



Stochastic Evolution of Drug-resistant Strains of HIV in Botswana

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Abstract

Approximately 40% of adults in Botswana are HIV-infected. Currently their antiretroviral program (that began in 2002) treats 34,000 patients, with a goal of treating 85,000 patients (~30% of HIV-infected adults) by 2009. Here, we predict whether this high treatment rate will lead to high levels of transmitted resistance. The World Health Organization (WHO) has designed a surveillance system for Africa to detect transmitted resistance once a threshold of 5% is exceeded. We present a new stochastic dynamic model of the emergence and evolution of drug resistance. We formulate a birth-death-immigration Master equation, and obtain an analytical solution of the probabilistic epidemic dynamics. We use this model to predict the evolution of transmitted resistance in Botswana. We predict that – even if rates of acquired resistance are high, but drug-resistant strains are only half as transmissible as wild-type strains – transmitted resistance will remain low (< 5% by 2009) and will be undetectable by the WHO. However, we predict that transmitted resistance in Botswana could increase to ~15% by 2009, if drug-resistant strains evolve that are as transmissible as the drug-sensitive strains.

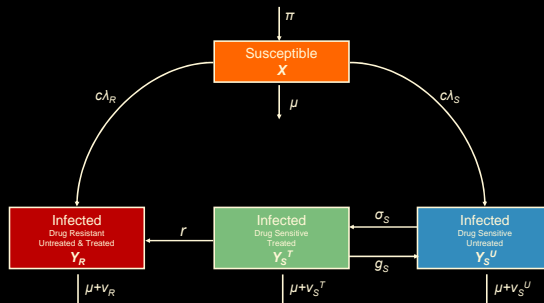


Fig. 1: Flow diagram illustrating the transmission dynamics of an HIV epidemic where ART is available. Sexually active adults are classified into one of four states: X , Y_S^U , Y_S^T and Y_R . Parameters given in Table 1. λ_S and λ_R are the time-dependent, per-capita drug-sensitive and drug-resistant HIV forces of infection, respectively, where $\lambda_S(t) = (\beta_S^U Y_S^U(t) + \beta_S^T Y_S^T(t)) / N(t)$ and $\lambda_R(t) = \beta_R Y_R(t) / N(t)$.

Introduction

The antiretroviral rollout in Africa is just beginning. A major public health concern is that widespread usage of antiretroviral therapy (ART) in Africa will quickly lead to high rates of transmitted resistance. The WHO has therefore drafted surveillance guidelines to monitor the emergence of both acquired and transmitted drug resistance during the rollout in Africa. The WHO plans to monitor newly diagnosed treatment-naïve individuals; their surveillance scheme is designed to detect levels of transmitted resistance that reach (or exceed) a threshold of 5%. However, no country-specific predictions have yet been made as to how quickly transmitted resistance is expected to evolve as the result of the rollout.

Here, we present a novel theoretical framework for forecasting the stochastic evolution of transmitted drug-resistant HIV. We use data from the Botswana ART rollout program to make specific predictions. We predict both the magnitude and the rate at which drug-resistant HIV will evolve by 2009. Specifically, we predict the effect on the stochastic evolution of transmitted resistance of (i) acquired resistance, and (ii) transmissibility of drug-resistant strains that may emerge.

Today, Botswana is one of the world's worst hit countries by the AIDS pandemic. An estimated 39% of Botswana's 730,000 adults between the ages of 15 and 49 are infected with HIV. In 2002 HIV/AIDS was declared the most serious threat to the country, and in that same year their ART program was introduced. Currently the program has 34,000 patients on treatment. The goal is to treat 85,000 patients (or equivalently 30% of HIV-infected patients) by 2009. Botswana has by far the highest treatment rate in Africa, and has currently exceeded their scheduled treatment goals. Botswana is now considered a test nation by foreign investors for ART programs in sub-Saharan Africa.

Conclusions

The WHO surveillance scheme for detecting transmitted resistance uses a binomial sequential lot quality assurance sampling (LOAS) method. The LOAS methodology determines a range for the minimum number of newly infected treatment-naïve adults to be sampled; the specified minimum range necessary to detect a 5% threshold of transmitted resistance ranges from 50 to 70. The LOAS methodology is easy to implement and is cost-effective, but does not yield a prevalence estimate; the surveillance scheme only determines whether the specified threshold has been exceeded, or not.

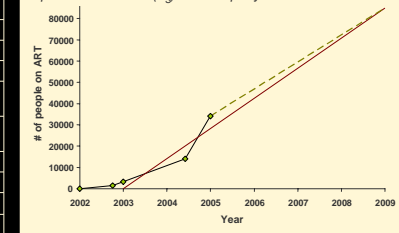
Botswana will have achieved high treatment rates by 2009. However, unless the strains of drug-resistant HIV that evolve in Botswana are extremely transmissible, the WHO threshold for detection of transmitted resistance will not be triggered by 2009. We suggest that WHO surveillance should be initiated in Botswana (and other African countries) only when transmitted resistance is expected to have exceeded the threshold.

The WHO will detect transmitted drug resistance in other sub-Saharan African countries that have less ambitious treatment programs than Botswana.

Table 1: Parameter definition and parameter values used in simulations.

Parameter definition	Symbol	Estimates
Inflow rate of new sexually active adults	π	49300 / year
Number of sexual encounters or contacts a susceptible adult is expected to have per year	c	1.76 / year
Average time an adult acquires new partners	$1/\mu$	34 years
The per capita effective treatment rate	σ_S	0.050 / year
Mean time for untreated infected adults to progress to AIDS	$1/\nu_S^U$	10 years
Mean time for treated infected adults to progress to AIDS	$1/\nu_S^T$	18 years
Mean time for drug resistant infected adults to progress to AIDS	$1/\nu_R$	12 years
Average time required for a treated person to develop drug resistance	$1/r$	3 - 5 years
The yearly proportion of cases suspending treatment	g_S	0.100
Untreated drug sensitive transmissibility coefficient	β_S^U	0.12
Treated drug sensitive transmissibility coefficient	β_S^T	0.04
Drug resistant transmissibility coefficient	β_R	0.03 - 0.12

Fig. 2: Observed statistical data are shown by the green diamonds. The aim is to reach 85,000 patients by 2009 (green dashed line). The treatment rate used by our model uses a linear fit shown by the orange line; this gives a constant per-capita treatment rate (σ_S) of 0.054 per year.



Methods

To predict the stochastic evolution of transmitted resistance we developed a continuous time Markov chain model. A diagram of our model is shown in Fig. 1.

Each year a proportion of the HIV-infected population can begin or discontinue treatment. Treatment benefits are modeled by increasing survival ($1/\nu_S^T > 1/\nu_S^U$) and by reducing transmissibility: $\beta_S^T > \beta_S^U$. Individuals on therapy have a constant annual probability (r) of acquiring drug resistance and progress to AIDS faster than drug-sensitive treated individuals ($1/\nu_S^T > 1/\nu_R$). Individuals infected with drug-resistant strains can transmit these strains; the transmissibility of drug-resistant strains is specified by β_R .

We derived a birth-death-immigration Master equation. We then solved the Master equation analytically and used this solution to determine a full description of the stochastic dynamics of the evolution of transmitted resistance. We then predicted the temporal stochastic evolution (to 2009) of transmitted resistance in Botswana.

We calculated the treatment rate (σ_S) for our predictions from data from the Botswana ART program. The program plans to treat 85,000 patients by 2009 (Fig. 2).

The evolution of transmitted resistance is driven by two key parameters: the rate at which acquired resistance develops in patients (r) and the transmissibility of the drug-resistant strains (β_S). Hence, we varied these two key parameters to make six predictions. We assumed that the drug-resistant strains that would evolve could be: (i) 25%, (ii) 50%, or (iii) equally as transmissible, as wild-type strains. Further, we assumed that patients (on average) could acquire resistance in either three or five years. Other parameter values are described in Table 1.

Results

Our predictions show that whether the WHO surveillance threshold of 5% is exceeded (or not) by 2009 will be very dependent upon both the transmissibility of the drug-resistant strains that evolve, and the rate of acquired resistance (Fig. 3).

If the drug-resistant strains that evolve are only 25% as transmissible as the wild-type strains then the WHO surveillance threshold will not be exceeded by 2009, even if the rate of acquired resistance is very high (Fig. 3A and 3B).

We predict that the WHO surveillance threshold will be exceeded by 2009 (and reach 7.5% if the rate of acquired resistance is very high and the drug-resistant strains that evolve are 50% as transmissible as the wild-type strains (Fig. 3D); however, the surveillance threshold will not be exceeded if the rate of acquired resistance is high (Fig. 3C).

Finally, if the drug-resistant strains that emerge are as transmissible as the wild-type strains then the WHO threshold will be reached in 2006 (Fig. 3F) or 2007 (Fig. 3E); levels of transmitted resistance could be as high as 15% by 2009 (Fig. 3F).

Obviously, if drug-resistant strains evolve that are more transmissible than wild-type strains the levels of transmitted resistance will be even higher (results not shown).

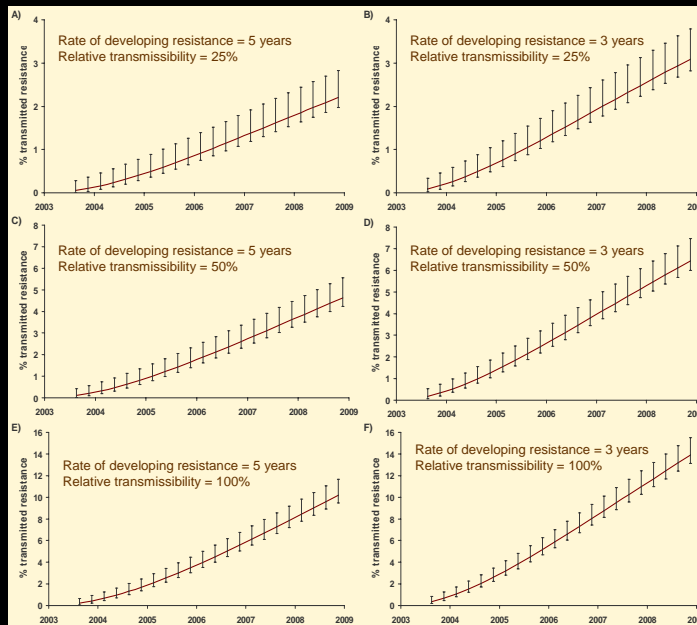


Fig. 3: Predictions showing quarter yearly expected percentage values of newly infected treatment-naïve adults that are drug-resistant. Red lines show the mean-field predictions, and the vertical bars are the fluctuation range within one standard deviation. Data are calculated using the model shown in Fig. 1. (A, C, E) a treated individual develops drug resistance in 5 years; (B, D, F) a treated individual develops drug resistance in 3 years. Drug-resistant transmissibility relative to the wild-type strains is taken to be 25% in (A, B), 50% in (C, D), and 100% in (E, F).

Acknowledgments

We thank Erin Bodine, Romulus Breban, Tom Chou, James Kahn, Justin Okano and David Wilson for technical discussions. RV and SB are grateful for the financial support of NIH/NIAID (RO1 A1041935).