SUPPLEMENTAL DIGITAL CONTENT –

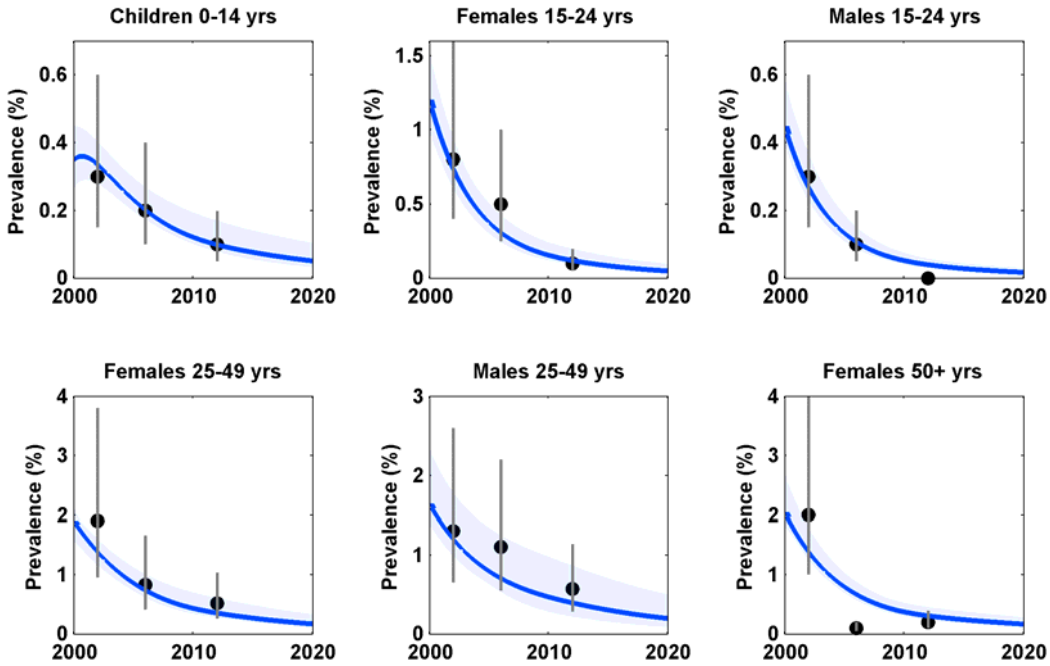
Technical appendix

I. Calibration of the Optima model to the HIV epidemic

To investigate the HIV epidemic in Niger the model is calibrated to available epidemiological data. The calibration process involves finding posterior distributions of the model parameter values such that the model generates accurate prevalence estimates. Given the challenges inherent in quantifying all known constraints on the epidemic, we initially calibrated the model manually. We then enter the resulting prior distributions in a Monte Carlo Markov chain (MCMC) algorithm, which uses both epidemiological and behavioral data to calculate the log-likelihood for a given set of model parameters. The parameter value distributions obtained by the MCMC represent the posteriors, which we use for all our epidemiological and economic analyses.

We used all available demographic, epidemiological, behavioral, and clinical data to calibrate Optima to the HIV epidemic in Niger (figure A1 and A2). In general, prevalence in Niger is declining rapidly in most population groups, due to both reductions in incidence and deaths of people currently living with HIV. Exceptions include MSM, migrants, and prisoners, for whom there are not sufficient data to confidently determine epidemic trends; however, current indications are that HIV prevalence is relatively stable among these populations.

Figure A1: Calibration of model to the HIV epidemic in Niger. Black discs represent available data for HIV prevalence. Lines attached to these discs represent uncertainty bounds, where available. The solid curve is the best fitting simulation and the light band represents the 95% confidence interval for the model outputs**.**



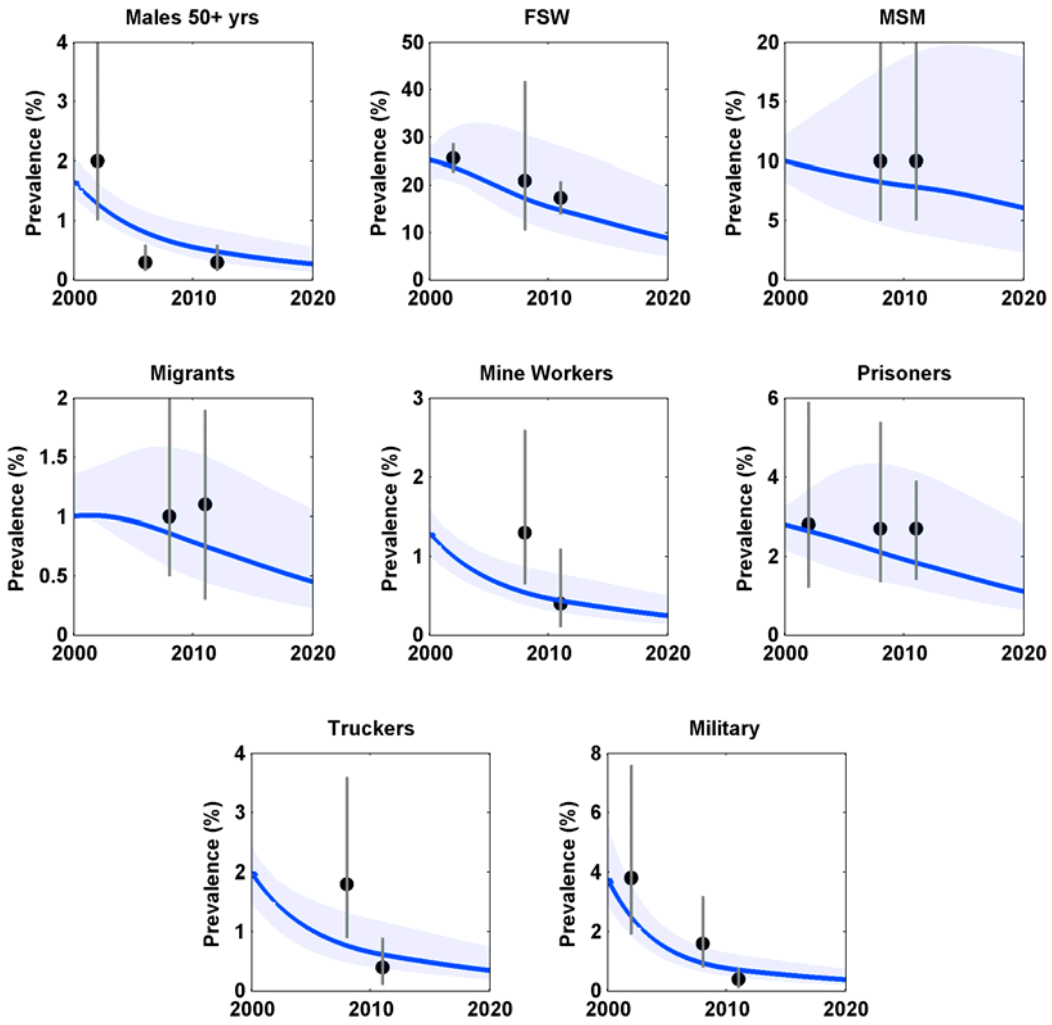
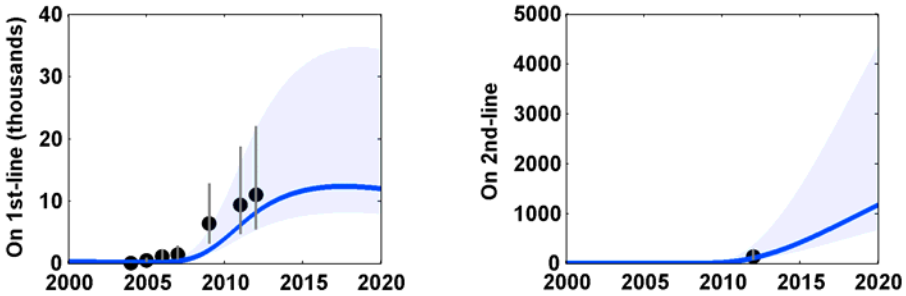


Figure A2: Calibration of model to the HIV epidemic in Niger. Black discs represent available data for the number of people on first and second line anti-retroviral treatment. Lines attached to these discs represent uncertainty bounds, where available. The solid curve is the best fitting simulation and the light band represents the 95% confidence interval for the model outputs**.**

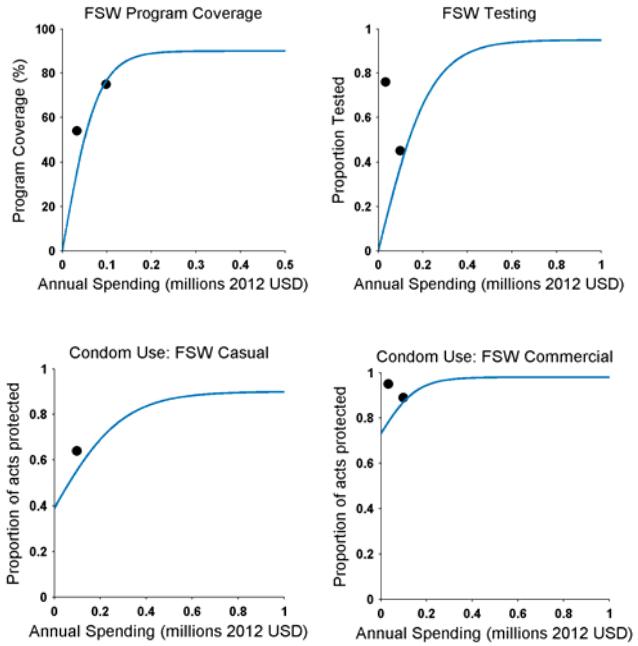


II. Cost-outcome relationships and assumptions

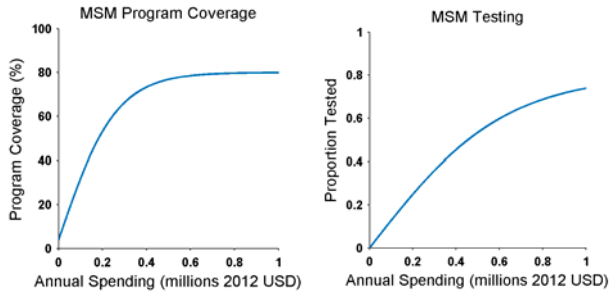
Our analysis requires specific cost-outcome relationships for each population and HIV program. In our analysis, we used logistic/sigmoid functions to describe the relationships between an outcome of a program (such as a change in coverage, condom use, or number on ART) and the total cost for implementing the program. We fit these cost-outcome curves to available data as best as possible. Using these relationships, any change in HIV program funding directly affects risk behaviors and changes the HIV epidemic.

All the cost-outcome relationships for Niger are shown in the figures below with a description of the assumptions we used to create these relationships for each package.

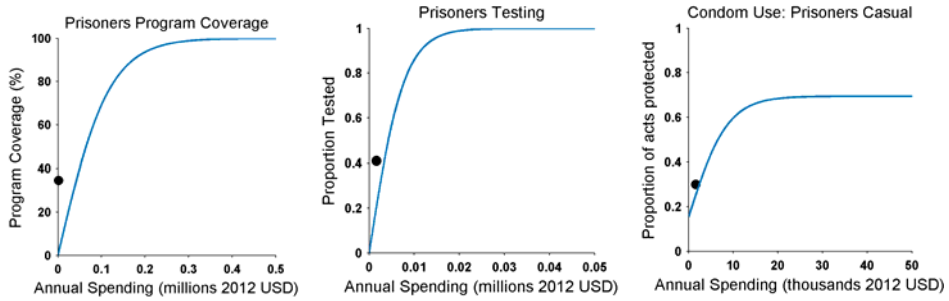
Targeted FSW intervention package: In the model, we assume the targeted FSW intervention package affects FSW testing and condom use (the actual service package for FSW in Niger includes HCT, condom provision, and mobilization activities which sometimes involve peer education). Available testing data for FSW in Niger on reports "ever tested" rather than testing in the previous year, hence the data values are upper bounds on the annual testing rate. We assumed the testing data for the higher and more recent spending value is more accurate.



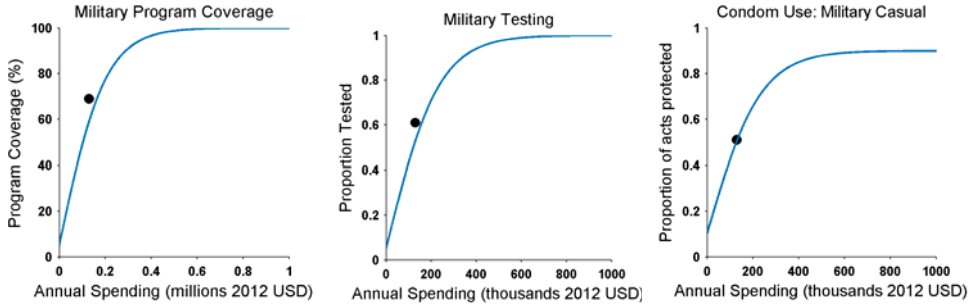
Targeted MSM intervention package: There is no overall spending data available for this package. We created subjective cost-outcome curves based on a per package delivery cost of USD 78 from Niger's government endorsed Resource Needs Model. We assumed this package affects MSM testing. Given the lack of behavioral data for MSM, we could not create a specific relationship between MSM package spending and condom use. Therefore, we assumed the same cost-condom-use relationship as for the condom promotion package below.



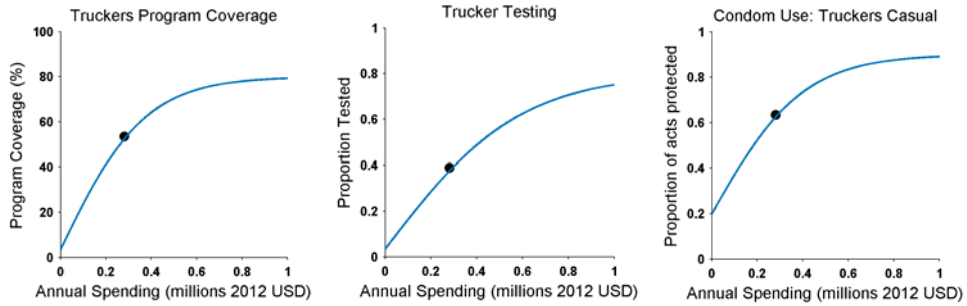
Prevention services targeted at prisoners: We assumed this program affects testing and casual condom use. Given prisoners are easily accessible we assumed a 100% coverage and testing rate as the theoretical maximum.



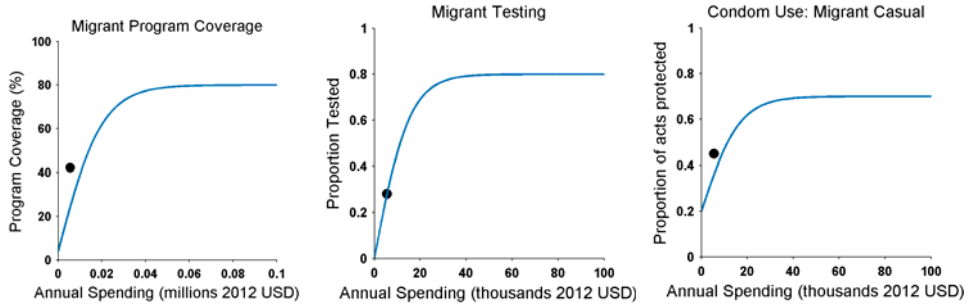
Prevention services targeted at uniformed security personnel: We assumed this program affects testing and casual condom use. We assumed it is relatively easy to provide this program to all uniformed security personnel and assumed a 100% coverage and testing rate for the theoretical maximum.



Prevention services targeted at truckers: We assumed this program affects testing and casual condom use in truckers based on the available data for Niger.

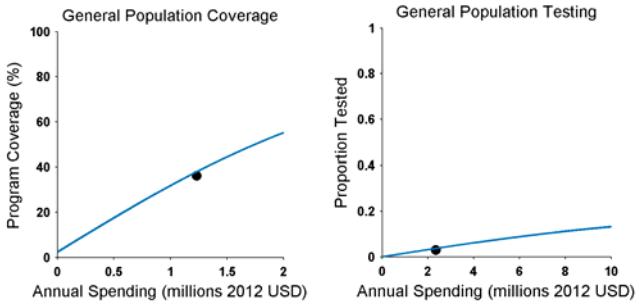


Prevention services targeted at labor migrants: We assumed this program affects testing and casual condom use in truckers based on the available data for Niger.

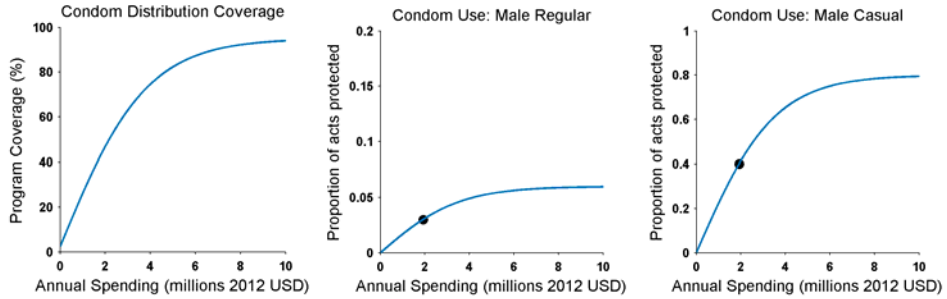


Prevention services targeted at mine workers: There is no overall spending data available for this package. We assumed this program affects testing and casual condom use in mine workers. We subjectively created the curves using the assumed minimum and maximum values. The shape of the curve was informed by the available data for casual condom use in low-risk males.

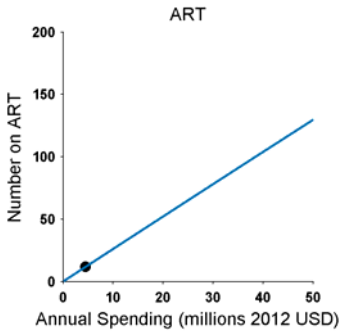
Prevention services for general population: We assumed this program only affects testing with condom use in the general population determined by the spending on public and commercial condom distribution and social marketing of condoms below.



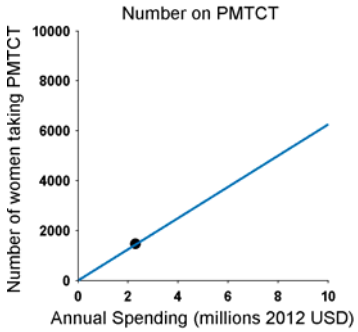
Public and commercial sector condom distribution and social marketing of condoms – General population: We assumed condom distribution programs only affects casual and regular condom use in male populations. The curve for commercial condom use for the targeted FSW intervention package determines condom use between FSW and their clients (commercial partnerships). Given the lack of data for most of the male population, we assume casual and regular condom use has the same value for all male populations, unless already specified in the outcomes for a targeted package.



Antiretroviral treatment (ART) services: Using the data for the number of people on ART, we created a linear cost-outcome relationship. The slope of this curve represents the unit cost of providing ART.



Prevention of mother-to-child transmission of HIV (PMTCT): Using the data on the number of HIV+ pregnant women who received PMTCT, we generated a unit cost relationship between women receiving PMTCT and cost (as for ART).



III. HIV epidemic model

Optima is based on a dynamic, population-based HIV model; **Figure A1B** shows the disease progression implemented in the model. Optima tracks the entire population of people living with HIV (PLHIV) across four stages of CD4 count (the CD4 count stages are aligned to the progression of WHO treatment guidelines). Key aspects of the antiretroviral therapy (ART) service delivery cascade are included: from infection to diagnosis, ART initiation on first-line therapy, treatment failure, second-line therapy, and HIV/AIDS-related or other death. The primary purpose of HIV testing is to identify those who are HIV-positive. With the new UNAIDS global targets of 90% of PLHIV identified by 2020, 90% of them on treatment, and 90% of these virally suppressed, the structure of the disease progression model in Optima is designed to help countries measure and achieve this goal, and optimize resource allocations accordingly.

The model uses a linked system of ordinary differential equations to track the movement of PLHIV between HIV health states; the full set of equations is provided in the supplementary material. The overall population is partitioned in two ways: by population group and by HIV health state. Individuals are assigned to a given population group based on their dominant risk. However, to capture important cross-modal types of transmission, relevant behavioral parameters can be set to nonzero values (e.g., males who inject drugs may engage in commercial sex; some MSM may have female sexual partners).

HIV infections occur through the interaction between different populations via regular, casual, or commercial (including transactional) sexual partnerships, through sharing of injecting equipment, or through mother-to-child transmission. The force of infection is the rate at which uninfected individuals become infected, and it depends on the number and type of risk events to which individuals are exposed in a given period (either within their population groups or through interaction with other population groups) and the infection probability of each event. Mathematically, the force-of-infection has the form:

$$\lambda = 1 - (1 - \beta)^n$$

where λ is the force-of-infection, β is the transmission probability of each event, and n is the effective number of at-risk events (i.e., n gives the average number of interaction events with HIV-infected people where HIV transmission may occur). The value of the transmission probability β varies across CD4 count compartments (indirectly reflecting the high viral load at early and late stages of infection), differs for different modes of transmission (intravenous drug injection with a contaminated needle-syringe, heterosexual intercourse, homosexual intercourse, and mother-to-child), and may be reduced by behavioral interventions (for example, condom use or male circumcision) or antiretroviral therapy There is one force-of-infection term for each type of interaction (for example, casual sexual relationships between general males and female sex workers); the force-of-infection for a given population will be the sum of all interaction types.

For sexual transmission, the force-of-infection is determined by:

- The HIV prevalence (weighted by viral load) in partner populations;
- The average number of casual, regular, and commercial homosexual and heterosexual acts per person per year;
- The proportion of these acts in which condoms are used;

- The proportion of men who are circumcised;
- The prevalence of ulcerative STIs (which increase transmission probability);
- The proportion of partners on antiretroviral treatment (ART); and
- The efficacies of condoms, male circumcision, and ART at preventing HIV transmission.

For injecting-related transmission, the force-of-infection is determined by:

- The HIV prevalence (weighted by viral load) in populations of people who use a syringe and then share it);
- The number of injections per person per year;
- The proportion of injections that use shared equipment;
- The proportion of injections that use shared equipment that has been cleaned, and the efficacy of this cleaning; and
- The fraction of people who inject drugs on opioid substitution therapy and its efficacy in reducing injecting behavior.

For mother-to-child transmission (MTCT), the number of infections is determined by:

- The birth rate among women living with HIV;
- The proportion of women with HIV who breastfeed;
- The probability of perinatal HIV transmission in the absence of intervention; and
- The proportion of women receiving prevention of mother-to-child transmission (PMTCT), including ART.

In addition to the force-of-infection rate, which moves individuals from uninfected to infected states, there are seven other ways individuals may change health states. First, individuals may die, either due to an average background death rate for that population (which is greater for older populations or for people who inject drugs) or due to HIV/AIDS (which depends on CD4 count). Second, in the absence of treatment, individuals progress from higher to lower CD4 counts. Third, individuals can move from undiagnosed to diagnosed states based on their HIV testing rate, which depends on CD4 count (for example, people with AIDS symptoms or primary HIV infection may have a higher testing rate) and population type (for example, female sex workers may test more frequently than general males). Fourth, diagnosed individuals may commence ART, at a rate depending on CD4 count. Fifth, individuals may experience treatment failure due to lack of adherence to therapy or development of drug resistance, and sixth, people may initiate second-line treatment from treatment failure. Finally, while on successful first- or second-line treatment (i.e. effective viral suppressive therapy), individuals may progress from lower to higher CD4 counts.

The change in the number of people in each compartment is determined by the sum over the relevant rates described above multiplied by the population size of the compartments on which they act. For example, the change in the number of undiagnosed HIV-positive female sex workers with a CD4 count between 200 and 350 cells/μL is:

$$\frac{dU_{FSW200-350}}{dt} = U_{FSW_{350-500}}\tau_{350-500} - U_{FSW_{200-350}}(\mu_{200-350} + \tau_{200-350} + \eta_{FSW_{350-500}})$$

where $U_{FSW_{200-350}}$ is the current number of undiagnosed HIV-positive female sex workers with a CD4 count between 200 and 350 cells/μL, $U_{FSW_{350-500}}$ is the same population but with higher CD4 count (350–500 cells/μL), τ is the disease progression rate for the given CD4 count (where $1/\tau$ is the average time to lose 150 CD4 cells/μL), μ is the death rate, and η is the HIV testing rate. (Note: this example does not consider movement between populations, such as female sex workers returning to the general female population and vice versa.) Each compartment (**Figure A1B**, boxes) corresponds to a single differential equation in the model, and each rate (**Figure A1B**, arrows) corresponds to a single term in that equation.

Table 1 lists the parameters used in Optima; most of these are for calculating the force-of-infection. We interpret empirical estimates for model parameter values in Bayesian terms as prior distributions. The model must then be calibrated, which is the process of finding posterior distributions of the model parameter values

such that the model generates accurate estimates of HIV prevalence, the number of people on treatment, and any other epidemiological data that are available (e.g., HIV-related deaths). The calibration can be done automatically, manually, or a combination of both. This process of model calibration and validation should normally be done in consultation with governments in those countries where the model is being applied.

TABLE 1: INPUT PARAMETERS OF THE MODEL.

	Biological parameters	Behavioral parameters	Epidemiological/other parameters
Population parameters	Background death rate		Population sizes (TP)
HIV-related parameters	Sexual HIV transmissibilities* (H) STI-related transmissibility increase* Condom efficacy* Circumcision efficacy* HIV health state progression rates (H) HIV-related death rates (H)	Number of sexual partners* (TPS) Number of acts per partner* (S) Condom usage probability* (TP) Circumcision probability* (T)	HIV prevalence (TP) STI prevalence (TP)
MTCT parameters	Mother-to-child transmission probability*	Birth rate* PMTCT access rate* (T)	
Injection-related parameters	Injecting HIV transmissibility* Syringe cleaning efficacy* Drug-related death rate	Number of injections* (T) Syringe sharing probability* (T) Syringe cleaning probability* Methadone treatment probability (T)	
Treatment parameters	ART efficacy in reducing infectiousness* ART failure rates	HIV testing rates (TPH)	Number of people on ART (T)
Economic parameters	Health utilities		Costs of all prevention, care and treatment programs, enablers and management (TI) Cost-outcome curves (TI) Discounting and inflation rates (T) Healthcare costs

Key: T = parameter value changes over time; P = parameter value depends on population group; H = parameter depends on health state; S = parameter depends on sexual partnership type; I = parameter depends on intervention type; * = parameter is used to calculate the force-of-infection.

HIV resource optimization and program coverage targets

A novel component of Optima is its ability to calculate allocations of resources that optimally address one or more HIV-related objectives (e.g., impact-level targets in a country's HIV national strategic plan). Because Optima does not presuppose program coverage changes, but instead calculates the coverage levels required to achieve impact-level targets, it can be used to inform HIV strategic planning and the determination of program coverage levels. The key assumptions of resource optimization are the relationships between (a) the cost of HIV prevention and treatment programs, (b) the resulting coverage levels of targeted populations, and (c) how these coverage levels of programs influence behavioral, clinical and epidemiological outcomes. Such relationships are required to understand how incremental changes in spending affect HIV epidemics. A traditional approach is to apply unit cost values to inform a linear relationship between money spent and coverage attained. This is a reasonable assumption for programs like an established ART program that no longer incurs start-up or initiation costs, but less appropriate for condom promotion and behavior change communication programs. Most HIV programs typically have initial setup costs, followed by a more effective scale-up with increased funding, but attaining very high coverage levels requires reaching the most difficult to reach groups, which would require increased incremental investment for demand generation and related activities (i.e., there is a saturation effect with increased funding).

Optima uses a logistic function fitted to available input data to model cost-coverage and coverage-outcome curves. Logistic functions can incorporate initial startup costs and allow changes in behavior to saturate at high spending levels, thus better reflecting the program reality. Using all available spending, behavioral, and clinical outcome data, users fit an equation of the form:

$$L(x) = A + \frac{B-A}{1+e^{-(x-C)/D}},$$

where $L(x)$ relates spending to coverage (or coverage to outcome), x is the estimated amount of funding for the program, A is the lower asymptote value (adjusted to match the value of L when there is no spending on a program), B is the upper asymptote value (for very high spending), C is the midpoint, and D is the steepness of the transition from A to B. For our fits, we typically choose saturation values of the coverage (or outcome) to match behavioral data in countries with heavily funded HIV responses. Program coverage for zero spending, or behavioral outcomes for zero coverage of formal programs, are inferred using data from early on in the epidemic or just prior to significant investment in HIV programs. Practically, we also discuss the zero and high spending cases with local experts who can advise on private sector HIV service delivery outside the governments' expenditure tracking systems.

For each HIV program, we derive one set of (logistic) curves that relate funding to program coverage levels, and another set of curves (generally linear relationships) between coverage levels and clinical or behavioral outcomes (i.e., the impacts that HIV strategies aim to achieve). In future, Optima will include a default set of these cost-coverage-outcome curves, based on all available international evidence. Outcomes expected from changes in program funding are assumed by interpolating and extrapolating available data using a fitted logistic curve. A limitation of this approach is that all changes in behavior are assumed to be due to changes in program funding.

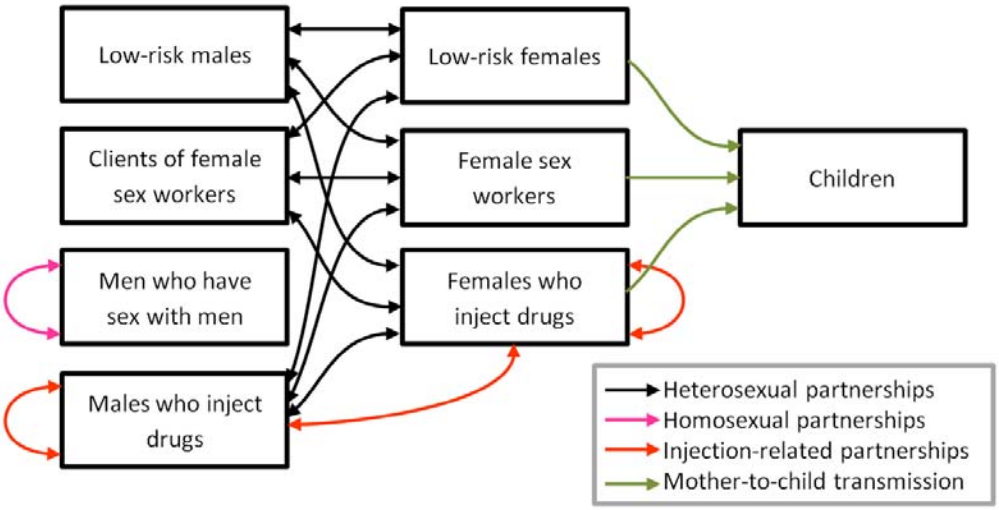
Optima can be used to minimize either (a) a given outcome (e.g., number of infections, number of disability-adjusted life years, number of HIV-related deaths, or future HIV-related costs) given a fixed total budget over a determined program period, or (b) the amount of funding required to meet a particular epidemiological goal (e.g., reducing HIV incidence by 50%). Optima can also determine the amount of money required to simultaneously meet multiple goals (e.g. all impact-level targets in an HIV national strategic framework) or the optimal allocation of a fixed amount of resources which will simultaneously get as close as possible to achieving one or multiple target objectives. Optima can also be used to help decide in which geographic areas to implement programs for which target populations, or how to most effectively re-invest the savings from technical efficiency gains. Constraints may be placed on the optimization; for example, the number of people on antiretroviral therapy or prevention of mother-to-child transmission program coverage may not be allowed to decrease.

To perform the optimization, Optima uses a global parameter search algorithm called Bayesian adaptive locally linear stochastic descent (BALLSD). BALLSD is similar to simulated annealing in that it makes stochastic downhill steps in parameter space from an initial starting point. However, unlike simulated annealing, BALLSD chooses future step sizes and directions based on the outcome of previous steps. For certain classes of optimization problems, we have shown that BALLSD can determine optimal solutions with fewer function evaluations than traditional optimization methods, including gradient descent and simulated annealing.

Uncertainty analyses

Optima uses a Markov chain Monte Carlo (MCMC) algorithm for performing automatic calibration and for computing uncertainties in the model fit to epidemiological data. With this algorithm, the model is run many (typically 1,000–10,000) times to generate a range of epidemic projections; their differences represent uncertainty in the expected epidemiological trajectories.

(A)



(B)

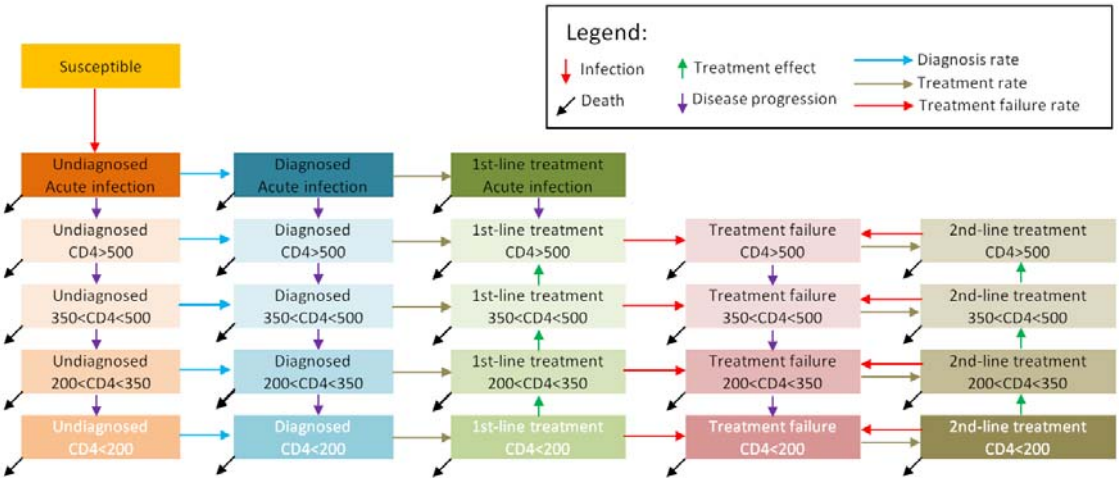


Figure A3: (A) Example population groups and HIV transmission-related interactions in Optima. (B) Schematic diagram of the health state structure of the model. Each compartment represents a single population group with the specified health state, while each arrow represents the movement of numbers of individuals between health states. All compartments except for “susceptible" represent individuals living with HIV. Death includes all causes of death.