |
| 25 – 29    | 0.324                   | 0.324      | 0.1458        | 0.0875            | 0.0616        |
| 30 – 34    | 0.271                   | 0.271      | 0.1221        | 0.0732            | 0.0515        |
| 35 – 39    | 0.201                   | 0.201      | 0.0905        | 0.0543            | 0.0382        |
| 40 – 44    | 0.125                   | 0.125      | 0.0563        | 0.0338            | 0.0238        |
| 45 – 49    | 0.053                   | 0.053      | 0.0239        | 0.0143            | 0.0101        |
| 50 – 54    | 0                       | 0          | 0             | 0                 | 0             |
| 55 – 59    | 0                       | 0          | 0             | 0                 | 0             |

### Table S7. HIV-associated mortality.
Values are estimates from observational studies of untreated HIV-positive persons. Persons age 0 to 4 and older than 50 are assumed to have greater mortality as observed.

| Age Cohort | HIV Mortality | Reference |
|------------|---------------|-----------|
|            | Acute CD4>350 | CD4 200 to 350 | CD4<200 |
| 0 – 4      | 0.47          | 0.47       | 0.47      | 0.47 |
| 5 – 9      | 0.47          | 0.47       | 0.47      | 0.47 |

Newell et al.97
**Table S8. Probability of HIV transmission by viral load.**

| Baseline Transmission Probability | Increase in transmission probability by HIV stage | Reference |
|-----------------------------------|-----------------------------------------------|-----------|
|                                  | Acute | VL<1,000 | VL 1,000-10,000 | VL 10,000-50,000 | VL>50,000 | ART |
| 0.00062240                       | 261   | 1        | 5.8             | 6.9             | 11.9      | 0.04 |

**Table S9. Baseline ART Coverage.**

| Time Period | ART Coverage | Reference |
|-------------|--------------|-----------|
| Before 2004 | 0%           | KZN Bulletin23 |
| 2004 to 2006| Linear increase from 0% to 35% for CD4≤200 cells/µL | KZN Bulletin23 |
| 2013        | 36% of all HIV-positive persons | Barnabas et al.9 |

**Table S10. Proportion of births from HIV-positive females that results in mother-to-child transmission.** The rate decreases linearly from 2004 to 2005 and from 2005 to 2008.

| Year | MTCT Rate | Reference |
|------|-----------|-----------|
| Before 2004 | 0.34 | Bobat et al.12 |
| 2005 | 0.202 | Rollins et al.14 |
| After 2008 | 0.071 | Horwood et al.13 |

**Table S11. The number of coital acts per partnership by gender and sexual risk group.** Values are calibrated to fit age-specific HIV incidence and prevalence data.

| Gender | Low-Risk | Moderate-Risk | High-Risk | Reference |
|--------|----------|---------------|-----------|-----------|
| Male   | 99       | 33            | 3.3       | Calibrated to fit data |
| Female | 77       | 22            | 3.3       |           |

**Table S12. Sexual mixing by age and sexual risk group.** The mixing parameter varies from random ($\epsilon = 1$) to assortative ($\epsilon = 0$), calibrated to fit age-specific HIV incidence and prevalence data.

| Year | Force of Infection Mixing | Reference |
|------|--------------------------|-----------|
| Before 1998 | $\epsilon_a$ (age) = 0.7 | $\epsilon_s$ (sexual risk) = 0.7 | Calibrated to fit data |
| 2003 | $\epsilon_a$ = 0.5 | $\epsilon_s$ = 0.5 | |
| After 2010 | $\epsilon_a$ = 0.1 | $\epsilon_s$ = 0.1 | |

**Table S13. Age-specific prevalence and incidence data used for parameterization.**

| Age Cohort | 2012 Prevalence | Reference | 2008 Prevalence | Reference | 2005 Incidence | Reference |
|-----------|----------------|-----------|----------------|-----------|----------------|-----------|
|           |                 | Males | Females |          | Males | Females |          |
| 0 – 4     | 0               | 0     | 0       |          | 0     | 0       |          |
| 5 – 9     | 0               | 0     | 0       |          | 0     | 0       |          |
| 10 – 14   | 0               | 0     | 0       |          | 0     | 0       |          |
| 15 – 19   | 11.3%           | 2.5%  | 6.7%    |          | 2.2%  | 4.7%    |          |
| 20 – 24   | 20.2%           | 5.1%  | 21.1%   |          | 3.8%  | 8.8%    |          |
| 25 – 29   | 36.0%           | 15.7% | 32.7%   | Barnabas al.30 | 9.1%  | 12.5%   | Shisana al.20 |
| 30 – 34   | 54.8%           | 25.8% | 29.1%   |          | 10.7% | 10.4%   |          |
| 35 – 39   | 62.7%           | 18.5% | 24.8%   |          | 8.1%  | 9.2%    |          |
| 40 – 44   | 41.7%           | 19.2% | 16.3%   |          | 7.6%  | 7.5%    |          |
| 45 – 49   | 39.0%           | 6.4%  | 14.1%   |          | 6.3%  | 6.7%    |          |
| 50 – 54   | 20.0%           | 10.4% | 12.2%   |          | 6.9%  | 0       |          |
| 55 – 59   | 13.4%           | 5%    | 5%      |          | 0     | 0       |          |
Table S14. HIV prevalence from 1990 to 2012 used for model validation. HIV prevalence for 2012 was gathered from a study of Home HIV testing and counseling for HIV in KZN.

| South Africa Data | Reference |
|-------------------|-----------|
| Year              | Prevalence|          |
| 1990              | 0.5%      |          |
| 1991              | 1.1%      |          |
| 1992              | 1.5%      |          |
| 1993              | 2.7%      |          |
| 1994              | 5.1%      |          |
| 1995              | 6.9%      | Motsoaledi44 |
| 1996              | 9.5%      |          |
| 1997              | 11.3%     |          |
| 1998              | 15.2%     |          |
| 1999              | 14.9%     |          |
| 2000              | 16.3%     |          |

| KwaZulu-Natal Data | Reference |
|-------------------|-----------|
| Year              | Prevalence|          |
| 2001              | 22.3%     | SA DoH45 |
| 2002              | 24.3%     |          |
| 2003              | 25.0%     |          |
| 2004              | 27.1%     |          |
| 2005              | 26.1%     |          |
| 2006              | 26.1%     |          |
| 2007              | 25.8%     |          |
| 2008              | 25.8%     |          |
| 2009              | 26.3%     |          |
| 2010              | 26.3%     |          |
| 2012              | 31.8%     | Barnabas et al.10 |

Table S15. Utility weights for estimating quality-adjusted life-years gained.

| Health State                  | QALY Weight |
|-------------------------------|-------------|
| HIV-negative                  | 1           |
| HIV-positive CD4>350          | 0.94        |
| HIV-positive CD4 200-350      | 0.82        |
| HIV-positive CD4<200          | 0.70        |
| HIV-positive on ART           | 0.94        |
| Dead                          | 0           |

Table S16. Relevant costs for estimating cost-effectiveness. Costs for home HTC, ART, and hospitalization of people living with HIV with and without ART.

| Expenditure                      | Cost                                | Reference                                    |
|----------------------------------|-------------------------------------|----------------------------------------------|
| Annual Home HTC with Community Care Workers' ART | HIV-positive: $28.06 per person HIV-negative: $8.22 per person | Smith et al.17, Sharma et al.18 |
| Hospitalization: pre-ART CD4<200 cells/µL | $121 per HIV-positive person per year | Meyer-Rath et al.19 |
| Hospitalization: pre-ART CD4 200-350 cells/µL | $58 per HIV-positive person per year | Meyer-Rath et al.19 |
| Hospitalization: pre-ART CD4>350 cells/µL | $39 per HIV-positive person per year | Meyer-Rath et al.19 |
| Hospitalization: post-ART CD4 200-350 cells/µL | $111 per HIV-positive person per year | Meyer-Rath et al.19 |
| Hospitalization: post-ART CD4>350 cells/µL | $45 per HIV-positive person per year | Meyer-Rath et al.19 |
IV. References

1. International Data Base: South Africa 1985. U.S. Census Bureau.
2. Statistics South Africa. Primary tables KwaZulu-Natal: Census '96 and 2001 compared. 2004.
3. Press WH, Flannery BP, Teukolsky SA, Vetterling WT. Runge-Kutta Method. Numerical Recipes in FORTRAN: The Art of Scientific Computing. 2 ed. Cambridge, England: Cambridge University Press; 1992: 704-16.
4. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; 362(5): 427-39.
5. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; 367(5): 399-410.
6. Hontelez JA, de Vlas SJ, Tanser F, et al. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. *PLoS One* 2011; 6(7): e21919.
7. Johnson L, Dorrington R, Bradshaw D, Van Wyk V, Rehle T. Sexual behaviour patterns in South Africa and their association with the spread of HIV: Insights from a mathematical model. *Demographic Research* 2009; 21(11): 289 - 340.
8. Badri M, Lawn SD, Wood R. Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study. *Lancet* 2006; 368(9543): 1254-9.
9. Barnabas RV, van Rooyen H, Tumwesigye E, et al. Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: a prospective, observational intervention study. *Lancet HIV* 2014; 1(2): e68-e76.
10. Barnabas RV, Van Rooyen H, Baeten J, et al. High testing uptake and linkages to HIV treatment through home-based HIV counseling and testing and facilitated referral in Kabwohe, Uganda and KwaZulu-Natal (KZN), South Africa. Treatment as Prevention. Vancouver, Canada; 2012.
11. Van Rooyen H, Phakathi Z, Krows M, et al. High Testing Uptake and Linkages to HIV Treatment through Home-based HIV Counseling and Testing and Facilitated Referral: KwaZulu-Natal, South Africa. CROI. Seattle; 2012.
12. Bobat R, Coovadia H, Coutsoudis A, Moodley D. Determinants of mother-to-child transmission of human immunodeficiency virus type 1 infection in a cohort from Durban, South Africa. *Pediatr Infect Dis J* 1996; 15(7): 604-10.
13. Horwood C, Vermaak K, Butler L, Haskins L, Phakathi S, Rollins N. Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of interventions for the prevention of mother-to-child transmission. *Bull World Health Organ* 2012; 90(3): 168-75.
14. Rollins N, Little K, Mzolo S, Horwood C, Newell ML. Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening. *AIDS* 2007; 21(10): 1341-7.
15. Adler WH, Baskar PV, Chrest FJ, Dorsey-Cooper B, Winchurca RA, Nagel JE. HIV infection and aging: mechanisms to explain the accelerated rate of progression in the older patient. *Mech Ageing Dev* 1997; 96(1-3): 137-55.
16. Mills EJ, Bakanda C, Birungi J, et al. Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. *AIDS* 2011; 25(6): 851-5.
17. Garnett GP, Gregson S. Monitoring the course of the HIV-1 epidemic: The influence of patterns of fertility on HIV-1 prevalence estimates. *Mathematical Population Studies* 2000; 8(3): 251-77.
18. Ott MQ, Bärnighausen T, Tanser F, Lurie MN, Newell ML. Age-gaps in sexual partnerships: seeing beyond 'sugar daddies'. *AIDS* 2011; 25(6): 861-3.
19. Anderson R, May R, Ng T, Rowley J. Age-Dependent Choice of Sexual Partners and the Transmission Dynamics of HIV in Sub-Saharan Africa. *Phil Trans R Soc London B* 1992; 336: 135 - 55.
20. Shisana O, Rehle T, Simbayi L, et al. South African nation HIV prevalence, incidence, behavior and communication survey 2008: A turning tide among teenagers? Cape Town, South Africa, 2008.
21. Burington B, Hughes JP, Whittington WL, et al. Estimating duration in partnership studies: issues, methods and examples. *Sex Transm Infect* 2010; 86(2): 84-9.
22. Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 2009; 9(2): 118-29.
23. The Epidemiology Unit. KwaZulu-Natal Epidemiology Bulletin: Weekly Monitoring System of the Antiretroviral Therapy for HIV/AIDS in KZN. Pietermaritzburg: KwaZulu-Natal Department of Health; 2005.
24. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009; 23(11): 1397-404.
References

25. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. 
   *N Engl J Med* 2011; 365(6): 493-505.
26. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral 
   therapy: a prospective cohort analysis. *Lancet* 2010; 375(9731): 2092-8.
27. Jahn A, Floyd S, Crampin AC, et al. Population-level effect of HIV on adult mortality and early evidence 
   of reversal after introduction of antiretroviral therapy in Malawi. *Lancet* 2008; 371(9624): 1603-11.
28. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men 
   who have sex with men. *N Engl J Med* 2010; 363(27): 2587-99.
29. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual 
   HIV transmission in Botswana. *N Engl J Med* 2012; 367(5): 423-34.
30. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled 
   intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. 
   *PLoS Med* 2005; 2(11): e298.
31. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: 
   a randomised trial. *Lancet* 2007; 369(9562): 657-66.
32. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: 
   a systematic review and meta-analysis. *AIDS* 2000; 14(15): 2361-70.
33. Hallett TB, Singh K, Smith JA, White RG, Abu-Raddad LJ, Garnett GP. Understanding the impact of male 
   circumcision interventions on the spread of HIV in southern Africa. *PLoS One* 2008; 3(5): e2212.
34. Williams BG, Lloyd-Smith JO, Gouws E, et al. The potential impact of male circumcision on HIV in Sub-
   Saharan Africa. *PLoS Med* 2006; 3(7): e262.
35. Barnabas RV. Mathematical Modelling of the Natural History of Human Papillomavirus Infection and 
   Cervical Carcinoma: The Impact of Intervention Strategies on Disease Incidence: University of Oxford; 2005.
36. South Africa Basic Indicators. http://www.unicef.org/infobycountry/southafrica_statistics.html.
37. Life Tables for WHO Member States: South Africa. Geneva: World Health Organization.
38. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human 
   immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000; 342(13): 921-9.
39. Bärnighausen T, Tanser F, Gqwede Z, Mbizana C, Herbst K, Newell ML. High HIV incidence in a 
   community with high HIV prevalence in rural South Africa: findings from a prospective population-based study. 
   *AIDS* 2008; 22(1): 139-44.
40. Motsoaledi P. Country Progress Report on the Declaration of Commitment on HIV/AIDS: Republic of 
   South Africa, 2010.
41. National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2009. Department of 
   Health; 2010.
42. Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. *Med Decis Making* 2002; 22(6): 
   475-81.
43. Smith JA, Sharma M, Levin C, et al. Cost-effectiveness of community-based strategies to strengthen the 
   continuum of HIV care in rural South Africa: findings from a systematic population-based study. 
   *AIDS* 2008; 22(1): 139-44.
44. Sharma M, van Rooyen H, Celum C, Baeten J, Levin C, Barnabas R. The Cost of Community Based HIV 
   Counseling and Testing and Linkage to Care in Rural South Africa: Estimates from the Linkages Randomized 
   Control Trial. HIV Research for Prevention. Cape Town; 2014.
45. Meyer-Rath G, Brennan AT, Fox MP, et al. Rates and cost of hospitalization before and after initiation of 
   antiretroviral therapy in urban and rural settings in South Africa. *Journal of acquired immune deficiency syndromes 
   (1999)* 2013; 62(3): 322-8.
V. Additional Model Outputs

Model Outputs for ART Scale-Up under 2013 and 2015 WHO ART Eligibility:

Figure S4. Viral suppression among people living with HIV over time. Viral suppression is a proxy for ART coverage.

Figure S5. HIV prevalence with optimistic ART coverage scenarios.
### Table S17. Incremental Cost-Effectiveness Ratios (ICER) for optimistic ART coverage scenarios.

| Scenario          | Total Incremental Cost Over Ten Years (Millions USD) | ICER per HIV Infection Averted | ICER per HIV-Related Death Averted | ICER per DALY Gained |
|-------------------|-----------------------------------------------------|--------------------------------|-----------------------------------|-----------------------|
| Current           | Baseline                                            | Baseline                       | Baseline                          | Baseline             |
| CD4 ≤ 500 cells/µL | $690                                                 | Dominated (234,000)             | $3,370 (206,000)                  | $2,710 (255,000)     |
| Test and Treat    | $1,330                                               | $2,620 (501,000)                | $4,310 (354,000)                  | $3,660 (430,000)     |

Figure S6. HIV incidence with optimistic ART coverage scenarios.
Model Outputs for the Impact and Cost-Effectiveness of Home HTC with Varying Campaign Frequency:

**HIV Prevalence by HTC Frequency**

![Graph showing HIV prevalence with varying frequencies of Home HTC]

- **Current ART**
- **1 yearly**
- **3 yearly**
- **5 yearly**
- **7 yearly**
- **No Intervention**

Figure S7. HIV prevalence with varying frequencies of Home HTC.

**HIV Incidence by HTC Frequency**

![Graph showing HIV incidence with varying frequencies of Home HTC]

- **Current ART**
- **1 yearly**
- **3 yearly**
- **5 yearly**
- **7 yearly**
- **No Intervention**

Figure S8. HIV Incidence with varying frequencies of Home HTC.
### Table S18. Incremental Cost-Effectiveness Ratios (ICER) for varying frequencies of Home HTC

| Frequency (years per campaign) | Total Incremental Cost over Ten Years (Millions USD) | ICER per HIV Infection Averted | ICER per HIV-related Death Averted | ICER per QALY Gained |
|-------------------------------|---------------------------------------------------|-------------------------------|----------------------------------|----------------------|
| 7                             | $1,316                                            | Dominated                      | Dominated                        | $780                 |
| 5                             | $1,573                                            | Dominated                      | Dominated                        | $790                 |
| 3                             | $2,029                                            | Dominated                      | Dominated                        | $870                 |
| 1                             | $3,136                                            | $4,600                         | $4,420                           | $1,280               |