Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries

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Technical appendix (as supplied by author)

We developed a mathematical model of HIV/AIDS, adapted from the Goals model described previously.[1;2] The model includes underlying demography, sexual mixing between defined risk groups, transmission of HIV infections, progression from HIV to AIDS and AIDS to death, and transmission of other sexually transmitted infections (STI). A range of different interventions may be incorporated, with impacts on risk behaviors and progression rates. The model is implemented in an Excel spreadsheet. The @RISK package[3] is used to undertake multiple simulations of the model through sampling of uncertain parameter ranges, which allows both calibration of parameter values by fitting to observed data and uncertainty analysis of model outputs.

Model structure

Demographic and behavioral model

In this study, the model has been calibrated to two WHO subregions: Afr-E and Sear-D. Afr-E contains countries in sub-Saharan Africa with very high levels of adult mortality and high child mortality (Botswana, Burundi, Central African Republic, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe), and Sear-D refers to countries in South East Asia where levels of child and adult mortality are both high (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar and Nepal).

The model focuses on adult populations (ages 15 to 49 years), a subset of whom are sexually active. Population size in each year is based on country-specific demographic projections drawn from the 2002 United Nations Projections[4], to which the impact of AIDS is added using the Spectrum package[5] and then aggregated to regional level. New entrants into the adult population each year are assumed to be uninfected. Baseline population projections are modified in scenarios that include treatment to account for increased survivorship of treated AIDS patients.

The model divides the sexually active population into five interacting risk groups: single men and women, married men and women, and female sex workers (FSW). Four types of partnerships may be formed: between single men and single women, between married men and married women, and between single or married men and female sex workers. In line with the predominant epidemiologic pattern of HIV spread through heterosexual contact, we have excluded men who have sex with men from the analysis. Single men and married men have distinct probabilities of visiting sex workers in addition to their partnerships with single or married women. Group sizes, numbers of partnerships, and number of sexual acts per partnership determine the total number of acts in each risk-group pairing.

To balance the total number of acts between males and females in the various types of partnerships, the distribution of women across risk groups is not entered as an input into the model, but rather calculated based on other inputs. Male demand for sex work determines the number of FSW in the population up to a specified limit:

total demand for sex work = (number of active single men × proportion who visit sex workers × number of visits per year) + (number of active married men × proportion who visit sex workers × number of visits per year)

number of FSW = total demand for sex work / average annual number of visits per sex worker

When the total demand would produce a larger number of FSW than the specified population limit, male demand is scaled down, preserving the ratio between demand from single and married men. The number of married women is determined based on the number of married men:

number of married women = number of married men × average number of wives per husband

The number of single women is then calculated as the residual:

single women = total women – married women – FSW

The number of acts per partnership for single men is determined by demand from single women. Within risk groups, condom use and sex acts per year may vary between those with or without clinical AIDS, and by treatment status among those with AIDS.

Disease models

The HIV disease model distinguishes five states: uninfected, primary HIV infection, post-primary / pre-AIDS infection, untreated AIDS, and treated AIDS. For the purpose of this analysis, the label *AIDS* is intended as shorthand for advanced disease rather than as a strict clinical definition. In the model, this characterization distinguishes those persons regarded as being in most urgent need of treatment according to treatment initiation guidelines from WHO.

Progression from HIV to AIDS is calculated using a Weibull function with parameters consistent with recommendations from the UNAIDS Reference Group on Estimates, Modelling and Projections (see below).[6]

The STI disease model includes three states: uninfected, genital ulcerative disease (GUD), and non-ulcerative disease (non-GUD). For purposes of parameterizing initial prevalence, transmissibility, and duration of STI states, GUD is assumed to include syphilis, chancroid, and herpes simplex virus-2; non-GUD includes chlamydia, gonorrhea, and trichomoniasis. For the initial year of 1999, HIV prevalence is based on UNAIDS/WHO estimates, and STI prevalence is based on the Global Burden of Disease Study.[7]

Model transitions

HIV transmission

For each of the five risk groups, the probability of infection during each one-year period is calculated, and this probability is multiplied by the uninfected population at the start of the year to calculate the annual number of new infections. A binomial model of HIV transmission is used, based on a modification of the equation originally presented by Weinstein et al.[8] and implemented in the AVERT model[9] and Goals, as follows:

$$P_{is} = 1 - \prod_k \prod_j \left[1 - b_{isj}\left(1 - c_k\right)\right]^{a_k N_k x_{jk}}$$

where *i* indicates risk group, *s* indicates STI state (uninfected, GUD, non-GUD), *k* indicates partner type, *j* indicates HIV state (uninfected, primary HIV infection, post-primary / pre-AIDS infection, untreated AIDS, and treated AIDS), and

P_{is} = one-year probability of infection for an individual of risk group *i* and in STI state *s*

b_{isj} = probability of transmission for an individual in risk group *i* and in STI state *s* per (unprotected) contact with a person in HIV state *j*.

c_k = effective condom use during contacts with partner type *k*

a_k = average number of sexual contacts per year per partnership of type *k*

N_k = number of partners per year of type *k*

x_{jk} = proportion of contacts with *k*-type partners in which partners are in HIV state *j*

Married and single women have only one partner type, so the equation may be simplified for these groups to:

$$P_{is} = 1 - \prod_j \left[1 - b_{isj}\left(1 - c_k\right)\right]^{a_k N_k x_{jk}}$$

The proportions of contacts in different HIV states are determined by the prevalence of HIV infection and AIDS in the partner group at the beginning of the year, and the level of treatment coverage. Note that in this equation we include "uninfected" as an HIV state, but the term in the product that includes this partner type is simply 1 since the associated transmission probability is 0.

Our modified binomial specification provides a close approximation of the risks determined by the original formulation and has the advantage of allowing explicit modeling of behavior change specific to partners in a particular HIV state; i.e. behavior of treated individuals may be targeted by interventions separately from behavior among untreated individuals, and reduced transmissibility through treatment is linked specifically to sexual contacts with treated partners.

Per-contact transmission probabilities (*b*) vary according to the HIV disease stage of the partner (with highest rates during primary infection, low rates during post-primary HIV, and medium-high rates during clinical AIDS) (see Table A3).[10] Probability of transmission also depends on the STI state of the uninfected partner (modeled as cofactor effects on susceptibility to infection from having GUD or non-GUD). Note that although *b* is indexed by risk group *i*, the transmission probabilities are constant for the various risk groups of a given sex, conditional on HIV disease state and STI state. HIV prevalence within each risk group is adjusted each year to reflect transitions from one risk group to another (e.g. movements in and out of commercial sex work, or changes in marital status).

STI transmission

Prevalence of GUD and non-GUD is computed in monthly cycles due to shorter durations of infection, based on net changes through new infection and remission. For a given category of STI, prevalence in risk group *i* (S_i) is computed in monthly time steps (*t*) as follows:

$$S_i(t+1) = S_i(t)e^{r_i}$$

The rate of change in prevalence of an STI (by category) in risk group *i* is given by:

$$r_i = \left[1 - \prod_k \left(1 - g_i\left(1 - c_k\right)\right)^{a_k N_k Y_k}\right]\left(1 - S_i(t)\right) - \left(\frac{1}{d}\right)S_i(t)$$

where

g_i = probability of transmission for an individual in risk group *i* per (unprotected) contact with a person having an STI (category-specific)

c_k = effective condom use during contacts with partner type *k*

a_k = average number of sexual contacts per year per partnership of type *k*

N_k = number of partners per year of type *k*

Y_k = prevalence of STI (category-specific) among partner type *k*

d = average duration of an STI (category-specific), in months

The average duration of an STI is computed based on input parameters defining the duration of treated infections, the duration of untreated infections, and the proportion of infections that are treated, which may vary in different prevention scenarios. The reciprocal of the duration approximates the exit rate from the class of prevalent infections over a one-month time period. For female sex workers we found that even the one month time step produced a poor approximation given large numbers of sex acts combined with the relatively high transmissibility of STIs. We therefore used a simpler approach for female sex workers in which we assumed that relative changes in STI prevalence would mirror relative changes in average duration, computed based on the proportion treated and the specified durations of untreated and treated infections.

Progression to AIDS and death

Newly infected individuals are exposed to survivorship curves that govern progression from HIV to AIDS and from AIDS to death. Consistent with recommendations from the UNAIDS Epidemiology Reference Group[6], HIV to AIDS progression is based on a Weibull function with median progression time to AIDS of 7.5 and 8.5 years for men and women, respectively; median survivorship with AIDS is 1 year in the absence of treatment; and antiretroviral therapy confers a median of 3 to 8 years of additional survivorship, depending on the type of treatment intervention (see below).

The prevalent cohort of HIV-infected individuals in the first year of the model (1999) is subject to a different survivorship curve since this cohort includes surviving members of multiple incident cohorts from a range of prior years, each with different conditional survival probabilities in any given calendar year. The initial survivorship schedule was computed by applying the standard survivorship function described above to UNAIDS/WHO estimates of incidence in each year since the start of the epidemic and then summing the remaining survivors from all previous cohorts in each of the years following 1999.

Model calibration

Overview

Baseline projections of country-specific HIV epidemics were developed by UNAIDS and WHO and aggregated into the regions used in this analysis. We specified ranges around uncertain behavioral and biological parameters in the present model based on published studies and survey data. Values were sampled randomly from these ranges in order to undertake multiple model simulations, and modeled outcomes from each sampled parameter set were assessed in terms of fit to the baseline projections of male and female prevalence over the period 1999 to 2020.

Baseline projections

Baseline projections are taken from UNAIDS/WHO country estimates. Details of the methods used to develop these estimates are published elsewhere and summarized here.[5;11;12] HIV prevalence among pregnant women attending antenatal clinics was used to estimate prevalence in all adults between ages 15 and 49 years.[12] Epidemic curves were fit to prevalence data from pregnant women for past years, separately for urban areas and rural areas, using the Estimation and Projection Package (EPP)[11], with adjustments for representativeness of surveillance sites in rural areas. National epidemic curves were estimated by applying the urban/rural population distribution to the separate urban and rural epidemic curves. Baseline projections to 2020 in EPP were computed under the assumption of no future behavioral change. The Spectrum software package[5] was used to derive estimates of adult incidence and mortality based on the EPP prevalence estimates.

Parameter ranges

Ranges around behavioral parameters in the model for AfrE and SearD were specified based on review of the literature and data from the Demographic and Health Surveys where possible (Tables A1 and A2). For biological parameters, the same ranges were used as starting points for simulations in both regions (Table A3).

AIDS-specific parameters

Persons with clinical AIDS were assumed to have half as many partners per year as the rest of the sexually active population, as studies have reported that AIDS-defining illnesses lead to increased morbidity and reduced sexual behavior.[13;14] The transmissibility of untreated AIDS patients was set at 3 times that of persons with post-primary / pre-AIDS infection, based on the study by Quinn et al. showing that transmission probabilities per sex act increased by a factor of 2.45 for each log increment in viral load,[15] and the increase in viral load by a factor of 10 or more between asymptomatic HIV and AIDS observed in numerous studies.[16-18]

Simulations and goodness-of-fit

For both regional models, we used @RISK software to undertake 10,000 simulations. In each simulation, parameter values were sampled randomly from uniform distributions defined by the ranges described above. Projected prevalence numbers in the simulations, from 1999 to 2020 and by gender, were compared to the corresponding baseline projections, and goodness-of-fit was computed as the squared percent deviation of modeled prevalence from baseline. The parameter set that minimized the maximum deviation across all years was identified as the best-fit set of parameter values and used for scenario analysis.

Modeling interventions

Following the standard approach used in the other analyses reported in this series on the health MDGs, we modeled costs and effects of interventions implemented over the period 2000-2009. Costs of implementing interventions were measured only for the 10 year period, but we allowed for waning residual intervention impacts on behavior over the subsequent five years, and traced out the full stream of health consequences in the population resulting from the intervention period.

For prevention interventions, impacts were computed as described previously by Stover et al.,[2] starting from literature-based estimates of effects of individual interventions on specific behaviors (Table A4). Details on how coverage and effectiveness were incorporated in the model to generate behavioral impacts

are described below. Derivation of the estimates of intervention effects is detailed in Bollinger et al.[19] and we have used the latest impact estimates based on an update of the literature review undertaken by the Futures Group (John Stover, personal communications).

The combined impact of multiple interventions on a particular behavioral outcome is estimated using a multiplicative model, constrained by a defined maximum. The maximum values (specific to different populations) were defined as 85%, 75% and 50% for condom use and 90%, 80% and 70% for treatment seeking for STIs among FSW, single and married populations, respectively.[2] Use of condoms and treatment seeking for STIs in a given year is calculated as follows:

$$\text{Use} = \text{MaximumUse} - (\text{MaximumUse} - \text{BaseUse}) * \Pi_i(1 + \text{Impact}_i)$$

where

MaximumUse = maximum possible level of use

BaseUse = level of use in the absence of interventions in a given year

Impact_i = impact for a given intervention *i* (from TableA4)

Yearly numbers of partners for an individual in a given risk group are calculated as:

$$\text{Number of Partners} = \text{BaseYearPartners} * \Pi_i(1 + \text{Impact}_i)$$

where

BaseYearPartners = number of partners in the absence of interventions in a given year

The following sections provide additional information on the modeling of specific interventions.

Mass media

Coverage was multiplied by effectiveness values from Table A4, further scaled by the proportion of the population reporting weekly exposure to television, radio or newspapers (around half in both regions) from representative surveys.[20] We assumed the media campaigns would run every other year, and that the impacts of the intervention would be halved in years when no media campaign occurred.

Voluntary counseling and testing

Impacts of VCT were implemented based on the number of individuals expected to complete the testing process and regional risk group-specific HIV prevalence. We assumed that with universal coverage 2 individuals would complete the testing process per prevalent case[21] and that individuals would be retested on average once per five years. Therefore, with 95% coverage, if prevalence in a specific risk group were 10%, then: 0.10 x 2.08 x 0.95 / 5 = 4% of that group would complete testing each year. We assumed a shared, average impact for HIV+ vs. HIV- individuals; the prevalence-specific likelihood of completing VCT increased the impact of VCT in higher risk groups.

Peer education of FSW

Effectiveness was multiplied by coverage and implemented directly. To maintain the balance of total sex acts in the model, for all interventions that involve a reduction in FSW partnerships we reduce the probability that men visit FSW by the same amount.

Peer education and STI treatment for FSW

Partnership and condom use impacts were implemented in the same way as *Peer education of FSW*. The STI treatment impact was taken from the general population STI value for FSW.

School-based programs

Coverage was multiplied by the proportion of the sexually active single population that was 15-19 years of age and in school. Behavior changes (condom-use, STI treatment and partnership reductions) were then computed as the product of this adjusted coverage and the associated effectiveness. Change in age of sexual debut was implemented as reducing the percentage of the 15-49 population that was sexually active. This was calculated as: coverage * impact * 'decrease in percent sexually active for each one year delay in onset of sexual activity', where coverage is the same adjusted coverage as for the other SBE behavioral impacts described above:

SBE coverage * impact / [(50-15) * (% male sexually active + % female sexually active)/2]

General STI

Effectiveness was multiplied by coverage and implemented directly. Men who visit sex workers were assumed to be subject to the same impact as sex-workers. This was implemented by assigning the weighted average of STI intervention effectiveness for FSW- and non-FSW visiting men, based on the proportion of men who visit sex-workers.

Prevention of mother-to-child transmission

Prevention of mother-to-child transmission was modeled as having two effects; it decreased condom non-use among women receiving pMTCT and reduced the number of HIV-positive births. The impact of pMTCT on condom use was implemented in an identical fashion to VCT, although the final proportion of individuals decreasing condom non-use was reduced by the percentage of the adult female population in a given year that was pregnant. The impacts of pMTCT on reducing the number of HIV-positive births were calculated as a function of: the number of HIV-positive pregnant women, intervention coverage, proportion accepting the test (0.7), proportion returning for test results (0.8), proportion with a positive test result accepting nevirapine (0.75), proportion complying with treatment protocols (0.9) and the effectiveness of nevirapine (0.47).[22-26] Pregnant women on HAART were not included in the PMTCT intervention but were assumed to have the same effectiveness for transmission reduction as women receiving PMTCT.

Antiretroviral therapy

Individuals with advanced disease (labeled as *AIDS*) may be treated in the model, consistent with the primary focus of delivering antiretroviral (ARV) therapy to those in most urgent need. Treated patients are allowed different sexual behavior and transmissibility than untreated patients. Indirect effects of treatment on sexual behavior of untreated patients due to changes in supply and demand dynamics are implemented as adjustments to the distribution of sexual contacts for those without AIDS as follows: the number of contacts with non-AIDS partners is the same as in the counterfactual of no treatment; the number of contacts with partners having untreated AIDS is reduced in proportion to the reduction in the population of untreated AIDS patients (due to delivery of treatment); in instances where excess demand is generated by treatment of AIDS patients (through prolonged survivorship or behavior change), the excess demand is satisfied by pre-AIDS partners in proportion to their relative contributions to overall demand.

It is currently not known what long-term survivorship will be from antiretroviral therapy for AIDS patients in resource poor settings.[27] We combined data from several studies to estimate survivorship curves for AIDS patients beginning antiretroviral therapy under four scenarios, namely with and without second-line drugs and with and without intensive monitoring (directly observed therapy). We assumed that treatment for opportunistic infections would be necessary for 40% of patients for purposes of costing and assumed that the survivorship curves reflected treatment of these infections. Second-line drugs reduced treatment failure, and directly observed therapy increased adherence. Under the most comprehensive treatment program patients received second-line drugs, and intensive monitoring resulted in adherence above 95%. Survivorship for patients under comprehensive treatment conditions was estimated by scaling down a Weibull curve with median survivorship of 8.5 years (comparable to King et al.'s survivorship for patients with CD4 < 200 cells/μl at treatment initiation) by the percent difference in year one from this curve and the observed survivorship in Khayelitsha field trials.[28;29] This resulted in a median survivorship for "intensive monitoring, first- and second-line drugs" of approximately 8 years.

Survivorship curves for the remaining three scenarios were modifications to this comprehensive treatment scenario curve. We assumed a 0.43 increase in risk of treatment failure with first-line drugs for each year following initiation of treatment.[30] Under scenarios without second-line treatment, individuals who failed treatment in a given year followed untreated AIDS progression to death (median survival 1 year). To capture the effect of reduced adherence in the absence of directly observed therapy, we used a linear extrapolation of survivorship for patients with CD4 < 200 cells/μl at treatment initiation and adherence less than 75%, again scaling down by the percent difference in year one survivorship between this study and that from Khayelitsha.[29;31] Average progression from AIDS to death while on treatment was then calculated by blending fully adherent and partially adherent curves and allowing for treatment failure in the absence of second-line drugs. Without intensive monitoring, it was assumed that only 70% of patients would be fully adherent. Survivorship curves for the four ARV scenarios are presented in Figure A1.

For all four ARV scenarios, we assumed that individuals on ARV therapy would maintain lower rates of sexual activity than the general population (i.e., one half the number of acts per year, which was the same as untreated AIDS individuals). Condom use remained the same for those receiving treatment. We also assumed that ARV therapy would reduce the transmissibility of HIV. A review of the literature did not reveal obvious estimates of the impact of treatment on per-act transmission probability. Using Quinn et al.'s estimate of a 2.45 change in per-act transmissibility per log change in viral load as a guide,[15] we assumed that under "intensive monitoring, first- and second-line drugs" transmissibility was reduced by 99% and that under "no intensive monitoring, first-line drugs only" transmissibility was reduced by 90%. Transmissibility was reduced by 91% and 97% for "intensive monitoring, first-line drugs only" and "no intensive monitoring, first- and second-line drugs", respectively, based on differences in median survival.

Calculation of DALYs

We used the Spectrum program[5] to project region-specific age distributions of HIV incidence in 5 year age intervals for ages 15 – 80+ years from 2000 to 2015. Survival from HIV to AIDS and AIDS to death (both with and without treatment) was assumed to be constant across age groups, and we assumed a constant transition rate into older age groups of 0.2 per year (approximating the complete transfer of survivors from one five-year cohort to the next over a five-year period). Disability-adjusted life years (DALYs) were then calculated based on progression distributions from HIV infection to AIDS and death. DALYs equaled the sum of years lived with disability (YLDs), using disability weights for HIV and AIDS from the Global Burden of Disease Study (individuals receiving treatment were assumed to have the same disability weight as those with HIV), and years of life lost (YLLs) due to premature mortality, applying standard life expectancies to the number of deaths in each age group, and including a 3% discount rate and non-uniform age weights.

Sensitivity and uncertainty analyses

We conducted a variety of sensitivity analyses to assess changes in incremental cost-effectiveness (i.e., expansion paths) and point estimates of average cost-effectiveness for single interventions. For costing, we recalculated expansion paths under four different conditions that were applied to all interventions concurrently: halved program costs, doubled program costs, halved patient costs and doubled patient costs. For Afr-E, under conditions of halved program costs or doubled patient costs the following changes occurred: mass media became incrementally less cost-effective than all three coverage levels of FSW peer-counseling with STI treatment, PMTCT became incrementally less cost-effective than general STI at enhanced coverage, VCT became incrementally less cost-effective than general STI at 95% coverage, and school-based education became incrementally more cost-effective than all forms of ARV therapy. For Afr-E under conditions of doubling program costs or halving patient costs, ARV therapy with intensive monitoring, first-line drugs only became incrementally more cost-effective than school-based education. For Sear-D, under conditions of halved program costs or doubled patient costs, school-based education was incrementally more cost-effective than ARV therapy with intensive monitoring, first-line drugs only; under conditions of doubled program costs or halved patient costs PMTCT became incrementally more cost-effective than ARV therapy. With the exception of mass media in Afr-E under the conditions of halving program costs or doubling patient costs, none of these four scenarios resulted in an intervention changing by more than one place in incremental cost-effectiveness ordering.

To determine the sensitivity of model results to changes in intervention effectiveness, we recalculated expansion paths and single intervention average cost-effectiveness ratios under conditions that relatively increased or decreased intervention impacts by 20%. Impacts included changes in condom use, number of partnerships, treatment seeking for STIs, probability of men visiting female sex workers, age of sexual debut, effectiveness of nevirapine and transmissibility of HIV when receiving ARV therapy (condom use and number of partnerships were also changed for individuals receiving ARV therapy). Increasing intervention effectiveness by 20% had no effect on expansion paths for either region; decreasing effectiveness by 20% led to the removal of FSW-peer counseling with STI at 50% coverage from the Afr-E expansion path and, for Sear-D, PMTCT becoming incrementally more cost-effective than ARV therapy. For single interventions, increasing effectiveness by 20% did not result in the average cost-effectiveness ratios changing by more than 20%. When effectiveness was reduced by 20%, average cost-effectiveness ratios increased by 18-25%, with the exception of ratios for both ARV therapy scenarios without second-line drugs increasing by 40% in Afr-E and 35% in Sear-D. This result implies that it is especially important that basic ARV therapy programs are implemented in a manner that ensures patient compliance with medication and provides counseling on low-risk sexual behaviors.

The final set of sensitivity analyses involved recalculating expansion paths without including age weights or discounting in the calculation of DALYs. For Afr-E, school-based education became incrementally more cost-effective than ARV therapy, and for Sear-D PMTCT became incrementally more cost-effective than ARV therapy.

Uncertainty analyses were conducted by looking at the range of average cost-effectiveness ratios for each single intervention and changes in the expansion path when using the 10 best-fit parameter sets ("best-fit" as defined above) (Table A5 and A6 and main text). In a secondary analysis, 10 randomly selected parameter sets from all parameter sets that deviated by no more than 50% from UNAIDS prevalence projections for males and females from 1999 to 2020 were used to generate average cost-effectiveness ratios for single interventions. Uncertainty ranges under these conditions were very comparable to those generated from the approach using the 10 best-fit parameter sets.

Modeling limitations

Our modeling approach places a heavy emphasis on the impact of interventions on transmission, which differentiates it from the state-transition models used to examine the cost-effectiveness of treatment and care alternatives based on simulating disease progression in defined cohorts (see, for example, recent applications from the United States[32] and Cote d'Ivoire[33]). The latter models typically include much more extensive detail on disease staging and complications but exclude transmission effects. Our model derives from past work on computing infection risks as a function of partnerships, acts per partnership, condom use and transmissibility,[1;8;9] with extensions to account for variability in behaviours and transmissibility relating to disease stage and treatment.

Within the category of dynamic models that account for transmission, there are a range of methodologic choices that reflect tradeoffs between complexity and analytic tractability. Our use of a deterministic model rather than a stochastic model[34] results in a comparatively simple spreadsheet-based implementation but sacrifices the flexibility to capture heterogeneities and to reflect random processes in finite samples. We have captured mixing between risks groups and transmission probabilities within groups in a simplified way that might be improved upon with pair formation models[35] that account explicitly for duration of partnerships and constrain infection risks to occur only in the context of serodiscordant pairs. For the broad analysis presented here, it was important to have sufficient flexibility to consider a wide range of different types of interventions without adding details requiring further assumptions with limited empirical support. As work proceeds in this area, however, it will be essential to tailor the choice of models to the particular questions under consideration, and a rich research agenda remains on the development of transparent but rigorous approaches to modeling HIV/AIDS epidemics for policy.

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Table A1. Ranges and best fit values for behavioral parameters in model, Afr-E.

Parameter	Min	Max	References	Best Fit
Sexually active population				
Male (proportion of all adult males)	0.67	0.84	[20]	0.76
Female (relative proportion)[a]	0.88	0.93	[20]	0.92
Proportion married among sexually active males	0.68	0.68	[20]	0.68
Partners per year				
Married males (excluding FSW partners)	1.07	1.17	[20]	1.09
FSW	500	1200	[36-40]	633
Single females	2	3	[20]	2.2
Married females	1	1	assumption	1
Probability male visits FSW	0.1	0.13	[37;41]	0.11
Number of visits to FSW per year				
Single male	25	89	[42;43]	52
Married male	25	89	[42;43]	67
Acts per partnership				
Single male	7	17	[20]	7
Married female	30	70	[20;41]	36
Risk group transitions (annual probability				
Single male - married male	0	0.2	assumption	0.15
FSW - single female	0	0.2	[37-40]	0.11
Single female - married female	0	0.2	assumption	0.03
FSW maximum proportion of female population[b]	0.01	0.014	[25]	0.014

Table A2. Ranges and best fit values for behavioral parameters in model, Sear-D.

Parameter	Min	Max	References	Best Fit
Sexually active population				
Male (proportion of all adult males)	0.8	0.8	[20]	0.8
Female (relative proportion)[a]	0.94	1	[20]	0.97
Proportion married among sexually active males	0.71	0.71	[44]	0.71
Partners per year				
Married males (excluding FSW partners)	1	1.09	[44]	1.05
FSW	572	1040	[44-46]	941
Single females	1	2.4	[44]	2.3
Married females	1	1	assumption	1
Probability male visits FSW	0.04	0.15	[45;47;48]	0.14
Number of visits to FSW per year				
Single male	16	50	[45;47;48]	42
Married male	16	50	[45;47;48]	48
Acts per partnership				
Single male	7	17	assumption	9
Married female	24	61	[20]	24
Risk group transitions (annual probability)				
Single male - married male	0	0.2	assumption	0.16
FSW - single female	0	0.2	[46]	0.01
Single female - married female	0	0.2	assumption	0.16
FSW maximum proportion of female population[b]	0.010	0.026	[45]	0.021

Abbreviation: FSW = female sex worker

[a] Ratio of active proportion of all adult females to active proportion of all adult males.

[b] Male demand determines the number of sex workers until FSW proportion reaches this level, after which male demand is scaled downwards, preserving the ratio between demand from single v. married men.

Table A3. Ranges and best fit for biological parameters in model.

Parameter	Min	Max	References	Best Fit	
				Afr-E	Sear-D
HIV transmission probability (per act)					
Male - female[a]	1x	3x	[15;45;49;50]	2.8	1.4
Female - male	0.0008	0.0015	[51]	0.0010	0.0012
Primary infection cofactor[b]	10	20	[10;50]	17.0	13.3
GUD cofactor					
Male - female	2	15	[50;52]	9.5	9.8
Female - male	2	15	[50;52]	11.1	11.1
Non-GUD cofactor					
Male - female	2	5	[50;52]	4.4	3.8
Female - male	2	5	[50;52]	3.5	3.7
GUD transmission probability (per act)					
Male - female	0.2	0.3	[50;53]	0.20	0.29
Female - male	0.1	0.2	[50;53]	0.20	0.10
Non-GUD transmission probability (per act)					
Male - female	0.15	0.25	[50;53]	0.16	0.20
Female - male	0.1	0.2	[50;53]	0.14	0.17
Duration (years)					
GUD, untreated	0.08	0.18	[50;53;54]	0.15	0.09
Non-GUD, untreated	0.15	0.30	[50;53;54]	0.19	0.20
GUD, treated	0.02	0.06	[55]	0.06	0.02
Non-GUD, treated	0.02	0.06	[55]	0.04	0.03

Abreviations: GUD = genital ulcerative disease; non-GUD = non-ulcerative disease.

[a]Value multiplied by female-to-male transmissibility to determine male-to-female transmissibility.

[b]Primary HIV infection is assumed to last 0.2 years [10;50]

Table A4. Prevention interventions and their impacts on behavior.

Intervention	Reduction in condom non-use			Reduction in non-treatment of STI			Reduction in number of partners		Increase in age of sexual debut	Reduction in probability of men visiting FSW
	FSW	Single	Married	FSW	Single	Married	FSW	Single		
Mass media	..	17%	14%	..	..	..	..	..	..	..
VCT	44%	24%	12%	..	..	..	..	..	..	..
Peer counseling – FSW	44%	..	..	..	..	..	11%	..	..	11%
Peer counseling and STI treatment - FSW	44%	..	..	63%	..	..	11%	..	..	11%
School-based programs	..	17%	..	..	18%	..	..	33%	0.1	
STI treatment	..	2%		63%	31%	..	..	..	..	..
pMTCT	..	24%	12%	..	..	..	..	..	..	..

Abbreviations: VCT = voluntary counseling and testing programs for HIV/AIDS; FSW = female sex worker; STI = sexually transmitted infection; pMTCT = prevention of mother-to-child transmission.

Figure A1: Survivorship curves for four ARV treatment scenarios.

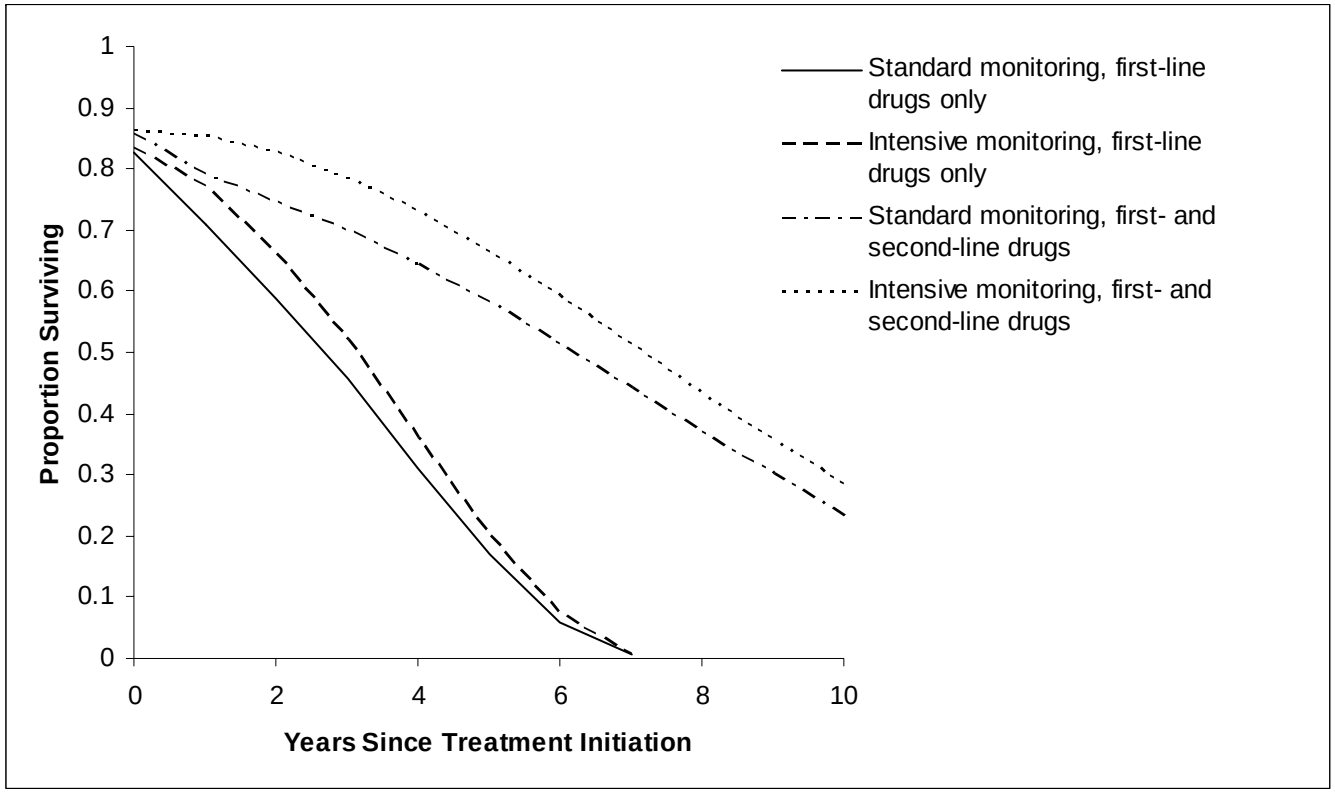

Table A5. Minimum and maximum yearly costs, DALYs averted and average cost-effectiveness ratios for individual interventions from 10 best-fit iterations, Afr-E.

Intervention	Coverage Level	Total Yearly Costs ($Int, millions)		Total Yearly DALYs Averted (millions)		Average CER ($Int/DALY Averted)	
		Min	Max	Min	Max	Min	Max
Mass media	100%	15	16	2.9	6.9	2	5
Educating sex workers	50%	18	47	5.5	9.9	3	7
	80%	26	71	8.6	15.5	3	6
	95%	30	83	10.0	18.1	3	6
Educating sex workers and treatment of sexually transmitted infections	50%	19	49	6.4	12.5	2	6
	80%	27	75	9.8	19.1	2	6
	95%	31	87	11.4	22.2	2	6
School-based education	50%	58	58	0.1	1.2	49	530
	80%	77	77	0.2	1.8	42	444
	95%	77	77	0.2	2.2	36	376
Preventing mother-to-child transmission	ANC	161	161	4.0	5.2	31	40
Treatment of sexually transmitted infections	current	42	47	1.0	3.7	13	44
	ANC	109	120	2.4	8.7	14	47
	95%	226	239	3.1	11.3	21	73
Voluntary counseling and testing	95%	402	417	3.2	5.7	73	128
Antiretroviral therapy:							
no intensive monitoring, first-line drugs only	ANC	1,329	1,398	2.4	3.4	396	556
intensive monitoring, first-line drugs only	ANC	1,483	1,561	2.5	3.6	413	598
no intensive monitoring, first- and second-line drugs	ANC	6,335	6,661	3.1	4.8	1,321	2,116
intensive monitoring, first- and second-line drugs	ANC	6,841	7,186	3.4	5.4	1,286	2,092

Table A6. Minimum and maximum yearly costs, DALYs averted and average cost-effectiveness ratios for individual interventions from 10 best-fit iterations, Sear-D.

Intervention	Coverage Level	Total Yearly Costs ($Int, millions)		Total Yearly DALYs Averted (millions)		Average CER ($Int/DALY Averted)	
		Min	Max	Min	Max	Min	Max
Mass media	100%	33	36	1.1	5.0	7	33
Educating sex workers	50%	52	78	18.7	28.6	2	3
	80%	76	115	27.7	42.6	2	3
	95%	87	133	31.6	48.6	2	3
Educating sex workers and treatment of sexually transmitted infections	50%	54	83	21.9	35.2	2	3
	80%	79	122	31.4	50.5	2	3
	95%	91	141	35.2	56.5	2	3
School-based education	50%	174	174	0.05	0.5	370	3,729
	80%	175	175	0.1	0.7	239	2,362
	95%	176	176	0.1	0.9	205	2,003
Preventing mother-to-child transmission	ANC	268	268	0.8	1.3	204	332
Treatment of sexually transmitted infections	current	167	183	3.1	7.1	24	55
	ANC	280	308	6.0	13.8	21	47
	95%	333	374	9.8	22.7	15	34
Voluntary counseling and testing	95%	201	212	4.1	6.6	32	49
Antiretroviral therapy:							
no intensive monitoring, first-line drugs only	ANC	525	571	1.0	1.3	444	576
intensive monitoring, first-line drugs only	ANC	559	610	1.0	1.3	472	604
no intensive monitoring, first- and second-line drugs	ANC	1,555	1,757	1.2	1.5	1,143	1,408
intensive monitoring, first- and second-line drugs	ANC	1,652	1,866	1.3	1.6	1,106	1,371