The United Nations and the Quest for the Holy Grail (of AIDS)

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Summary

In response to the HIV/AIDS pandemic, worldwide interest in HIV treatments has grown, but uncertainty remains about how to fund treatments. Nations must choose between combinations of sexual education, antiretroviral treatments (ART), and vaccine research. We aim to quantify the effects of each of these treatments in order to determine how best to confront AIDS.

We propose an iterative deterministic model for measuring the progression of HIV through 2050. The crux of our model is use of expressions that predict infection and death rates. Our model accounts for the three main factors in transmission: unprotected intercourse, non-sterile drug needles, and births of children to HIV-positive mothers. Furthermore, we analyze country-specific parameters, such as prevalence of HIV among subpopulations (e.g., homosexuals) as well as condom usage and risky-sex rates, and model the influence of treatments. Additionally, we investigate the impact of multiple-drug resistance. Using data extrapolated from South African prenatal clinics, we recreate historical trends to demonstrate our model's capacity for accurate prediction.

Our goal is to assess which methods minimize the number of HIV cases in both the short run and the long run, and to use these results to guide policy decisions. Condom usage, ARV therapy, and a vaccine all affect the course of HIV development. Current aid efforts, including sexual education, which reduce risky sex and promote condom use, are very valuable.

We predict that current downward trends will continue and that the HIV outbreak is beginning to recede. If ART does not decrease the transmission rate, its widespread use may increase the scope of an outbreak; if it does decrease the

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transmission rate, it can be an important factor in containing HIV. We conclude that vaccines provide the greatest promise for long-term prevention.

We propose an economic model for distributing resources. Even with a vaccine, economic considerations promote ARV usage. We finally recommend universal sexual education, distribution of ARVs based on infection profiles, and adequate endowment for research toward a vaccine, the holy grail of HIV.

Introduction

We focus on countries selected for diversity of the origin of their outbreak and ability to be extrapolated to other outbreaks:

- South Africa has a large HIV/AIDS population but little drug use.
- India has an enormous population and a small but growing AIDS presence.
- Russia has a large HIV-positive injected-drug community.
- The United States has a fairly small HIV population (clustered among its homosexual population) limited by the high safe-sex rate.

Experimental

Overview

An important factor in the continuation of an epidemic is R_0, a measure of the reproductive rate of the disease: on average, each HIV carrier infects R_0 other people [Velasco-Hernandez 2002]. An epidemic spreads only if R_0 is greater than 1. A treatment is preventive if it decreases the reproduction rate.

We create an iterative deterministic model. In each iteration, the number of new HIV/AIDS cases is a function of the previous state of the system, along with the expected rate of disease transmission. Hence,

$$R_0 \propto \frac{d(\text{total AIDS population})}{d(\text{time})}.$$

Because R_0 is useful as a measure of the change in total population, we discuss results in terms of trends and total HIV-positive populations.

The model determines the change in HIV/AIDS victims based on both new cases of HIV as well as deaths of previous HIV victims due to AIDS.

The three primary vectors for transmission of HIV are unprotected sexual intercourse, use of "dirty" (reused) drug needles, and childbirth by HIV-positive mothers. We balance these factors against the death rate in order to determine the net number of new cases. We use a feedback-based model for death, where the number of AIDS deaths is based on the expected life span of a victim and the number of victims who contracted HIV at specific previous points in time.

Basic Model

The general system of the previous section can be written as:

$$\#\text{aids}(t) = \text{newInfections}(t) + \#\text{aids}(t-1) - \text{deaths}(t),$$

where $\#\text{aids}(t)$ is the total number of living HIV / AIDS victims in year t. Our initial point, t_0, is the year 2000. Values at indices $t < 0$ are from historical data.

New Infection Rate

The basic model assumes that HIV transmission occurs only during sex, that is, $\text{newInfections}(t) = \text{intercourseT}(t)$, the number of new HIV victims due to unprotected sexual intercourse. Later we model other methods of transmission.

We model HIV transmission due to sex as related to the number of instances of intercourse times a rate of transmission per sex act [Smith 2005]. The transmission rate male $\rightarrow$ female is twice as high as the rate female $\rightarrow$ male. We use ρ to represent the total risk of transmission through sexual contact; the number of instances of intercourse is proportional to ρ. We assume an average intercourse rate of 3 times per week, or about 160 times per year [Leynaert et al. 1998]. Taking into account heterosexual anal intercourse causes an increase of the risk factor ρ to 200 (or more).

Since we assume primarily heterosexual intercourse, we track separately the HIV / AIDS population of each sex. We use subscript M to denote a function (or variable) that includes only men, and F to denote a function including only women. Hence we represent the intercourseT rates as

$$\begin{aligned}\text{intercourseT}_{\text{M}}(t) = {} & (\text{percent unaffected men}) \times (\text{number of affected women}) \\ & \times (1 - (\text{condom use rate})) \times (\text{risk constants}).\end{aligned}$$

That is, for men:

$$\begin{aligned}\text{intercourseT}_{\text{M}}(t) = {} & (1 - \%\text{aids}_{\text{M}}) \times \#\text{aids}_{\text{F}}(t-1) \times (1 - \text{condomRate}) \\ & \times \left(\rho \times \text{riskSexCons}_{\text{M}}\right);\end{aligned}$$

and for women:

$$\begin{aligned}\text{intercourseT}_{\text{F}}(t) = {} & (1 - \%\text{aids}_{\text{F}}) \times \#\text{aids}_{\text{M}}(t-1) \times (1 - \text{condomRate}) \\ & \times \left(\rho \times \text{riskSexCons}_{\text{F}}\right).\end{aligned}$$

Assumptions

- Condom usage is static over time, a worst-case scenario, since it is unlikely that condom usage would decrease if sexual education programs follow the status quo or become increasingly well-funded and organized.

- Condoms are 100% effective. This assumption is very close to reality (>99% effective) and is a useful simplification.
- All sexual acts have the same (very low) chance of infection. This assumption allows us to treat monogamous and promiscuous sexual behaviors as equally likely to spread HIV.

Death Rate

Most carriers of HIV eventually die of AIDS; we assume that all do. On average, it takes 9 years for an HIV infection to become AIDS [Morgan 2002]. We assume that regular sexual activity stops when symptomatic AIDS occurs; hence, the number of years of activity after HIV infection is 9–10. We denote this parameter as averageDeath. We use a feedback loop for the death rate:

$$\text{deaths}(t) = \text{newInfections}(t - \text{averageDeath}).$$

Assumptions

- All HIV carriers die of AIDS. This major simplifying assumption prevents having to track population ages. Overall it causes a (slight) increase in the average life span of the HIV carrier, and hence is a worst-case estimate. This assumption is also tempered by our treatment of ART (see below).
- While ART increases life span, the average age at HIV contraction plus the new life span cannot exceed the life expectancy. This assumption minimizes the impact of the assumption that all carriers die of AIDS.
- Each carrier dies after being infected for exactly averageDeath years.

Additional Model Parameters

Transmission Due to Reproduction

A major social impact of HIV/AIDS is creation of an orphan population whose parents have both died of AIDS, a common phenomenon with large percentages of HIV-infected adults (such as in South Africa). The birth of infected babies, however, does not impact new cases, because they die before they participate in any form of transmission (intercourse, drug-needle use, and childbirth). For risk of transmission at childbirth, we use 35% in undeveloped countries and 1%–5% in developed countries [UNAIDS and WHO 2005]. Transmission due to childbirth is calculated as

$$\text{birthT}(t) = \text{birthRate} \times \#\text{aids}_{\text{F}}(t-1) \times \text{riskBirth}.$$

Assumptions

- All infected children die before contributing to the spread of HIV/AIDS.
- Women with AIDS are as likely as other women to have a child; because of the previous assumption, this assumption has low impact on the model.

Transmission Due to Drug Needles

Needle-sharing is an important factor in HIV transmission in many countries, including India and Russia. To incorporate drug needles, we re-express the infection rate as

$$\text{newInfections}(t) = \text{intercourseT}(t) + \text{needleT}(t).$$

We calculate the needle transmission rate based on a drug risk factor ρ_D, the average number of drug injections per drug user per year. We also assume that the dirty-needle rate is 35% [UNAIDS and WHO 2005]. We account for the sex difference in drug use (an 80/20 male/female split). We take the risk of infection from a single drug use (riskDrugCons) from Leynaert et al. [1998]. Hence, the drug transmission rate is

$$\begin{aligned}\text{needleT}(t) = {} & (\text{number of drug users HIV negative}) \times \\ & (\text{chance of sharing a drug needle with someone HIV positive}) \times \\ & (\text{risk factors and constants}),\end{aligned}$$

that is,

$$\text{needleT}(t) = \#\text{HIV}^{-}\text{DrugUsers}_{\text{M}} \times (0.35 \times \%\text{HIV}^{+}\text{Drug}) \times (\rho_D \times \text{riskDrugCons}).$$

Assumptions

- Constant dirty-needle rate.
- For each drug use, the chance of HIV transmission is the same.

Transmission Due to Homosexual Intercourse

In most countries, HIV/AIDS is not associated with the homosexual community; rather, the more common carriers are (heterosexual) sex workers. In the United States, however, a disproportionate portion of HIV victims are homosexual. In the model, we compute transmission due to homosexual intercourse very similarly to intercourseT(t). The major change is assuming that homosexuals have solely homosexual sex, with a different risk per sexual act constant (also from Leynaert et al. [1998]).

$$\begin{aligned}\text{intercourseT}_H(t) = {} & (\text{percent unaffected gay men}) \times \\ & (\text{number of affected gay men}) \times (1 - \text{condom use}) \times (\text{risk constants}),\end{aligned}$$

or

$$\text{intercourseT}_H(t) = (1 - \%\text{aids}_H) \times \big(\#\text{aids}_H(t-1)\big) \times (1 - \text{condomRate}) \times \big(\rho \times \text{riskSexCons}_H\big).$$

Antiretrovirals

The foremost effect of ARVs is not to prevent transmission but to extend life span. There is no scientific consensus on the effect of ART on transmission [Anderson 1992; Krieger 1991; Royce 1997]. Hence, we incorporate this effect as an input parameter, arvFactor; we let it vary between 0.25 and 1. Another input parameter is arvPortion, the percentage of HIV-positive individuals who receive ARV treatment. We implement ART by assuming that large-scale treatment begins around 2015, after deployment of infrastructure. We assume that ARV patients have a slightly decreased amount of risky sex, due to increased sexual education from repeated contact with health personnel.

We calculate the transmissions due to ART patients and other HIV victims separately:

$$\text{newInfections}(t) = \text{intercourseT}(t) \times (1 - \text{arvPortion}) + \text{intercourseT}(t) \times \text{arvPortion} \times \text{arvFactor}.$$

We assume 100% adherence (except when talking about resistant-strain development; see below).

Drug Resistance

A risk involved in antiretroviral therapy is the creation of treatment-resistant strains of HIV. This can occur when an ART patient follows the treatment regimen incompletely; selection pressures on the virus eases, allowing HIV to replicate once again in greater numbers resistant to the drugs.

We model drug resistance using the parameters in the problem statement. ARV-resistant infections are tracked separately, so that, while ARV-resistant carriers may continue to take ART, they do not benefit. The number of new ARV-resistant strains that develop as a direct result of missing ARV treatments is modeled as

$$\text{newInfections}_{\text{resistant}}(t) = (\%\text{ aids victims on ARV}) \times (1 - (\text{adherence rate})) \times (\text{chance to mutate}).$$

We assume that 85–95% of ART patients adhere to treatment [Rutenburg 2006].

The Holy Grail, or, The AIDS Vaccine

We model a vaccine by assuming that as immunizations increase, a growing portion of the population is unable to contract HIV. This is in direct contrast to

the way in which ARV affects HIV/AIDS rates. Originally we had

$$\text{intercourseT}_{\text{F}}(t) = (1 - \%\text{aids}_{\text{F}}) \times \#\text{aids}_{\text{M}}(t-1) \times (1 - \text{condomRate}) \times \big(\rho \times \text{riskSexCons}_{\text{F}}\big).$$

The factor $(1 - \%\text{aids}_{\text{F}})$ determines what portion of the population can catch HIV, which in the case of a vaccine becomes $\big((1 - \%\text{aids}_{\text{F}}) - \%\text{vaccinated}\big)$. We assume the same vaccination rate for both men and women, hence apply no subscript to that term.

To simulate %vaccinated, we fit a logistic curve. We assume that a vaccine will be available by 2015 and a well-regulated vaccine program will achieve steady-state vaccination by 2030. The curve starts at 0% and plateaus at a steady-state level equal to the second-dose tetanus-typhoid vaccination rate for that country (as given in 2002 WHO data for the problem statement). We use a logistic curve because the rate of increase

- will be low at first, since awareness will be low and infrastructure is needed;
- will increase as awareness builds and as infrastructure becomes established; and
- will decline as people become vaccinated and fewer remain unvaccinated.

Assumptions

- The vaccine is 100% effective.
- The vaccine distribution program is well-organized.

Country Choice and Country-Specific Parameters

To determine the countries most critical in terms of HIV/AIDS from 2006 to 2050, we used five indicators:

- trends in prevalence rates,
- demographics of infected population,
- level of HIV/AIDS education and awareness,
- routes of transmission,and
- integrity and availability of current and historical HIV/AIDS statistics,

Based on these indicators, we selected a country from each of the continents Africa, Asia, Europe, North America, and Australia, namely, South Africa, India, Russia, U.S.A., and Australia.

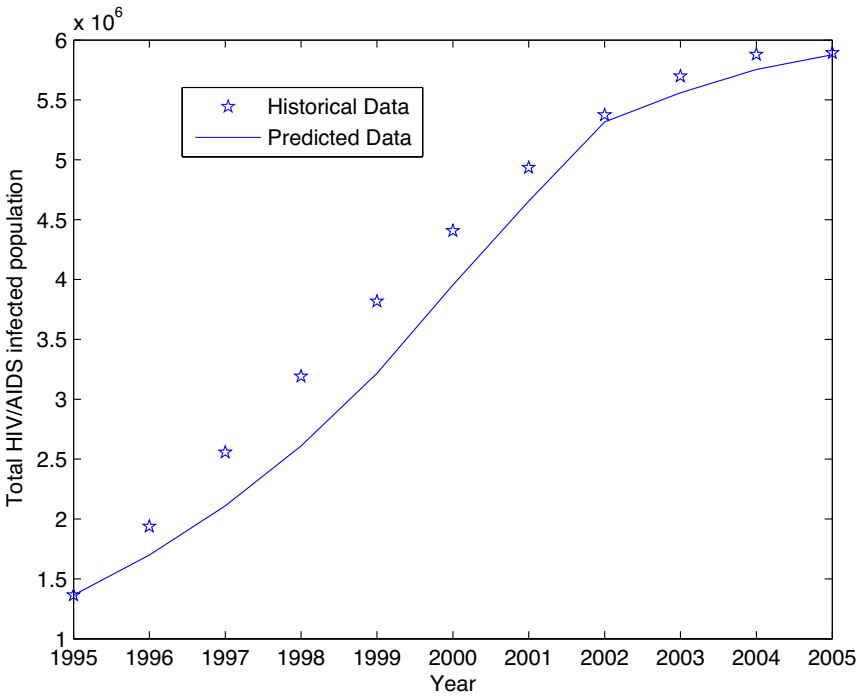

Figure 1. Comparison of model to South African historical data.

Results

Historical Fitting

We validate our model by examining historical HIV rates from prenatal clinics in South Africa between 1995 and 2005 (**Figure 1**). Our model fits the data well with three minor changes:

- a slight decrease in the life span of the average HIV patient (to 7 years from 9; this difference is probably due to lower sensitivity of HIV detection tests at earlier time points);
- an increase in the risky-sex rate constant (which is very unsurprising, since the data predate much sexual education effort); and
- increasing condom use rate over time.

Results by Country

The model predicts the following trends in the HIV / AIDS population:

- An increase in condom usage leads to a decrease in cases.
- An increase in the average life span of a patient leads to an increase in cases.
- A decrease in the transmission rate leads to a decrease in cases.

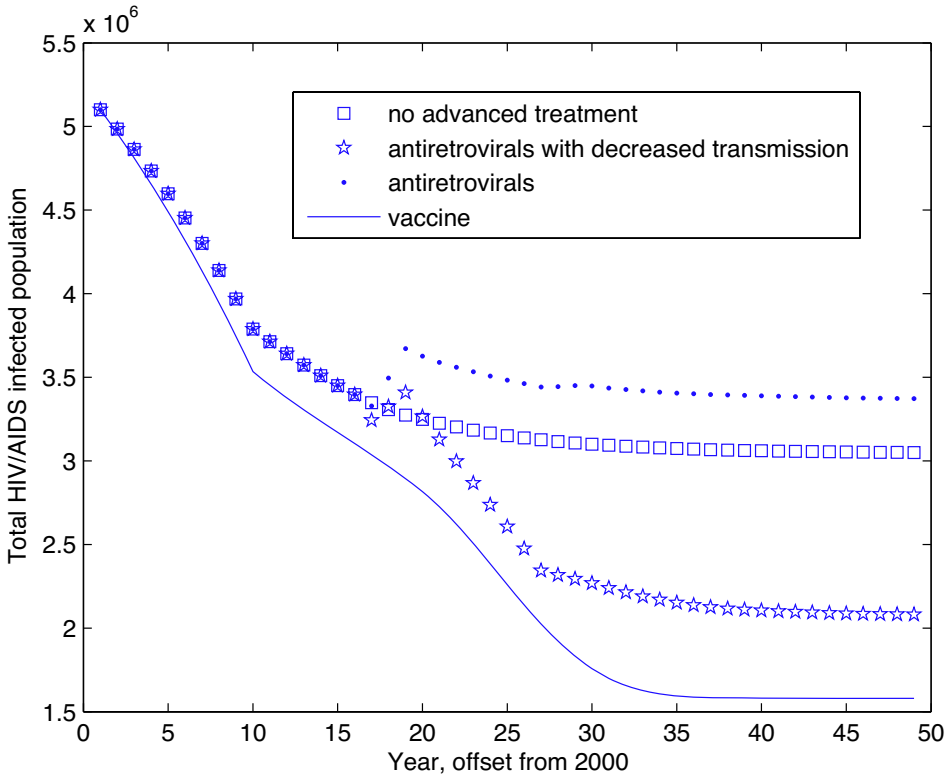

Figure 2. Prediction of HIV / AIDS epidemic in South Africa.

- Distribution of ARV drugs reduces the number of cases due to sexual acts only if ARVs cause a decrease in the per-act transmission rate.
- Steady distribution of a vaccine steadily decreases cases to a baseline level.

South Africa

The model (**Figure 2**) predicts a decrease in cases prior to 2015 for all scenarios. Introduction of ART shifts the steady-state level—to higher if no decrease in transmission, to drastically lower with decrease in transmission. The sudden increase in 2020 results from the assumption that ART instantaneously increases the life span of all infected individuals, thereby suddenly lowering the death rate. Thus, the deviation is an artifact of our assumptions.

Implementation of a well-regulated vaccine program starting in 2015 leads to a gradual decrease in cases over the next 20 years, with a significant portion of the disease eradication occurring between 2020 and 2025.

India

The model (**Figure 3**) indicates a steady increase in cases over the next 45 years. This differs from the observed trend in South Africa most notably because of significant drug usage in India.

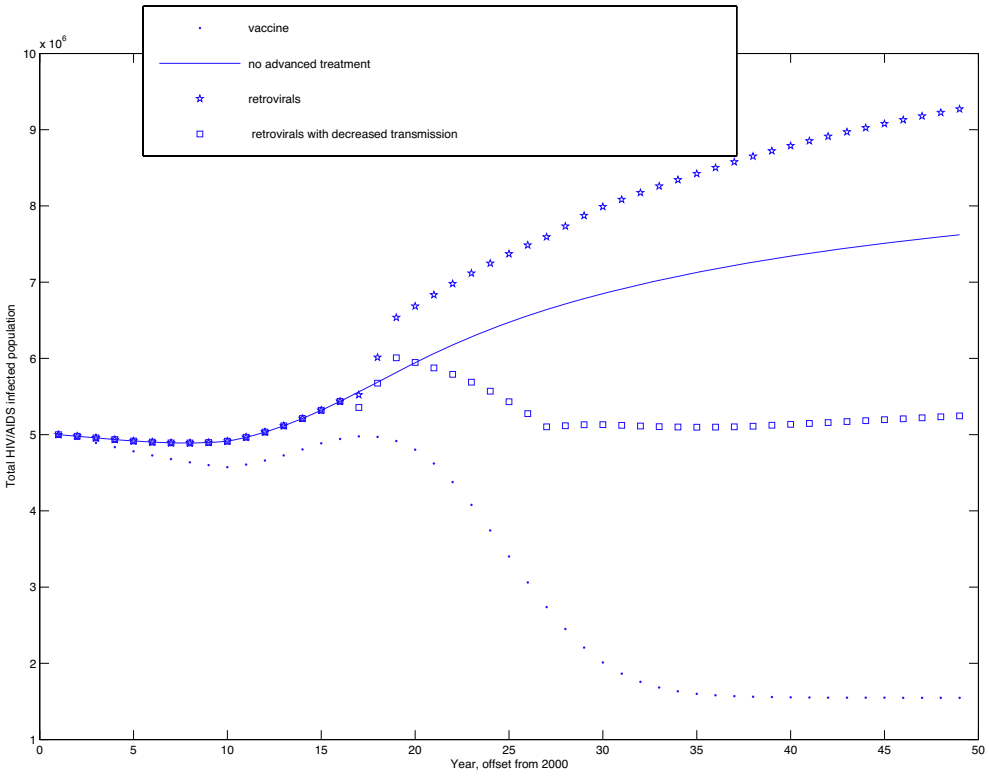

Figure 3. Prediction of HIV/AIDS epidemic in India.

The introduction of ART that increases only the life span increases cases every year; with accompanying decrease in transmission, cases decline. Again there is a small sudden jump around 2020, a consequence of our assumptions.

With a vaccination program, possibly supplemented with ARV drugs, the model predicts that cases will plateau soon after 2030, again with the most significant decrease 5 to 10 years after implementation of the vaccination program in 2020 to 2025.

United States

In the United States, HIV/AIDS is predominantly spread through homosexual interaction. The model predicts the number of cases to exceed 6 million by 2050 if no advanced treatment is available (**Figure 4**).

In the U.S., unlike the other countries that we examine, ARV drugs that do not affect transmission rate have no effect on cases. ARV drugs that decrease transmission curb new cases; the model predicts a stable number of slightly over 3 million cases after 2030.

A well-regulated vaccination program largely eradicates the virus by 2035.

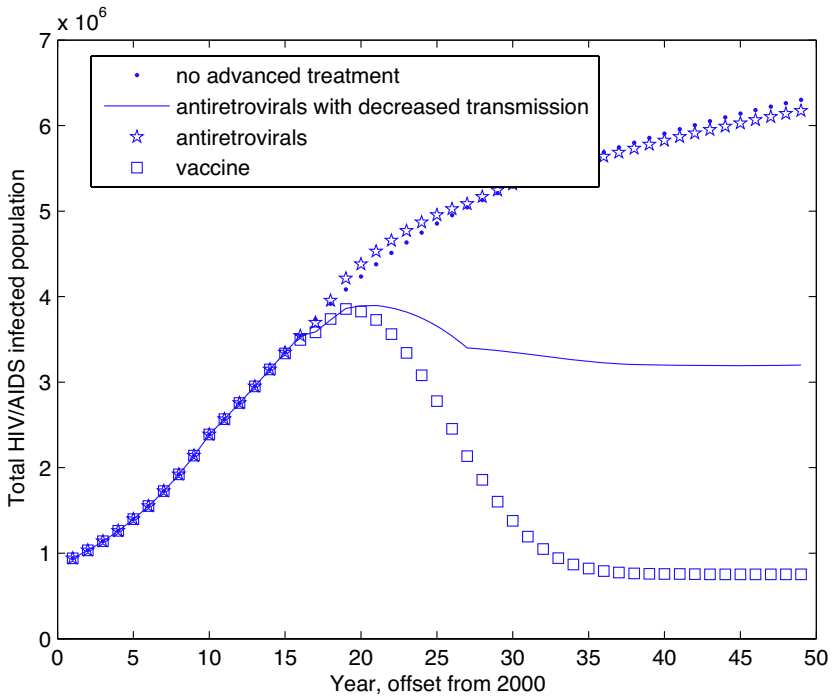

Figure 4. Prediction of HIV / AIDS epidemic in the United States.

Russia

The predominance of transmission through injected-drug use in Russia is much greater than in India and plays a larger role in spreading the virus.

For ART that decreases transmission, cases increase initially but level off much more quickly than for India or the U.S.

At the normal vaccination rate for a Russian adult, an HIV / AIDS vaccine causes the number of cases to decline from 2 million cases in 2020 (5 years after the implementation of the vaccine program) to 1 million cases by 2050. A vaccine program in Russia is not as effective as for India or the U.S. because of an unusually low adoption rate for vaccines (37%) in Russia. **Figure 5** shows a much faster eradication of the virus with a higher vaccination rate. Thus, Russia can significantly thwart cases by spending resources on increasing the general vaccination rate among adults.

Analysis

All of the models predict that vaccination is be the most effective method of HIV / AIDS eradication.

If ARV drugs do not influence the transmission rate, their introduction could be catastrophic. Increasing the life span of HIV / AIDS patients provides more time for each individual to spread the disease. Our model predicts more cases over the next 45 years for this scenario than for any other, for all countries.

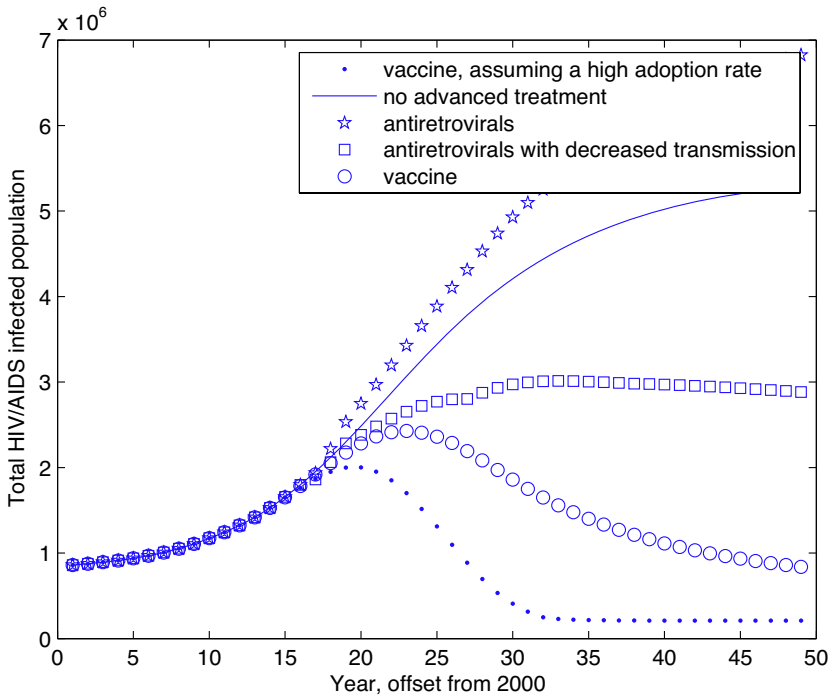

Figure 5. Prediction of HIV/AIDS epidemic in Russia.

The United States is an exception, where 63% of cases are among homosexuals [UNAIDS and WHO 2005]; an ARV program with no effect on transmission rate does not increase the number of cases. A possible reason is that though we assume that the use of ART implies that individuals are more informed and therefore less likely to perform risky sexual acts, there is not enough effect on people in the other countries modeled, while in the United States there is enough reduction in risky sexual acts to counterbalance the increase in life span.

ARV drugs that decrease transmission effectively curb the spread of HIV in every case, causing cases to remain fairly constant after 2030.

One of the least expected results is the decrease in cases in South Africa: The incidence of HIV/AIDS has peaked and is now on a downward turn. This however, is not completely unexpected, since HIV/AIDS has been present for the longest time in South Africa and general awareness about the disease has increased. Over time, an equilibrium point is reached; eventually the number of new cases equals the number of deaths due to AIDS, and the population of infected individuals remains fairly constant.

Analysis of Sensitivity and Individual Parameters

We tested condomRate (percentage of sexual acts performed with condoms) and arvPortion (percentage of HIV/AIDS population with access to ARV drugs). We also tested the effect of differences in transmission rate decreases due to ARV treatment and drug resistance.

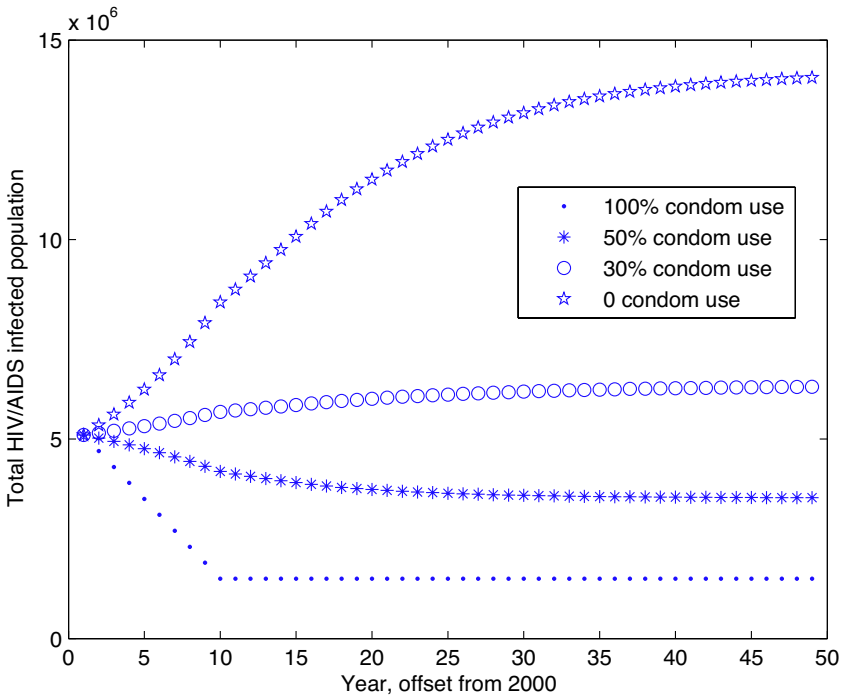

Figure 6. Effects of condom usage rate on model outcome

Figure 6 shows the effects of different values of condomRate on the number of cases in South Africa. The model is quite sensitive to the value. A rate of 50% results in gradual decrease in cases, and complete condom use results in disease eradication in 10 years (the time for pre-existing cases to die).

Figure 7 shows the effect of varying arvPortion. The assumption is that ART increases the life span of the patient but does not decrease the transmission rate; people infected now have a longer time to spread the disease. Fairly large changes in ART use lead to large changes in the number of cases, as expected.

Figure 8 assumes that ARV drugs reduce transmission rate by 25%.

Figure 9 shows the effects of ART adherence rates on the number of cases when ARV drugs lower the transmission rate. ART begins in 2020 and is swiftly followed by a decrease in the number of cases. When adherence is 100%, cases level off. As adherence decreases, multi-drug resistance is observed, resulting in a negation of the lower transmission rates of initial treatment with ARV drugs and a steady increase in cases in the following years. Moreover, the onset of multi-drug-resistant HIV/AIDS is earlier for lower adherence rates, which is intuitively correct. Our model is sensitive to the fairly large changes in adherence rates, which is what we would expect.

Economic Model for Administering ARVs

We discuss an economic model for administering ARVs abstractly in the absence of data, due to the difficulty of its collection.

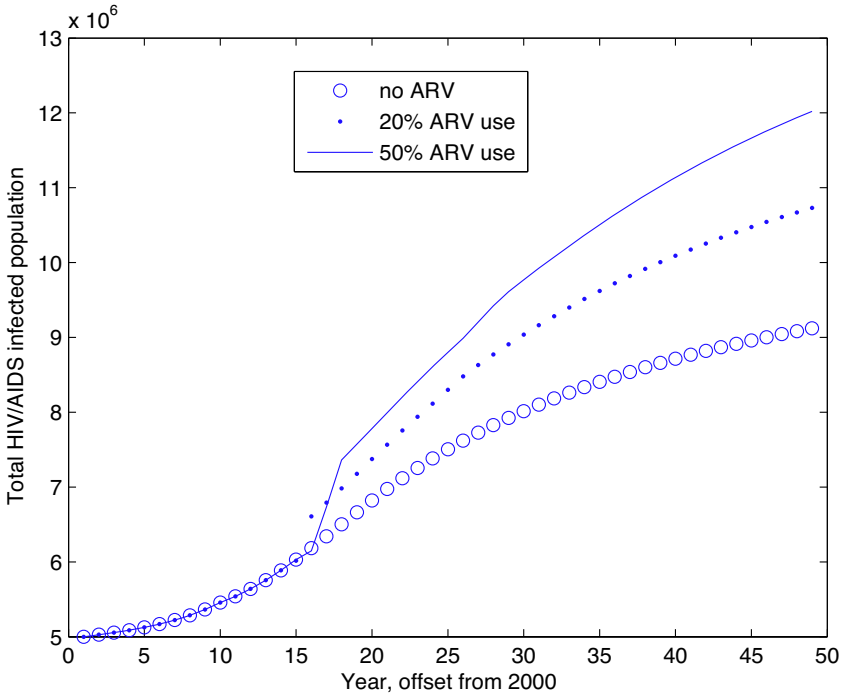

Figure 7. Effects of ARV therapy on model outcome, assuming no impact on transmission rate

Negative externalities can result from higher rates of infection as HIV / AIDS victims enjoy increased life expectancy and therefore have greater opportunity to spread the virus. Positive externalities can result from the cost savings that rich countries enjoy indirectly by reducing the infection rate in poor countries. For example, in Australia more than half of HIV infections attributed to heterosexual intercourse in 2000–2004 were in people from a high-prevalence country or whose partners were [UNAIDS and WHO 2005]. Hence, reducing infection rates in high-prevalence poor countries might reduce the rate of infection in rich countries.

[EDITOR'S NOTE: We omit the details of the authors' optimization analysis.]

Discussion and Conclusions

Strengths and Weaknesses

Strengths

- Ability to incorporate many data sources, such as condom usage rates, drug populations, and historical AIDS death rates.
- Scalable and easy to expand to account for new populational factors. Easy to adapt to new locations.
- High accuracy in fitting historical data.

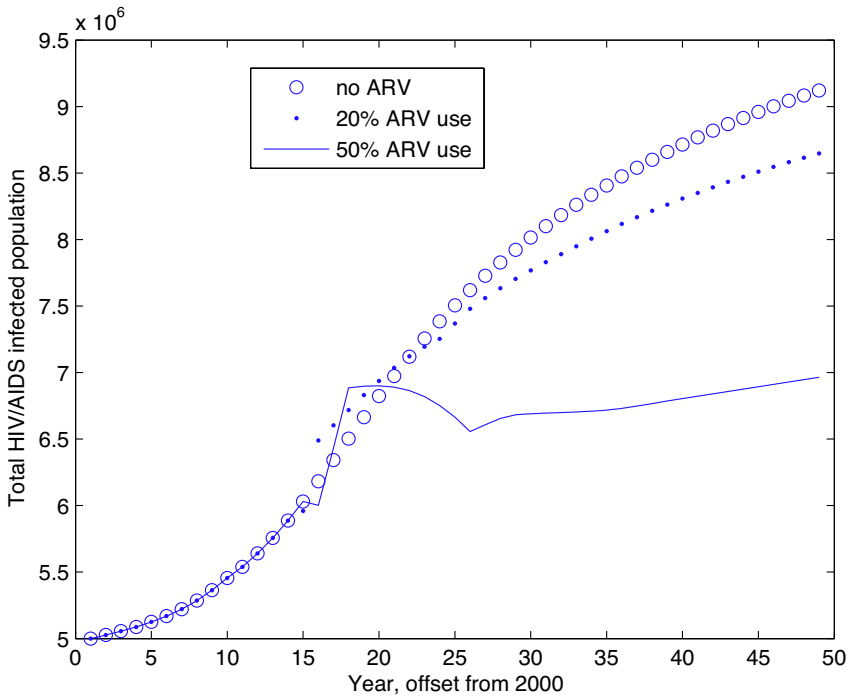

Figure 8. Effects of ARV therapy on model outcome, with ARV patients 25% less contagious.

- Comprehensive. Takes into consideration all the major factors concerned in HIV, including transmission factors, prevention techniques and economic considerations.

Weaknesses

- Large amount of prerequisite data required, some of which may be hard to acquire, such as historical HIV / AIDS death rates.
- Countries treated as isolated entities (does not account for migration).
- Fails to account for random differences between individuals, such as time to death after infection.

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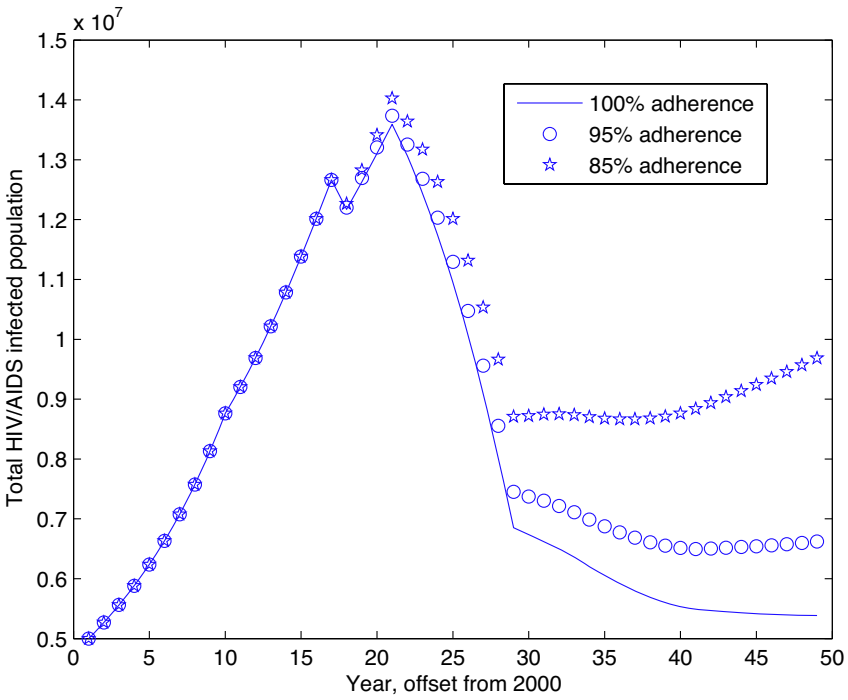

Figure 9. Effects of multiple drug resistance on transmission rate, assuming 100% ARV usage, and that ARV decreases transmission rate.

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