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MAJOR ARTICLE

Predicting Trends in HIV-1 Sexual Transmission in Sub-Saharan Africa Through the Drug Resource Enhancement Against AIDS and Malnutrition Model: Antiretrovirals for Reduction of Population Infectivity, Incidence and Prevalence at the District Level

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Background. The use of antiretrovirals to reduce the incidence of human immunodeficiency virus (HIV) infection has been evaluated in mathematical models as potential strategies for curtailing the epidemic. Cohort data from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Program was used to generate a realistic model for the HIV epidemic in sub-Saharan Africa.

Methods. Two combined stochastic models were developed: patient and epidemic models. Models were combined using virus load as a parameter of infectivity. DREAM data that assessed patient care in Mozambique and Malawi were used to generate measures of infectivity, survival, and adherence. The Markov chain prediction model was used for the analysis of disease progression in treated and untreated patients. A partnership model was used to assess the probability that an infected individual would transmit HIV.

Results. Data from 26 565 patients followed up from January 2002 through July 2009 were analyzed with the model; 63% of patients were female, the median age was 35 years, and the median observation time was 25 months. In the model, a 5-fold reduction in infectivity (from 1.6% to 0.3%) occurred within 3 years when triple ART was used. The annual incidence of HIV infection declined from 7% to 2% in 2 years, and the prevalence was halved, from 12% to 6%, in 11 years. Mortality in HIV-infected individuals declined by 50% in 5 years. A cost analysis demonstrated economic efficiency after 4 years.

Conclusions. Our model, based on patient data, supports the hypothesis that treatment of all infected individuals translates into a drastic reduction in incident HIV infections. A targeted implementation strategy with massive population coverage is feasible in sub-Saharan Africa.

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A recent article by Granich et al [1] tested, through a mathematical model, the hypothesis that universal voluntary testing and treatment represents a chance to eradicate the human immunodeficiency virus (HIV) epidemic in an acceptable period of time. Based on actual cohort data from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Program, we generated a new model and assessed its validity in the sub-Saharan Africa context. The

extrapolation of parameters obtained in the field, based on real data from public health programs, is paramount for key variables such as mortality, retention, and adherence. These measures affect the epidemic trend and, consequently, the reliability of the model. Given that the proposal for rapid implementation of treatment is challenging due to cost constraints and need for high-skilled personnel, we tested the effects of a district-based strategy followed by gradual scale-up with high-prevalence areas targeted first. Our hypothetical model differs from that of Granich [1], in that we propose to initiate antiretroviral therapy (ART) using the World Health Organization (WHO) CD4 count threshold of 350 cells/mm^3, with the intent of extending treatment to the entire HIV-infected population within a short period of time. Our assumption was also that all new HIV infections would be immediately treated and retained in treatment through annual testing.

METHODS

Study Design

To develop a hypothetical model of the HIV epidemic in a sub-Saharan population, the following assumptions were made: (1) all new infections arose from heterosexual coital acts, without condom use; (2) the population size was that of a medium-sized district (300 000 persons); (3) social differences or geographical distances between individuals were not considered; (4) population mobility was estimated at 3%, with a balance between immigration and emigration flux. We assumed that mobility did not affect age distribution and that individuals entering or exiting were randomly susceptible to HIV infection. There were no assumptions that individuals established in the district were older or younger or more or less susceptible to HIV infection. Our average district was rural, with no factories, mines, or relevant economic activities to justify an immigrant flux of young people for job reasons.

Two combined stochastic models were used. The first described disease progression in a single patient, whereas the second described the interaction between a single patient and the evolution of the epidemic in the population. To combine both models, we used viral load as a parameter of infectivity [2–4].

Patient Model

To generate the model, DREAM Program data from adult patients who visited DREAM medical centers in Mozambique and Malawi from January 2002 through July 2009 were used. Clinical progression was monitored (with measurement of CD4 cell counts quarterly and viral loads every 6 months, clinical visits every 3 months, and follow-up every 3 months) in individuals receiving ART (eligible per WHO guidelines) and those who did not reach clinical or laboratory thresholds for ART initiation. The DREAM Program routinely collected pill count data, but even if there was a good correlation with viral load [5], we preferred to include the latter in the model, especially because of its usefulness in assessing individual and population infectivity. In this way, it was possible to calculate measures of survival time, annual mortality rate, patients lost to follow-up, and refusal rates in the population. These parameters were introduced in a Markov chain prediction model for the analysis of disease progression in treated and untreated patients.

Parameters were categorized as follows: CD4 cell counts, <200, 200–350, or >350 cells/mm^3; HIV-1 virus load, not available, ≤1700, 1700–12 000, 12 000–38 500, or >38 500 copies/mL; and ART use, yes or no. Viral load thresholds were selected based on prior infectivity studies [2–6], and CD4 cell count categories were based on clinical survival thresholds [7, 8].

The clinical evolution of patients was assessed every 6 months, to coincide with the timing of complete blood cell counts. At each step, the health status of a patient was determined by the combination of viral load and CD4 cell count values and ART parameters. Consequently, 31 health states were possible, including death. Health states were modeled in a Markov chain as shown in Figure 1, with patients modeled as agents in a complex simulation system.

Markov Chain

A Markovian process is a stochastic process in which the probability of migrating from one state to another depends on the current state, irrespective of the previous path. Therefore,

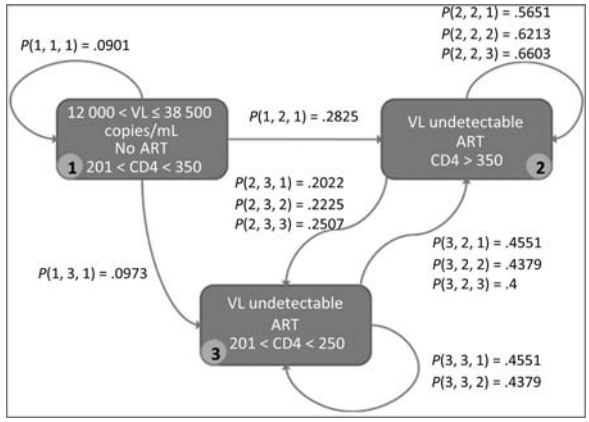

Figure 1. A small portion of the Markov chain used in the model. Each rectangle represents a patient state, characterized by a viral load (VL) value, a CD4 cell count value and a Boolean value indicating whether or not the patient is receiving triple antiretroviral therapy (ART). Arcs represent the probability that a patient will change state; for example, $P(i,j,k)$ represents the probability that a patient will pass from state i to state j after k semesters (or 6 month blocks). Abbreviation: ART, antiretroviral therapy.

the Markov chain is a discrete random process that uses the Markov property. The Markov probability matrix expresses the transition probabilities for all the possible state transitions. More precisely, given the probability matrix Q, the matrix element q_{ij} represents the probability of transition from state i to state j. In this study, each state of the Markov chain was represented by the health status of a patient. Markov chains can have graphic representations, where the nodes represent the states and the edges the transition probabilities (Figure 1). Subsequently, the clinical histories of the patients are described as states sequences, and the transition probabilities are extracted for all possible state transitions.

Epidemic Model

This model describes disease evolution in the whole population. Patient infectivity by viral load value was determined according to prior studies [2]. As illustrated in Table 1, the probability of infection was assigned according to viral load ranges, and it was possible to assess infectivity risk per coital act at any point of observation. Relationships among individuals, including multipartner relationships, were modeled according to Kretzschmar and Morris [9]. In that model, given 2 individuals x and y, the probability that a relationship was established was calculated by a formula, where: partners(x) and partners(y) are the numbers of present partners respectively of x and y; d is the maximum value of partners(z), for all individuals z in population observed at that time ; π is a parameter that takes into account a preference among partners x and y, based on the geographical closeness. In our study we assumed that $\pi = 1$, because we considered individuals from the same district. In the epidemic model, the evolution of the epidemic was determined by new infections caused by HIV-infected individuals having relationships with uninfected subjects.

We assumed that sexual mixing was disassortive, in the sense that "high-activity individuals mix with low-activity individuals and vice-versa," according to Kretzschmar [9], and also considering the Malawian environment and society. The number of partners was considered based on a probability derived by a mixing function [9]. There is a probability that 2 individuals at each time step unit form a partnership, and there is also a probability that at each time step, partnerships are broken, generating the time span of relationships. Hence, the number of partnerships for each agent is a function of the population and of the probabilities of formation and breakage of relationships. In the analysis of the partnership function, the mean number of partnerships was about 3 for a population of 300 000 at a given time step. Similarly, the frequency of sexual contacts was derived from Rakai studies [6]: number of coital acts was a function of age, sex, and health conditions. In summary, a Markov chain was used to determine disease progression in a single patient model, and a partnership model was used to assess the probability that an infected individual would transmit HIV to a serodiscordant partner.

Table 1. Probability of HIV Infection per Coital Act by Plasma Viral Load

HIV Viral Load, Copies/mL	Probability per Coital Act
≤1700	0.0001
>1700 to ≤12 000	0.0013
>12 000 to ≤38 500	0.0014
>38 500	0.0023

Abbreviation: HIV, human immunodeficiency virus.

Population

Demographic parameters were used for general population models and DREAM Program data were used for the model simulation of HIV-infected patients. A general population sample size of 300 000 individuals was considered, assuming a balance of immigration and emigration flux of 3% each. The demographic pattern of a typical rural district in Malawi was assumed, and age distributions were determined according to country data. An implementation latency time, defined as the number of months needed for achievement of full coverage of the population, was considered with 3 scenarios at 12, 24, and 36 months, respectively. At 3 years, full coverage of the candidate population was assumed. The demographic variables used in the model are shown in Tables 2–4 and were based on country statistics [10]. Baseline parameters used for the model simulation of HIV-infected patients obtained from the DREAM Program data in Malawi are shown in Table 5. The initial HIV prevalence rate was estimated at 12%. In addition, the model assumed annual universal voluntary testing of adults, immediate treatment of HIV-infected individuals with CD4 cell counts <350 cells/mm^3 and/or symptomatic disease (WHO categories 3–4), treatment of patients with CD4 cell counts >350 cells/mm^3 on reaching this CD4 cell count threshold over time, and treatment of all HIV-infected pregnant women irrespective of immunologic or virologic status [11].

The time distribution switch between groups was a consideration in the model. Over time, 13% of patients who initially entered the model with CD4 cell counts >350 cells/mm^3 reached lower values after 1 year, 35% after 2 years and 18% after 3 years. The model assumed that 66% of patients with initial CD4 counts >350 cells/mm^3 would be receiving treatment after 3 years, and 81% after 5 years. The model took into consideration the mortality rate of untreated patients who would likely be receiving ART in a few years even with a good immunologic status, as illustrated in Figure 2, which demonstrates the projected transition in CD4 cell counts from >350 to <350 cells/mm^3 over the years.

Table 2. Age Distribution of Malawian Population

Age, Years	Population, %	
	Male	Female
0 – 4	8.68	8.63
5 – 9	7.41	7.38
10 – 14	6.50	6.48
15 – 19	5.52	5.52
20 – 24	4.72	4.76
25 – 29	4.03	4.05
30 – 34	3.27	3.13
35 – 39	2.47	2.26
40 – 44	1.86	1.73
45 – 49	1.44	1.47
50 – 54	1.15	1.29
55 – 59	0.91	1.09
60 – 64	0.70	0.87
65 – 69	0.51	0.66
70 – 74	0.34	0.45
75 – 79	0.19	0.26
80 – 84	0.08	0.12
85 – 89	0.02	0.04
90 – 94	0.00	0.01
95 – 99	0.00	0.00
≥100	0.00	0.00

Source: US Census Bureau International Database 2011 [10].
These data were used in the prediction model for categorization of age.

Cost Analysis

The cost-effectiveness of the model was determined by comparing a universal treatment scenario (scenario A) with a scenario in which a stable figure of 45% of individuals eligible for ART in Malawi receive it (scenario B), leading to a hypothetical decline in HIV prevalence of 0.1% per year. This prevalence was obtained from the DREAM model, assuming that 45% of eligible patients were receiving treatment over the years. Other assumptions of the model included an annual cost of $1342 for triple ART (including staff and infrastructure) [12], an annual cost of $950 for an HIV-infected patient not receiving ART [12], a voluntary testing and counseling cost of $3 per individual, a district population of 300 000 residents with 50% adults, and an baseline HIV prevalence of 12%.

Table 3. Demographic Parameters Used in the Model

Variable	Rural District	Malawi
General population, No.	316 000	13 900 000
Annual growth rate in 1998–2008, %	2.3	2.8
Total growth in 1998–2008, No.	63 000	…
Crude death rate, %	…	15.2
Life expectancy, years	…	50

Source: Malawi Census 2008, preliminary report [10].

Table 4. Probability of Death in Malawi by Age

Age Range, Years	Probability of Death
15 – 19	0.00911
20 – 24	0.01934
25 – 29	0.04381
30 – 34	0.07873
35 – 39	0.11001
40 – 44	0.11593
45 – 49	0.11394
50 – 54	0.11440
55 – 59	0.11620
60 – 64	0.12693
65 – 69	0.17904
70 – 74	0.26834
75 – 79	0.38761
80 – 84	0.53768
85 – 89	0.70511
90 – 94	0.80573
95 – 99	0.85982
≥100	1.00000

Source: Life tables for WHO member states http://apps.who.int/whosis/database/life_tables/life_tables.cfm [10].

RESULTS

Data from 26 565 patients followed up at Mozambique and Malawi DREAM centers for >7 years were inputted into the model; 63.0% of the patients were female (n = 16 745), the median age was 35.0 years (interquartile range, 29.0 – 42.8 years), and the median observation time was 25 months (interquartile range, 13 – 40 months). Pregnant women were not included. Population variables are described in Table 5. The impact of the simulation on infectivity, population virus load, incidence and prevalence over time is shown in Figure 3. A dramatic 5-fold decrease in infectivity from 1.6% to 0.3% was observed, reflecting the reduction of individual viral load with a collective reduction in infectivity after the use of triple ART in the community. The logarithmic curve in the population viral load represents the median estimated viral load in treated and untreated individuals (entire population). After a steep decline in the first 3 years, a plateau "safety" value of 2211 copies/mL of plasma was reached.

Annual incidence rates declined from 7% to 2%. This was achieved in 2 years and was further reduced to less than 1% within 20 years. The significant reduction in incident cases makes the annual death balance negative, thus contributing to

Table 5. Baseline Parameters for HIV-Infected Patients Used in Model Simulation

Variable	Patients, No. (N = 26 565)	Patients, %
CD4 cell count, cells/mm^3		
<200	13 891	52.3
200–350	7600	28.6
>350	5074	19.1
HIV viral load, copies/mL		
Not available	980	3.7
≤1700	1474	5.6
>1700 to ≤12 000	3506	13.2
>12 000 to ≤38 500	5315	20.0
>38 500	15 288	57.6
ART initiated		
Yes	146	0.55
No	26 419	99.5
Lost to follow-up per year[a]	133	0.5
Adherence[a]		
Drug delivery index[a]		
>95%	…	80.1
90%–95%	…	10.7
<90%	…	9.3
Clinical visit index[a]		
>95%	…	69.3
90%–95%	…	13.4
<90%	…	17.3

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

[a] For the adherence categories, there are no baseline values, and adherence parameters include patients who eventually died or were lost to follow-up. Adherence was calculated as the combination of 2 ratios: that of drug delivery appointments prescribed to those completed and that of clinical visit appointments scheduled to those completed.

the reduction in prevalence. In approximately 11 years, the prevalence was halved from 12% to 6%. After decades, the estimated critical threshold of 1% prevalence was attained. The contributing factors to the decline in HIV prevalence were mortality in the HIV-infected population, reduction in incident infections, and the demographic growth of the general population.

Mortality in our model, as compared with the Granich model [1], is shown in Figure 4. Whereas the 50% survival in the populations is similar (10 and 11 years), the DREAM curve has a more pronounced early mortality rate but longer late survival rate. As a result, the reduction in prevalence is much slower in the DREAM model than in the CASCADE analysis [1]. Table 6 illustrates incidence and prevalence of HIV in the community during a 5-year period and was the basis of the cost analysis. Of note, there was nearly a 10-fold reduction in incident infections and almost a two-thirds reduction in deaths.

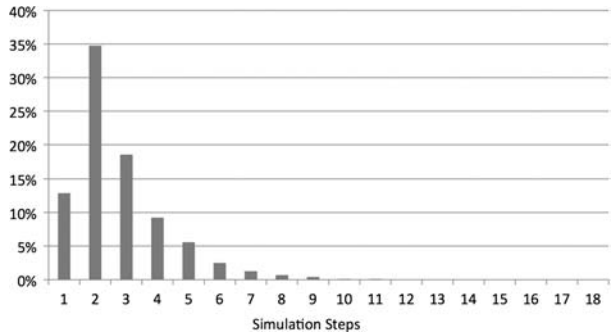

Figure 2. Projected transition of patients achieving CD4 cell counts of <350 cells/mm^3 over the years. This graph shows the percentage of patients arriving at Drug Resource Enhancement Against AIDS and Malnutrition centers with CD4 cell counts >350 cells/mm^3 and starting antiretroviral therapy after each 6-month simulation step. More than 75% of patients initiated therapy within the first 2 years.

Considering an annual ART cost of 1342 USD per person-year [12], the total cost of scenario A becomes lower in 22 years. An HIV-infected individual represents a cost to the healthcare system even if no ART is provided. This cost, estimated at $950 USD per person-year, was included in scenario B and demonstrates that universal treatment becomes economically efficient after 4 years. Figure 5 illustrates ART cost estimates of scenarios A and B and total costs of scenario B over time.

DISCUSSION

Our findings, based on parameters obtained from an existing cohort of patients in Malawi and Mozambique, support the main conclusions of the Granich study [1], that is, treatment of all infected individuals translates into a drastic reduction in incident HIV infections and leads to the "sterilization" of the epidemic. Both modeling approaches demonstrate a clear reduction of new cases well below the substitution threshold. Randomized controlled studies such as HPTN 052, which evaluated HIV sexual transmission in serodiscordant couples, effectively demonstrated a 96% reduction in HIV transmission when the index partner was treated with triple ART at a relatively higher CD4 cell count threshold (350–550 cells/mm^3) [13]. Data from mother-to-child transmission studies have extensively demonstrated that a marked reduction in HIV transmission is achievable with viral load suppression [14–16]. The model from our study, based on real-life parameters, confirms this assumption.

Our model demonstrated a slightly lower reduction in HIV incidence than the Granich simulation [1]. In our model, the 2% incidence threshold is reached in 2 years, but it takes 20

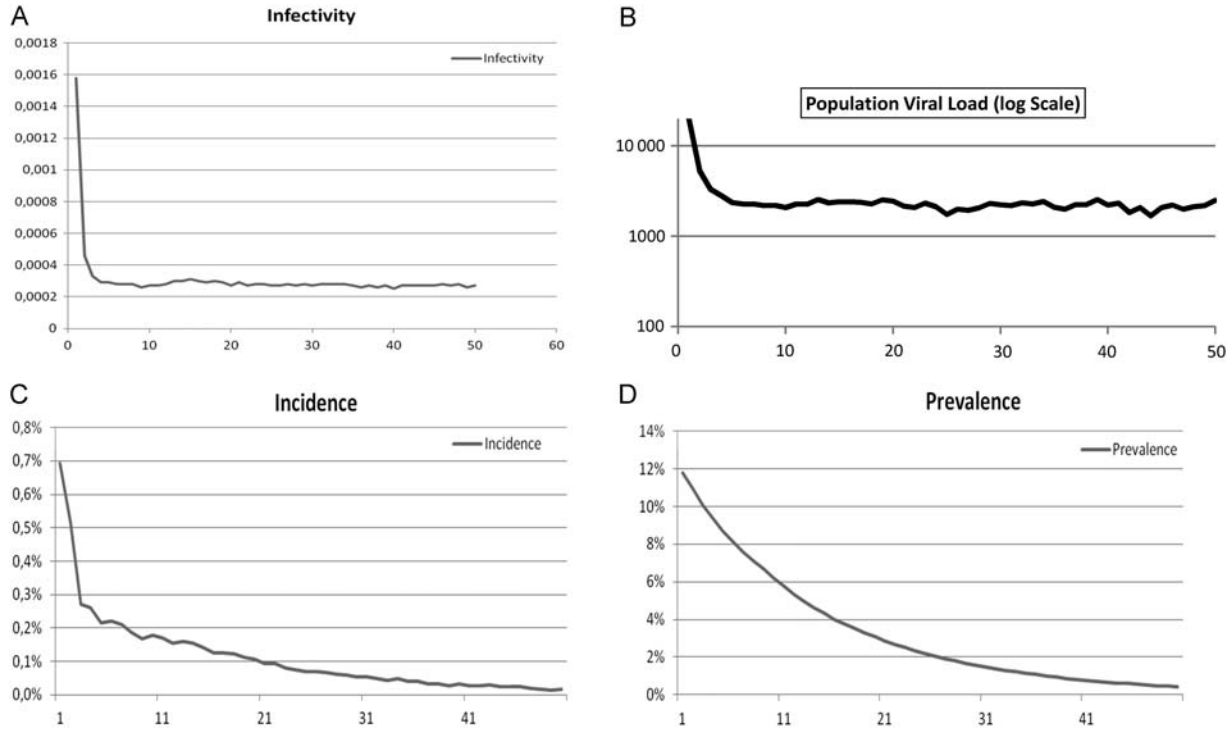

Figure 3. The simulation used the following parameters: population, 300 000; initial prevalence, 12%; population growth rate per year, approximately 2.3%; number of 6-month simulation steps, 100; probability that a patient will be lost to follow-up, 3%; death rate among patients lost to follow-up after 6 months, 50%; initial treatment coverage, 50%; and coverage after 1 year, 100%.

years (as opposed to 10 years in the prior model) for HIV incidence to fall below 1%. We do not consider this difference relevant, however, because it is probably due to differences in the timing of enrollment. In the Granich model [1], one parameter for the simulation is that there is immediate intervention for all HIV-infected patients. In our model, the access to intervention for patients with CD4 cell counts >350 cells/mm^3 is delayed until this threshold is reached. The most significant finding in our model was the substantial and stable reduction in viral load infectiousness in our population, even if a more gradual approach to ART initiation was implemented in our scenario. This was a conservative approach, as in our opinion, acceleration of the ART initiation process would be the optimal end point, because such a measure would enhance the sustainability of HIV/AIDS programs worldwide.

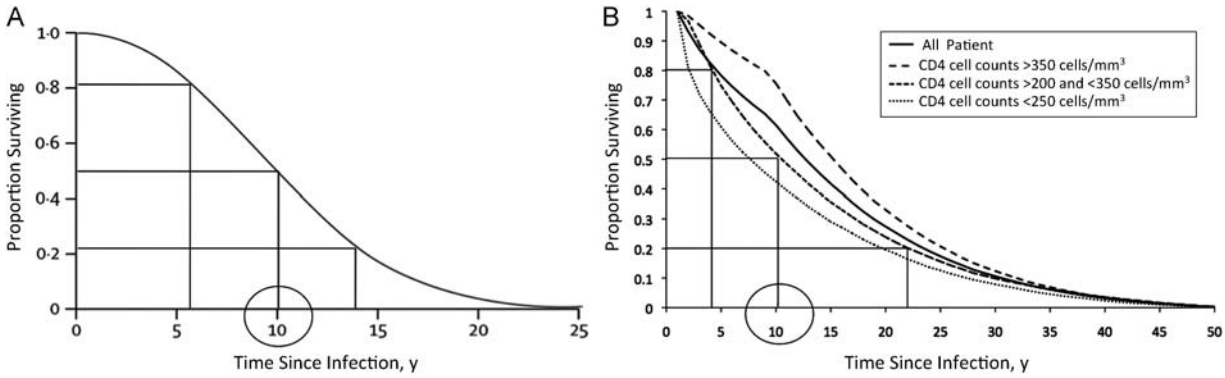

Figure 4. Mortality distributions in the model used by Granich et al (*A*) and the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) model (*B*). In the DREAM model, we considered 4 different scenarios on the basis of CD4 cell counts. In both models, the number of infected individuals declines by half in approximately 10 years.

Table 6. Cases of HIV Infection During a 5-Year Period in the Drug Resource Enhancement Against AIDS and Malnutrition Patient Model

Year	Total Cases	New Cases	HIV-Related Deaths	General Population (Adults)	Incidence Rate, %	Prevalence Rate, %
1	17 110	1190	2320	149 025	0.799	11.481
2	15 980	275	1290	149 475	0.184	10.691
3	14 965	185	1205	150 210	0.123	9.963
4	13 945	180	1100	150 960	0.119	9.238
5	13 025	185	820	151 945	0.122	8.572

Abbreviation: HIV, human immunodeficiency virus.

Estimates for the number of HIV infections and HIV-related deaths were generated by the patient model over a 5-year period, including corresponding incidence and prevalence rates.

Our model also differed in that the reduction in prevalence was steeper in our approach, with the 1% prevalence threshold attained at 40 as opposed to 50 years. However, both simulations corroborate each other, because small variations in patient loss to follow-up or adherence can produce considerable changes in the prevalence parameter. In our model, the rate of loss to follow-up was 3%, and although it was twice as high as the loss to follow-up reported in our program [17], we concluded that it would be a more realistic figure. The simulation predicts that in 10 years, the prevalence would be halved, and this seems to be the most reliable forecast. Both models have a structural limitation because of the duration of the observation. Although the data seem very robust over a 5–10-year range, it becomes very difficult to model 20–30 years forward because of the well-characterized clinical complications of HIV/AIDS and also the inherent difficulty posed to African health services with long-term care.

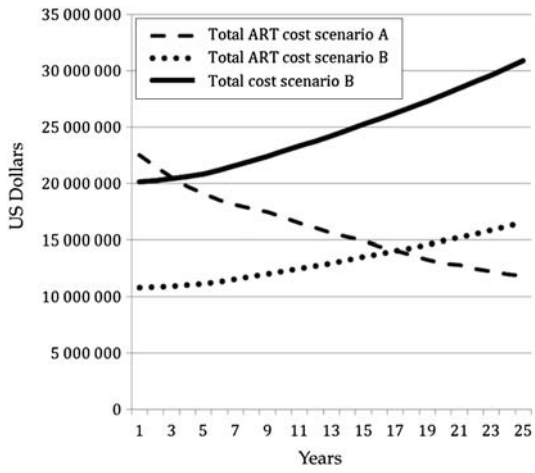

Figure 5. Antiretroviral (ART) cost estimates in US dollars. In the first scenario (scenario A), universal access to ART was considered, so the costs of treatment for all eligible patients are shown. In scenario B, we represent costs related to the treatment of the 45% of patients who were eligible patients. The total cost of scenario B include costs derived from the provision of ART to eligible patients and patient costs for individuals who have not yet started ART.

Although the CD4 threshold of 350 cells/mm^3 was used, a direct head-to-head comparison of the 2 models is not possible, because our model carries 2 important exceptions. It included immediate treatment of new cases identified through annual testing and immediate treatment of pregnant women regardless of CD4 count strata. Because of the decline in CD4 counts over time in patients who had counts of >350 cells/mm^3 at entry, in 3–5 years, the 2 models coincide in approach.

The DREAM model offers the advantage of gradual implementation at a district level that is chosen as a priority area. The main obstacle to universal voluntary counseling, testing, and treatment is the dimension of the ordeal, which poses enormous and unsolvable challenges from the economic and human resources perspective, and therefore, a focused approach is preferable. Sustainability cannot be attained in a short period of time, because these changes would profoundly affect the entire health system and require a complex organizational process. In our assessment, a mobile health organization with a strong focus on communication and information technology would need to be developed, implemented, tested and validated in well-defined areas. The focus on districts would facilitate policy choices, because areas of high prevalence or incidence could be targeted initially, or districts could be chosen if they possess adequate communication facilities and infrastructure. The critical end point is that after 3 years, based on the model, the policy would be economically sustainable.

Our economic analyses did not take into consideration the economic burden of the morbidity and mortality of HIV/AIDS in individuals not receiving ART, which, if included, would increase the economic sustainability of universal treatment [18]. Another factor to be considered is the reduction in number of orphans and pediatric HIV infections attributable to maternal treatment, which renders perinatal transmission rates of <2% [14, 16, 19–21] and reduced maternal mortality [22–23]. These variables do not affect the epidemic trend but

are critical in survival and economic analyses. A limitation of our model was that limited data were available for patient clinical history extending beyond 6–8 years. Moreover, the model focuses on sexual transmission or vertical transmission modalities only. However, such limitations did not affect the validity of the entire scenario and projections, although it is clear that the ability to rapidly implement universal ART may vary between districts and countries.

In conclusion, our model offers a reasonable compromise as an implementation strategy that combines massive population coverage albeit within current economic and human resource constraints. Sterilization of the HIV epidemic, district by district, would offer the opportunity for furthering a strategy that could be scaled up, with substantial benefits to health care systems in sub-Saharan Africa.

Notes

Author contributions. L. P., G. M. B., A. N., P. G., G. L., K. N. S., S. O., S. M., E. B., P. S., A. M. D. A., G. G., S. C., J. H., I. Z., N. A. M. and M. C. M. participated in the development of the conceptual framework, in the data analysis, drafting, and approval of the final version of this manuscript.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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