In any month within H-DEF, the number of infected persons currently alive is the sum of the numbers of persons who had been infected over all preceding months and who have survived to the current month. Let $t$ denote the “calendar time” month within H-DEF, whereas $m$ indexes time since infection for an individual. Then $N_{\text{inf}}(t)$, the total number of HIV-infected individuals alive at the end of month $t$, is given by Equation 1:

$$N_{\text{inf}}(t) = \sum_{m=0}^{t} T(t-m) \ast p(m)$$

where $T(t)$ denotes the number of new infections that take place in a given month $t$ within H-DEF. The derivation of $T(t)$ is described below.

After projecting survival, the model next calculates the overall infectivity of all individuals who are alive and HIV infected in each month, based on their distribution of viral load levels. Let $I_v(m)$ indicate the proportion of living individuals who are in each viral load stratum in month $m$ since infection, where $v$ takes values between 0 and 6 corresponding to the viral load strata in the CEPAC-I model ($>100,000$ copies/mL, $30,001$-$100,000$ copies/mL, $10,001$-$30,000$ copies/mL, $3,001$-$10,000$ copies/mL, $501$-$3,000$ copies/mL, $51$-$500$ copies/mL, 0-$50$ copies/mL); the values of $I_v$ will sum to 1 for all $m$. 

doi: 10.1310/hct1505-231
To assess the average infectivity in month \( m \), the model multiplies these proportions by viral load–specific transmission rates, \( R_v \). These transmission rates represent the expected number of transmissions per person-month from an HIV-infected individual in a wholly susceptible population, and they are typically derived from studies of serodiscordant couples. The overall transmission rate is calculated by taking a weighted average of these rates, as shown in Equation 2:

\[
R_{avg}(m) = \sum_{v=0}^{6} I_v(m) \times R_v
\]

where \( R_{avg}(m) \) is a measure of average transmissions per person-month in month \( m \) since infection. Additionally, the user can specify the duration of an acute infection stage, during which the values of \( R_v \) are increased by a user-defined multiple.

As noted previously, \( t \) denotes the “calendar time” month within H-DEF, whereas \( m \) indexes time since infection for an individual. At time \( t \) in H-DEF, there are individuals who were infected at various prior times and who are at a variety of different months \( m \) since infection. Thus, to describe the transmission rate of all infected individuals alive during month \( t \), the number of persons infected \( m \) months ago (the summand in Equation 1) is multiplied by the average infectivity during month \( m \) since infection from Equation 2 and is summed over all prior months to the present time \( t \):

\[
B(t) = \sum_{m=0}^{t} T(t-m) \times p(m) \times R_{avg}(m)
\]

\( B(t) \) can be thought of as the number of infections that would occur if the population of infected individuals alive during month \( t \) were placed in an infinitely large susceptible population for 1 month. To make realistic transmission projections based on this, the model must next describe the characteristics of the actual susceptible population, taking into account the prevalence of infected (ie, nonsusceptible) persons.

Outcomes of susceptible individuals

H-DEF simulates a susceptible pool of individuals older than 15 years who do not have HIV. Rather than separately accounting for birth, death,
and in/out-migration, the model simply takes as input $E(t)$, the number of entrants to the susceptible pool in each month $t$; note that this value could be positive or negative, depending on the underlying rates of death, birth, and in/out-migration. This value is incorporated into calculating the number of susceptible individuals using Equation 4:

$$N_{susc}(t) = N_{susc}(t-1) - T(t) + E(t)$$ (4)

where $N_{susc}(t)$ is the number of susceptible individuals alive at the end of month $t$.

To determine the value of $E(t)$, the model requires outside data on historical and projected future population sizes in the region of interest, typically from organizations such as the United Nations or World Bank; we will denote by $N_{exp}(t)$ the expected total population size in each month $t$ based on such outside data. Using these data, the model calculates the values of $E(t)$ that are necessary to reproduce the expected total population size at the end of each month as follows:

$$E(t) = N_{exp}(t) - N_{inf}(t) - \left[N_{susc}(t-1) - T(t)\right]$$ (5)

For the first treatment strategy simulated, this calculation ensures that expected population sizes are matched exactly. When simulating an alternative HIV treatment strategy, the model then uses the $E(t)$ values calculated from the original strategy as inputs, which ensures that susceptible entry rates under the 2 treatment strategies are identical over time. This method produces population dynamics in H-DEF that (1) reflect historical data and detailed future population projections from outside sources and (2) vary between strategies only insomuch as the strategies affect the survival of HIV-infected individuals and incidence of HIV. That is, increased survival and decreased HIV incidence will not have the additional effect of increasing the number of births in subsequent years, as it might if population growth were modeled using a birth rate multiplied by present population size.

**Transmission calculations**

With the susceptible population characterized, H-DEF can now project $T(t)$, the number of new infections in each month $t$. First, the model calculates the prevalence of HIV in month $t$:

$$P(t) = \frac{N_{inf}(t)}{N_{inf}(t) + N_{susc}(t)}$$ (6)

To project new infections in month $t$, the proportion of susceptible individuals at the end of the preceding month, $1 - P(t-1)$, is first multiplied by $B(t-1)$, defined in Equation 3 as the expected number of infections that would be transmitted to a wholly susceptible population. To account for heterogeneous mixing and other departures from a susceptible-infected (SI) model with random mixing, we follow Williams et al and define $J$, a calibration term used to account for heterogeneity in infection risk across the population. To increase transmission rates observed among serodiscordant couples to levels reflective of the general population, we also introduce a transmission rate multiplier denoted by $H$. Using these terms, the number of new infections in month $t$, $T(t)$, is calculated using Equation 7:

$$T(t) = \left[1 - P(t-1)\right] B(t-1) * H * e^{-J * P(t-1)}$$ (7)

Without $e^{-J * P(t-1)}$, Equation 7 would simulate random mixing. $J$ adjusts this equation to capture the effects of heterogeneity in sexual mixing and transmission risk; namely, that HIV prevalence can reach saturation quickly in the highest risk subpopulations, leading to a rapid reduction in new infections as overall prevalence increases. For additional discussion of the data and assumptions underlying the use of an exponential structure to capture this heterogeneity, the reader is directed to the supplementary material from Williams et al.

Because the effects of $H$ and $J$ encompass many different dimensions of risk (eg, number of partners, age, condom use, transmission risk group, geographic location, etc), they cannot be estimated empirically. Instead, values of $H$ and $J$ are selected by using these parameters to calibrate the H-DEF model to match historical HIV prevalence data, as described below in the HIV epidemic calibration section.

**Cross-cluster contamination**

Simulating cluster-randomized trials introduces additional complexity. Specifically, there is potential for contamination between the trial arms (individuals in control clusters may have sexual
contacts in intervention clusters and vice versa). To account for this possibility, H-DEF allows for a portion of sexual contacts to occur between clusters. The user specifies this portion, \( c_j \), and the model adjusts the infectivity terms as shown in Equation 8, where \( B_{\text{Cont}}(t) \) and \( B_{\text{Int}}(t) \) denote the total transmission rates calculated for all individuals in the control and intervention arms in month \( t \), and \( B_{\text{Cont,adj}}(t) \) and \( B_{\text{Int,adj}}(t) \) denote the same terms following adjustment for cross-cluster contamination:

\[
B_{\text{Int,adj}}(t) = c_c \times B_{\text{Cont}}(t) + (1 - c_c) \times B_{\text{Int}}(t)
\]

\[
B_{\text{Cont,adj}}(t) = c_c \times B_{\text{Int}}(t) + (1 - c_c) \times B_{\text{Cont}}(t)
\] (8)

Of note, this cross-cluster mixing structure is used only when projecting the future outcomes of a cluster-randomized trial, and thus it has no impact on the calibration and validation to historical data.

**CEPAC-I Model Structure**

**Overview**

The CEPAC-I model is a stochastic microsimulation of the progression and outcomes of HIV disease in a hypothetical cohort of patients in resource-limited settings. “Microsimulation” means that the model generates individual patients and simulates each individual’s disease progression and treatment outcomes. “Stochastic” refers to a random number generator and set of estimated probabilities that are used to determine the sequence of movements between health states for a particular patient. Each individual patient’s clinical course is followed from the time of entry into the model until death. A running tally is maintained of all clinical events and the length of time spent in each health state. Upon the patient’s death, summary statistics are recorded and a new patient enters the model. This process is then repeated for a large number of simulated patients (statistical convergence can typically be achieved with cohort sizes of 1 million), at which point trajectories of survival and infectivity are calculated.

**Health states**

In the CEPAC-I model, health states are chosen to be descriptive of the patient’s current health, relevant history, and resource utilization patterns. They are designed to be predictive of clinical prognosis, including disease progression, immune system deterioration, development and relapse of different opportunistic diseases (ODs), response to treatment, and mortality. The model defines general categories of health states: chronic infection, acute complication, and death. Most of the time, patients are in one of the chronic states where (in the absence of treatment) progression of disease and immune CD4 decline take place. Patients who develop an acute complication (eg, an OD or drug-related toxicity) temporarily move to an acute health state, where mortality rates are higher. Deaths can occur from either a chronic or an acute state and can be attributed to a particular OD, chronic AIDS (eg, wasting), or non-AIDS-related causes.

The chronic and acute health states are stratified by actual current and nadir CD4 cell count (>500 cells/\( \mu \)L, 351-500 cells/\( \mu \)L, 201-350 cells/\( \mu \)L, 101-200 cells/\( \mu \)L, 51-100 cells/\( \mu \)L, and 0-50 cells/\( \mu \)L) and current and set point HIV RNA level (>100,000 copies/mL, 30,001-100,000 copies/mL, 10,001-30,000 copies/mL, 3,001-10,000 copies/mL, 501-3,000 copies/mL, 51-500 copies/mL, 0-50 copies/mL). Drawing from user-specified distributions of patient characteristics (age, sex, CD4 count, and HIV RNA level), a patient is randomly assigned to a health state upon model entry. By permitting the user to define initial population distributions for patient age, sex, CD4 cell count, HIV RNA, and other demographic and clinical attributes, the model has the flexibility to examine a broad range of different patient cohorts.

At the start of each 1-month time-step, the model records the patient’s CD4 count, HIV RNA level, history of acute illness, and current therapies and uses these characteristics to determine the probabilities of transition to a new state in the subsequent month. Monthly probabilities of events are estimated directly from published sources and available databases and translated into risk functions for the model. These risk functions embody the key parameters of the natural history of HIV illness, AIDS, and ODs, including rates of disease progression, OD risks, survival probabilities, and the effects of therapy.

In the absence of antiretroviral therapy (ART), a patient’s CD4 count will decline at rate determined by HIV RNA level, current CD4 count, a between-subject coefficient of variation, and within-subject variation from month to month. Mean decline rates and variability for each of the CD4 and HIV RNA levels are estimated directly from published sources and available databases and translated into risk functions for the model.
RNA states within CEPAC-I were derived from the Multicenter AIDS Cohort Study (MACS) dataset. Based on these values, CEPAC-I determines the CD4 decline experienced by each patient \(i\) in each month \(m\) according to Equation 9:

\[
CD4_{\text{dec}}(i, m) = \mu(C, v) \times \text{btwssubj}(i) + \text{wthnssubj}(i, m)
\]  

(9)

where \(\mu(C, v)\) is the mean CD4 decline rate in CD4 stratum \(C\) and HIV RNA stratum \(v\), \(\text{btwssubj}(i)\) is randomly drawn once for each patient from a normal distribution with mean 1 and user-specified standard deviation, and \(\text{wthnssubj}(i, m)\) is randomly drawn each month for each patient from a normal distribution with mean 0 and user-specified standard deviation. We have validated that these US-based data provide a reasonable surrogate for the dynamics between CD4 count and HIV RNA in the African setting and are consistent with CD4 decline rates observed in KwaZulu-Natal.

We are careful to distinguish in the model “actual” CD4 cell count and HIV RNA (ie, the underlying immunologic and virologic state, regardless of whether it is measured by a laboratory test) from “observed” CD4 cell count and HIV RNA (that which is measured by a test and upon which clinical decisions can be made). Clinical events within the model are predicated on a patient’s “actual” CD4 count and viral load status, whereas treatment decisions within the model are predicated on “observed” status.

### HIV testing and linkage to care

Previously undetected individuals are able to be diagnosed with HIV and linked to care in 2 ways:

1. A routine testing program, with tests offered at specified intervals.
2. A user-defined probability of diagnosis and linkage upon presentation with an OD.

For mechanism 2, the likelihood of test acceptance and the probability of linkage to care after a positive test are incorporated into the user-specified event probabilities. For mechanism 1, these probabilities are simulated explicitly. Any individuals who do not accept a test or fail to link to care after a positive test become eligible for screening in subsequent months.

Screening tests are assumed to give false-negative results during the first 1-month period (acute phase) after HIV infection. Thereafter, we assume 100% sensitivity and specificity of testing, reflecting the use of a screening algorithm incorporating multiple screening tests as well as HIV RNA testing to confirm HIV status.

### Clinical visits and laboratory monitoring

Upon HIV diagnosis and linkage, patients undergo a clinic visit and CD4 and HIV RNA testing. At this initial visit, if specific criteria (eg, CD4 <350 cells/μL) are met, patients will initiate prophylaxis and antiretroviral therapies. Subsequent clinic visits will then be scheduled at regularly specified intervals to determine whether ART eligibility criteria are met later (in control clusters). As with clinic visits, ongoing CD4 and HIV RNA testing occurs at regular intervals; other conditions may also trigger additional tests, including observed ART failures that require confirmation by CD4 or viral load, depending on the confirmation method specified by the user.

### ART and ART efficacy

The model has the capacity to simulate up to 10 lines of ART, to be administered sequentially. The current analysis focused in South Africa utilizes 2 sequential regimens. A patient will be evaluated for starting, stopping, or switching the ART regimen at every clinic visit. The criteria for regimen change can be specified differently for each individual regimen. Upon meeting criteria for ART initiation (or switching), the patient will be started on the first (or next) specified regimen.

A patient may be evaluated to start an ART regimen based on the following criteria: current CD4 count (if observable data are available), current HIV RNA (if observable data are available), a combination of CD4 count and HIV RNA, observed ODs since the previous regimen, or CD4 count and observed ODs. Because this structure enumerates the logical combinations of the individual criteria, they can be independently specified and evaluated. If the specified criteria are met, the patient will be started on that ART regimen. The first regimen criteria are evaluated at each clinic visit until treatment is initiated.

For the purposes of determining ART outcomes, patients in CEPAC-I are stratified by intrinsic ART adherence level (0%-100%, defined by medication
possibility ratio). The overall distribution of adherence values is modeled as a logit-normal distribution, with user-specified mean and standard deviation; each simulated patient draws his or her adherence level from this distribution at random and keeps that adherence level for the rest of his or her life.

ART outcomes (e.g., 6-month HIV RNA suppression) are dependent on an individual’s adherence level, with patients grouped into 3 categories: poor adherence (adherence less than some user-defined limit, $L_1$), high adherence (adherence greater than some user-defined limit, $L_2$), and moderate adherence (adherence between $L_1$ and $L_2$). Patients in the high adherence category all receive the same ART outcomes ($O_H$), as do patients in the poor adherence category ($O_P$); outcomes for moderately adherent patients are determined by interpolating between the highly adherent and poorly adherent groups:

$$
\text{outcome at adherence } L = O(L) = \frac{O_H - O_P}{L_2 - L_1} (L - L_1) + O_1
$$ (10)

Upon initiating an ART regimen, each patient receives an initial probability of achieving suppression; this probability is determined by the patient’s adherence level and an outcome function (Eq. 10), with initial suppression as the outcome of interest. Patients with very low adherence will have a minimal probability of achieving suppression, and those with high adherence will have a high probability of achieving suppression. Those patients who do achieve suppression will experience a rapid increase in CD4 count during the first 2 months on ART, followed by a slow increase for as long as they remain suppressed; the rates of these increases are drawn randomly from user-specified normal distributions. Patients who do not achieve suppression will experience a decline in CD4 count at the same rate as before starting ART.

Patients on suppressive ART are subject to a monthly probability of late virologic failure. As with initial suppression, this failure probability is dependent on adherence: Highly adherent patients will have a lower failure probability than poorly adherent patients. To allow sufficient time for initial HIV RNA suppression to occur, these failure probabilities are not assessed until 6 months after a regimen is begun. Thus, for a patient with adherence $L$, the probability of maintaining HIV RNA suppression $n$ months after starting a regimen is:

$$
p_{\text{Supp}}(L,n) = \begin{cases} 
O_{\text{initSupp}}(L), & n \leq 6 \\
O_{\text{initSupp}}(L) \times [1 - O_{\text{lateFail}}(L)]^{n-6}, & n > 6 
\end{cases}
$$ (11)

where $O_{\text{initSupp}}(L)$ is the probability of initial suppression at adherence level $L$, and $O_{\text{lateFail}}(L)$ is the monthly probability of subsequent failure at adherence level $L$.

Those patients who do fail ART after initially achieving suppression will experience a gradual return to HIV RNA set point. Their CD4 counts will remain stable for a lag period of user-specified duration before beginning to decline.

The model makes a distinction between patients actually failing an ART regimen and those who are observed to fail a regimen. The former can be regarded as patients in whom therapy stops providing any substantive biological benefit to the patient. The latter simulates the clinical observation of a new OD, or laboratory detection of CD4 decline or viral load increase, indicating a regimen’s lack of continued benefit. After observed regimen failure, patients may be taken off the failing regimen and switched to a new regimen.

Upon laboratory-observed and confirmed failure, patients are given an opportunity to resuppress on first-line therapy with adherence reinforcement. As with initial regimens, the likelihood of resuppression is adherence-dependent. Because the CEPAC-I model is stochastic, a patient’s intrinsic likelihood to adhere, along with the suppression function, determines only the chance of being suppressed on a given regimen. Thus, when faced with a second opportunity to become suppressed on the same regimen, the patient still has the possibility of suppressing even if he or she was previously unsuppressed. The events are drawn independently. Patients with persistence or recurrence of virologic failure are then switched to a protease inhibitor–based second-line regimen. Reflecting the lower likelihood of developing clinically significant resistance on a protease inhibitor–based regimen, patients have 2 opportunities to resuppress following detected failure of second-line ART.
Cohort characteristics by baseline state

We specified the characteristics (age, CD4 counts, etc) of the individuals in each baseline state separately. Sources for these characteristics are described below:

**Acute infection.** Acutely infected patients had an initial CD4 count distribution of mean (SD) 560 (230) cells/μL, modeled as a truncated normal distribution fit to the reported CD4 cell counts at seroconversion from the CASCADE cohort. Their mean (SD) age was 23 (6) years, based on the age distribution of newly infected individuals in a study from KwaZulu-Natal. Sixty-nine percent of newly infected patients were female, based on estimates from the ACDIS; this gender distribution was used for all baseline states. The distribution of set point HIV RNA levels, also used for all other baseline states, was derived to match the distribution reported from the Hlabisa cohort (eTable 1).

**Undiagnosed, chronically infected.** At baseline, chronically infected undiagnosed patients had a mean (SD) CD4 count of 430 (270) cells/μL; this was derived by fitting a normal distribution to the reported CD4 counts of newly diagnosed individuals from a population serosurvey in Cape Town. The mean (SD) age of undiagnosed patients was 27 (8) years; this was based...
on the assumption that undiagnosed individuals would have an age distribution between that of acutely infected (23 years) and diagnosed, off-ART (30 years) individuals.

**Diagnosed, off ART.** Diagnosed individuals who were not on ART had a mean (SD) CD4 of 390 (220) cells/μL, based on data from ACDIS.\(^{28}\) Off-ART individuals had a mean (SD) age of 30 (10) years, based on data from the Hlabisa cohort.\(^{29}\)

**On first-line ART.** Patients on first-line ART had a mean (SD) CD4 of 380 (190) cells/μL, based on the CD4 distribution of on-ART individuals from ACDIS.\(^{28}\) Mean (SD) age was 35 (10) years, based on on-ART patients from the Hlabisa cohort.\(^{29}\)

**On second-line ART.** Patients on second-line ART were assumed to have the same CD4 distribution as those on first-line, consistent with reported immunologic outcomes of second-line ART in Limpopo province.\(^{30}\) We assumed that these individuals would have a mean age 2 years greater than those on first-line, based on the reported time

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**eTable 1. Additional model input parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case value</th>
<th>Range</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><strong>Epidemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial adult HIV prevalence, %(^{a})</td>
<td>23</td>
<td>17-27</td>
<td>21, 39</td>
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<tr>
<td>Monthly susceptible entrants</td>
<td>Calibrated</td>
<td>± 20%</td>
<td>36, 37</td>
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<tr>
<td>Calibrated sexual mixing heterogeneity parameter(^{b})</td>
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<td>1.16-1.74</td>
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<tr>
<td><strong>Cohort characteristics</strong></td>
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<td>Set point HIV RNA, % of HIV-infected(^{c})</td>
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<td></td>
</tr>
<tr>
<td>&lt; 3,000 copies/mL</td>
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<td>29</td>
<td></td>
</tr>
<tr>
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<td>29</td>
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<td></td>
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<tr>
<td>&gt; 100,000 copies/mL</td>
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<tr>
<td>Male/female sex, %</td>
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<tr>
<td>Mean (SD) age, years(^{c})</td>
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<td>Acute infection</td>
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<td>Undiagnosed, chronic</td>
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<tr>
<td>Diagnosed, off ART</td>
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<td>18–45</td>
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<tr>
<td>On first-line ART</td>
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<td>18–45</td>
<td>29</td>
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<tr>
<td>On second-line ART</td>
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<td>18–45</td>
<td>29, 31</td>
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<td><strong>HIV testing</strong></td>
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<td>Duration of false-negative tests after infection, months</td>
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<td><strong>ART efficacy</strong></td>
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<td>CD4 increase on suppressive ART, cells/μL/month</td>
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<td>Months 1-2</td>
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<td>40–110</td>
<td>32(^{d})</td>
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<td>Months 3+</td>
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<td>2–6</td>
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<td><strong>Natural history</strong></td>
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<td>Opportunistic disease incidence, per 100 PY(^{e})</td>
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<td>Stage III-IV visceral</td>
<td>0.4–17.2</td>
<td>± 50%</td>
<td>7(^{d})</td>
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<tr>
<td>Stage III-IV nonspecific</td>
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<tr>
<td>Tuberculosis</td>
<td>0.3–21.1</td>
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</tbody>
</table>

\(^{a}\)HIV prevalence at the end of calibration, in between prevalence estimates from sources used for calibration.

\(^{b}\)The sexual mixing heterogeneity parameter is calibrated to match historical HIV prevalence trends in KwaZulu-Natal.

\(^{c}\)Distributions calibrated to results reported in reference.

\(^{d}\)Model input value derived from primary data described in reference.

\(^{e}\) Opportunistic disease incidence varies with current CD4 count. Other disease categories included in the CEPAC-I model include mild fungal, other mild, visceral bacterial, and other severe.
to failure of first-line and switch to second-line in South African patients on ART.31

**ART efficacy**

ART efficacy parameter values were derived using patient-level data from individuals initiating first-line ART in the VOLTART cohort in Côte d’Ivoire.32,33 First, patients were stratified by adherence level, defined by medication possession ratio over a 12-month period. We evaluated the proportion of patients within each adherence stratum with undetectable HIV RNA at 6 months after regimen initiation and then used a linear outcome function (see Eq. 10) to replicate these adherence-specific suppression rates (see Table 1, in the article).

To determine rates of subsequent ART failure, we evaluated virologic suppression at 12 months within each adherence stratum. For each stratum, we then calculated the rate of virologic failure between 6 and 12 months (assuming a constant exponential decay in suppression), then used a linear outcome function to match these adherence-specific virologic failure rates (see Table 1, in the article).

**ART resuppression**

To assess the likelihood of resuppression on first-line ART after virologic failure, we pooled results from 7 studies of outcomes of adherence reinforcement in patients with virologic failure on first-line ART (5 of which were included in a recent meta-analysis by Bonner et al).17,34,35 HIV RNA thresholds, definitions of failure and resuppression, and time horizon varied substantially between studies; across all 7 studies, the proportion achieving resuppression varied from 41% to 92%. Using a weighted average, we found an overall resuppression rate of 50%.

We simulated resuppression using similar 6-month HIV RNA suppression parameters to initial first-line ART, but with a reduction in the probability of suppression across all adherence levels; we found that a 30% relative reduction in the probability of suppression reproduced the 50% resuppression from our pooled analysis above.

Given the lower likelihood of developing major resistance after failure of protease inhibitor–based regimens,19 patients were given 2 opportunities to resuppress following second-line ART. We used the same parameter values to model patients’ first opportunity to resuppress after second-line failure. To model the second resuppression opportunity, we assumed an additional reduction in the probability of suppression by a relative 25%. For patients who achieved resuppression on any line, we assumed the subsequent adherence-specific failure rates were the same as after initial suppression (see Table 1, in the article).

Resuppression probability following an adherence intervention was varied widely in sensitivity analysis, from a lower bound of zero resuppression to an upper bound of efficacy equivalent to initial first-line and second-line ART.

**Population data**

Age-stratified, historical population data came from the World Bank online database; we used these data to calculate the population aged >15 years in South Africa for every year from 1960 to 2011. Age-stratified population projections, at 5-year intervals from 2015 to 2100, came from the United Nations Population Division.37

Based on population size estimates from the South African Central Statistical Service, KwaZulu-Natal has comprised very close to 21% of the total South African population for every year between 1991 and 2011.38 We therefore used a multiplier of 0.21 to convert the data on adult population in South Africa to adult population in KwaZulu-Natal. Finally, we used linear interpolation between the annual/5-year time-points to estimate the population size on a monthly basis (eFigure 3).

**HIV Epidemic Calibration**

To parameterize the model’s estimates of HIV transmission rates and sexual mixing, we calibrated the model to historical HIV prevalence, incidence, and ART coverage data in KwaZulu-Natal. Three sources were used for these data: first, estimates of HIV prevalence by 5-year age
Initially, all newly HIV-infected persons entering the H-DEF model were set to never receive ART. Beginning in 1994, a proportion of the newly infected persons in each month were assigned to receive ART after 10 years; beginning in 1999, an additional fraction of the newly infected individuals were assigned to receive ART after 5 years; and beginning in 2004, some could receive ART immediately. By varying these proportions over the course of ART rollout, the ART coverage rates reported from ACDIS could be smoothly replicated.

After fitting ART coverage data, historical prevalence data were replicated by varying the values of $H$ (the transmission rate multiplier), $J$ (the sexual mixing heterogeneity parameter), and the initial HIV prevalence at the start of the H-DEF simulation (1980).

To calibrate to these data, the model was initialized in 1980 with a very low HIV prevalence (<10 per million). Several parameters were varied in this process. First, historical ART coverage rates were replicated by performing several runs of the CEPAC-I model with differing durations between the time of infection and the availability of ART (never, 10 years, 5 years, immediate). Initially, all newly HIV-infected persons entering the H-DEF model were set to never receive ART. Beginning in 1994, a proportion of the newly infected persons in each month were assigned to receive ART after 10 years; beginning in 1999, an additional fraction of the newly infected individuals were assigned to receive ART after 5 years; and beginning in 2004, some could receive ART immediately. By varying these proportions over the course of ART rollout, the ART coverage rates reported from ACDIS could be smoothly replicated.

After fitting ART coverage data, historical prevalence data were replicated by varying the values of $H$ (the transmission rate multiplier), $J$ (the sexual mixing heterogeneity parameter), and the initial HIV prevalence at the start of the H-DEF simulation (1980).

The 2 sources’ HIV prevalence estimates diverge somewhat over the period 2004 to 2011. Compared to the ASSA estimates, the ACDIS prevalence results are initially lower (19.0% vs 19.8% in 2004)
and end up higher (24.4% vs 20.0% in 2011). Given this divergence, we set the values of the 3 calibration parameters to produce a prevalence curve in between the 2 sets of estimates, ensuring that our historical simulation captured some of the increase in prevalence during the period of ART rollout reported by Zaidi et al (see Figure 1, in the article). These calibrated values of $J$ (eTable 1) and $H$ (see Table 1, in the article) were used in the main analysis, and then varied widely in sensitivity analysis.

The estimates of HIV incidence were calculated within H-DEF as a result of the prevalence and ART coverage calibration. Though our estimates of HIV incidence decline more slowly than that of ASSA 2008 data, they remain reasonably close to the large population-based survey by Bärnighausen et al. during the period of 2003-2007. We note that ASSA 2008 is, itself, a model, and it has been argued that ASSA 2008 estimates are low in ART coverage, HIV prevalence, and HIV incidence.41

H-DEF Model Validation

To assess the predictive validity of the H-DEF model, we compared model projections to HIV prevalence estimates for each of South Africa’s provinces from the Human Sciences Research Council HIV survey (HSRC).42,43 HSRC’s prevalence estimates covered adults aged 15-49 years; as above, we used age-specific prevalence ratios from ASSA 2008 to convert the HSRC data to >15 year prevalence estimates.

For each South African province, we varied H-DEF’s 3 calibration parameters ($H$, $J$, and initial prevalence) to fit ASSA 2008 estimates of HIV prevalence from 1990 to 2004. The calibrated parameter values in each province were then held constant and the H-DEF model was allowed to run through 2012 (using ART rollout rates as described above). For each province and for the country as a whole, we then compared the 2012 HIV prevalence values projected by H-DEF to the 2012 prevalence estimates from the HSRC survey. These estimates were released in mid-2013 (after the publication of the ASSA 2008 model estimates) and thus were fully independent from the H-DEF calibration through 2004.

As shown in eFigure 4, H-DEF produced realistic prevalence projections for all 9 provinces and for the country as a whole. Absolute deviations from the HSRC’s 2012 prevalence estimates varied between 0.1% (national) and 3.7% (Mpumalanga). H-DEF’s projections of 2012 HIV prevalence were closer to the HSRC estimates than were ASSA 2008’s projections in 6 of the 9 provinces (Eastern Cape, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, and Western Cape) and for the country as a whole. These findings suggest that H-DEF can produce realistic predictions of the evolution of an HIV epidemic over a short time horizon and across a range of HIV prevalence levels.

Supplemental Results

One-way sensitivity analysis

eTable 2 shows the results of one-way sensitivity analyses on 3 parameters in the intervention arm alone: rate of loss to follow-up, linkage to care after a positive HIV test result, and first-line ART suppression at 6 months for patients with adherence >95%. Results are expressed as the change in incidence reduction compared to the base case (shaded column) and are provided for the initial trial and both alternative trial characteristics. The most influential of the 3 parameters was first-line ART suppression, where reducing suppression by 20% diminished the incidence reduction by as much as 7% under an ART initiation threshold of CD4 <500/μL.

Alternative trial characteristics

eFigure 5, analogous to Figure 3 in the text, shows the effect of various parameters on the magnitude of incidence reduction associated with the intervention arm at the previous WHO ART initiation threshold of CD4 <350/μL. Similar trends were observed as those at a threshold of CD4 <500/μL (main text, Figure 3) but with greater magnitude. Increased trial time horizon, more frequent HIV testing in the intervention arm, and less frequent HIV testing in the control arm all increased the trial effect size and led to greater HIV incidence reduction.
eFigure 4. Epidemic model validation. The graphs show adult HIV prevalence over time estimated by the Actuarial Society of South Africa (ASSA) 2008 model (x), the Human Sciences Research Council National HIV survey (o), and the HIV Dynamic Epidemic Framework (H-DEF, –) model for each of South Africa's 9 provinces, along with national estimates. For each province, H-DEF model parameters were calibrated to match ASSA 2008 prevalence estimates from 1990-2004, then the H-DEF model was allowed to run through 2012. Between provinces, calibrated values of H, J, and 1980 HIV prevalence ranged from 1.9-2.1, 1.6-6.7, and 0.2-1.2 per million.
**eTable 2. Absolute change in incidence reduction compared to base case when varying parameter value in intervention arm alone**

<table>
<thead>
<tr>
<th>Parameter varied in intervention arm:</th>
<th>Base case inputs unchanged</th>
<th>Loss to follow-up rate</th>
<th>Linkage to care after positive test</th>
<th>First-line ART suppression, adherence &gt;95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative change in intervention arm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART at CD4 &lt;350/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>21%</td>
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<td>-4%</td>
</tr>
<tr>
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<td>-1%</td>
<td>-2%</td>
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<tr>
<td>Maximal</td>
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<td>-1%</td>
<td>-1%</td>
</tr>
<tr>
<td>ART at CD4 &lt;500/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>12%</td>
<td>0</td>
<td>0</td>
<td>-4%</td>
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<tr>
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<td>-2%</td>
</tr>
<tr>
<td>Maximal</td>
<td>41%</td>
<td>+1%</td>
<td>-1%</td>
<td>-2%</td>
</tr>
</tbody>
</table>

*In the base case, 91% of patients with >95% adherence achieve suppression after 6 months on first-line antiretroviral therapy (ART); thus, the highest possible value (100%), constitutes a 10% increase.

**eFigure 5.** Incidence reduction with varying trial characteristics. Projected trial incidence reduction with an antiretroviral therapy (ART) initiation threshold of CD4 <350/μL and varying combinations of control strategy HIV test frequency (6-36 months), intervention strategy HIV test frequency (1-6 months), and trial horizon (24-48 months). The shading at each point in the figure denotes the projected incidence reduction with that combination of trial design characteristics. Three scenarios are highlighted for further analysis (see Methods section for descriptions of these scenarios): (1) initial, square; (2) intensified, circle; (3) maximal, triangle. The predicted incidence reduction for each of these scenarios is shown in the legend.
REFERENCES


