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A Tale of Two Futures: HIV and Antiretroviral Therapy in San Francisco

S. M. Blower, H. B. Gershengorn, R. M. Grant

The effect of antiretroviral therapy (ART) in preventing human immunodeficiency virus (HIV) infections and averting acquired immunodeficiency syndrome (AIDS) deaths in the San Francisco gay community over the next 10 years was predicted. A transmission model was coupled with a statistical approach that enabled inclusion of a high degree of uncertainty in the potential treatment effects of ART (in terms of infectivity and survival), increase in risky behavior, and rate of emergence of drug resistance. Increasing the usage of ART in San Francisco would decrease the AIDS death rate and could substantially reduce the incidence rate.

Currently, 30% of the San Francisco gay community are HIV-infected (1). About 50% of these HIV-infected men are taking combination ART (2); these three or more drug regimens include recently developed protease inhibitors, nonnucleoside reverse transcriptase inhibitors, or both. Part of the recent decrease in the San Francisco AIDS death rate (3) could be attributable to the effect of ART, as ART decreases disease progression rates (4). However, because treated individuals are likely to retain some degree of infectivity, it is possible that ART could lead to an increase in the infection rate (5). Furthermore, drug-resistant HIV strains (that are less responsive to therapy) have emerged (6), and risky behavior has begun to increase in San Francisco (7). Therefore, whether the epidemic-level effects of ART will be beneficial or detrimental is unclear.

To predict with a degree of uncertainty the effectiveness of ART in the San Francisco gay community, we developed and analyzed a mathematical model. Our model includes the potential effects of ART on the transmission dynamics of both drug-sensitive and drug-resistant HIV strains. It is specified by five ordinary differential equations (8) (Fig. 1) and allows for drug-resistant strains (that differ in their infectivity and disease progression rates from drug-sensitive strains) to emerge during treatment and to be sexually transmitted (6). Acquired resistance develops because of a variety of factors (8); we model the aggregate effect of all these factors by a single parameter r. The model the potential treatment effects of ART by assuming that ART [by reducing viral load (9)] increases average survival time and reduces infectivity, and that drug-resistant strains will be less responsive to therapy than drug-sensitive strains (6). Treatment (in our model) has three outcomes. A patient can respond to ART and remain as a nonprogressor for a specified amount of time, experience clinical failure and death without developing drug resistance (9), or virologically fail treatment and develop drug resistance (10). Individuals can go on and off ART, and drug-resistant infections can revert to drug-sensitive infections if the selective pressure of treatment is removed (11) (Fig. 1).

We predicted the effectiveness of a high usage of ART over the next 10 years in the San Francisco gay community by analyzing our model with time-dependent uncertainty analyses (12, 13). Effectiveness was predicted in terms of the cumulative number of HIV infections prevented and the cumulative number of AIDS deaths averted (14). The San Francisco epidemic has been well studied, and the values of several of the parameters necessary for prediction are known (15); however, the values of other parameters are less certain. Hence, we conducted two uncertainty analyses (an optimistic and a pessimistic analysis) on the basis of different assumptions regarding the rate of increase in risky behavior and the rate of emergence of drug resistance. Both analyses included a high degree of uncertainty in the potential treatment effects of ART (on increasing survival and reducing infectivity). For the optimistic analysis we assumed that the rate of emergence of resistance would remain at a constant, fairly low value [only 10% of cases would acquire resistance per year (16)], and that risk behavior would not increase. For the pessimistic analysis we assumed that the rate of emergence of resistance could substantially increase [10 to 60% of cases could acquire resistance per year (17)], and that risk behavior could increase from almost no increase to a doubling (17).

For each uncertainty analysis we used our
model and Latin hypercube sampling (LHS), a type of stratified Monte Carlo sampling (18); LHS has been described elsewhere (12). To make predictions, we assigned each uncertain parameter a probability density function (pdf); the pdf reflected either the uncertainty in the value of the parameter, or the degree to which the parameter could vary if it was being used as an “experimental variable” (12). We used the usage rate of ART (F_S) as an “experimental variable” and predicted the effect of increasing usage rates that ranged from treating 50 to 90% of HIV-infected men; currently, only 50% of HIV-infected gay men in San Francisco take ART (2, 19).

We used a uniform pdf (range 0.5 to 0.9) to specify the uncertainty in F_S, where F_S represents the fraction of drug-sensitive cases. Fig. 1. Flow diagram of the transmission dynamics of an HIV epidemic in the presence of combination antiretroviral therapy (ART); for model equations see (8). The model keeps track of the temporal dynamics of five groups: susceptible individuals (X), untreated individuals infected with either drug-sensitive (Y_S^U) or drug-resistant strains (Y_R^U), and ART-treated individuals infected with either drug-sensitive (Y_S^T) or drug-resistant strains (Y_R^T). The parameter’s subscript specifies whether the infection is drug-sensitive (S) or drug-resistant (R); the superscript identifies whether the individuals are treated with ART (T) or untreated (U). Parameter definitions are as follows: \( \pi \) = rate at which gay men join the sexually active community; 1/\( \mu \) = average time during which a gay man acquires new sex partners; \( c \) = average number of new receptive anal sex partners per year; \( p \) = probability of a drug-resistant case (relative to a drug-sensitive case) transmitting drug-sensitive viruses; 1/\( q \) = average time for an untreated drug-resistant infection to revert to a drug-sensitive infection; \( r \) = rate of emergence of resistance due to acquired resistance; \( s \) = per capita effective treatment rate; \( e \) = relative efficacy of ART in treating drug-resistant infections; \( g \) = proportion of cases that give up ART per year; and \( v \) = average disease progression rate. \( \lambda \) specifies the per capita force of infection for drug-sensitive (\( \lambda_S \)) and drug-resistant (\( \lambda_R \)) HIV; \( \lambda_S \) and \( \lambda_R \) are calculated from Eqs. 6 and 7, respectively (8), and are a function of the number of infected people at any particular time (\( Y_S^U \), \( Y_R^U \), \( Y_S^T \), and \( Y_R^T \)) and the infectiousness (as specified by the transmissibility coefficients \( \beta_S^U \), \( \beta_R^U \), \( \beta_S^T \), and \( \beta_R^T \)) of each of the four types of infected people.

Fig. 2. Results of the two time-dependent uncertainty analyses on the effectiveness of ART on the San Francisco HIV epidemic. For each graph, every 6 months, the 1000 simulations are plotted as a box-plot; these plots show the median value (horizontal red line), upper and lower quartiles, and the outlier cutoffs. In (A) and (B), effectiveness is calculated in terms of the cumulative number of AIDS deaths averted (14); in (C) and (D), effectiveness is calculated in terms of the cumulative number of new HIV infections prevented (14). (A) and (C) show the optimistic predictions; (B) and (D) show the pessimistic predictions. ART decreases the death rate and reduces the incidence rate; these epidemic-level effects balance, hence the prevalence of infection remains fairly stable under both optimistic and pessimistic assumptions (29). However, after 10 years, a fairly high proportion (median value 42%) of the prevalent infections are drug-resistant (under pessimistic assumptions), whereas under optimistic assumptions, a substantially lower proportion (median value 26%) are drug-resistant (29).
The effectiveness of ART in terms of the cumulative number of AIDS deaths averted was the degree to which ART increased survival (1/\(v\)) (Table 1). The longer ART-treated individuals survived, the lower the cumulative death rate; under optimistic assumptions, this effect was relatively constant over time. Under pessimistic assumptions, this effect waned over time as the increased levels of risk behavior that initially caused a rise in the incidence rate were translated into an increasing death rate. The most important key factor in increasing effectiveness was the usage rate of ART (\(F_e\)) (Table 1). Increasing usage rates of ART significantly reduced the AIDS death rate and prevented a substantial number of new infections—under the optimistic assumptions and, perhaps surprisingly, even under the pessimistic assumptions. This conclusion is also shown by the unadjusted data generated by the uncertainty analyses (Fig. 3). Under optimistic or pessimistic assumptions, a high usage of ART substantially de-

<table>
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<tr>
<th>Parameter</th>
<th>Year 1</th>
<th>Year 5</th>
<th>Year 10</th>
<th>Year 1</th>
<th>Year 5</th>
<th>Year 10</th>
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<td><strong>PRCCs: Effectiveness calculated in terms of AIDS deaths averted</strong></td>
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<tr>
<td>Fraction of drug-sensitive cases treated ((F_e))</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
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<td>0.97</td>
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<td>Transmissibility coefficient of drug-sensitive, treated infection ((\beta'_T))</td>
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<td>-0.10</td>
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<td>Average survival time in drug-sensitive, treated individuals (1/(v_f))</td>
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<td>0.52</td>
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<td><strong>PRCCs: Effectiveness calculated in terms of HIV infections prevented</strong></td>
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<td>0.87</td>
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<tr>
<td>Transmissibility coefficient of drug-sensitive, treated infection ((\beta'_T))</td>
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<td>-0.96</td>
<td>-0.94</td>
<td>-0.51</td>
<td>-0.68</td>
<td>-0.72</td>
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<td>Transmissibility coefficient of drug-resistant, treated infection ((\beta'_R))</td>
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*Partial rank correlation coefficients (PRCCs) were calculated by using the 1000 values (generated by LHS) for each parameter included in the time-dependent uncertainty analyses and the 1000 predicted values of effectiveness (in terms of the cumulative number of AIDS deaths averted and new HIV infections prevented) generated by the model; PRCCs were calculated at each year in the 10-year time period. A parameter was identified as a key factor in determining effectiveness if the absolute value of the PRCC (at any year in the 10-year period) was greater than 0.5.

Table 1. Time-dependent sensitivity coefficients (PRCCs) for key parameters.
increased the death rate (Fig. 3A) and prevented a significant number of new infections (Fig. 3B).

Not surprisingly, effectiveness decreased as both the infectiousness of treated drug-sensitive (β2′) and drug-resistant patients (βR′) increased (Table 1). Hence, if infectiousness was reduced (either by increasing condom usage in treated patients or by developing more effective drugs for viral suppression), the effectiveness of ART would substantially increase. High rates of emergence of drug-resistant strains would result in a fairly high prevalence of drug-resistant infections (29), but our sensitivity results revealed that even these high rates of emergence of resistance would not significantly affect either the death rate or the incidence rate (30). The most important key factor that decreased the effectiveness of ART (both in terms of the number of deaths averted and the number of infections prevented) was the degree of increase in risk behavior (Table 1). Even under pessimistic assumptions, a high usage of ART decreased the incidence rate (Fig. 3B); however, an increase in risky behavior of only 10% was enough to counterbalance the benefits of ART (Fig. 3C). Greater increases in risky behavior resulted in the incidence rate increasing, and hence effectiveness becoming negative (Fig. 3C).

Since 1996–97 (when ART became readily available), the AIDS death rate in San Francisco has decreased (3). Our predictions show that a decreased death rate is to be expected under both optimistic and pessimistic assumptions. However, our optimistic and pessimistic assumptions lead to very divergent incidence predictions. Our results show that the higher the usage of ART, the greater the number of infections that will be prevented (Fig. 3B). Because the current usage rate of ART in the San Francisco gay community is ~50% (2, 19), the usage rate should be increased. Recently, increases in risky behavior in the gay community have been reported (7). Our results show that a high usage of ART could counterbalance the effect of increasing levels of risky behavior and prevent a substantial number of new infections. Our results imply that the incidence rate in San Francisco will first rise (to a level that will be determined by the degree of increase in risky behavior) and will then fall (to a level that will be determined by the degree of usage of ART).

Significant efforts should be made to prevent risk behavior increasing because even small increases will overcome the effect of ART on reducing the incidence rate (Fig. 3C). To maximize the effectiveness of ART, 13 treatment programs should be combined with effective behavioral intervention programs.

Mathematical models can be used as health policy tools to guide public health decisions (31). However, a model is always an abstraction of reality and never a mirror of reality. Our model reflects current biomedical understanding; we applied Occam’s razor to capture the essential processes of the transmission dynamics of drug-sensitive and drug-resistant strains in San Francisco. As biomedical knowledge accumulates our model can be made more complex, and as data accumulate we can reduce the uncertainty in our predictions. We have presented only short-term predictions because it is likely that more effective drugs and drug regimens will be developed over time; however, our model can also be used to evaluate the longer term consequences of ART (32). Here, we have used parameters that are specific for San Francisco, but our methodology can be applied to evaluate the impact of more widespread usage of ART in other HIV-infected communities.

References and Notes

2. R. Stall et al., in preparation.
9. ART suppresses viral load in blood (4), lymph nodes [W. Cavert et al., Science 276, 960 (1997)], cerebrospinal fluid [S. Staprans et al., AIDS 13, 1051 (1999)], and semen [P. Gupta et al., J. Virol. 71, 6271 (1997); S. R. Fauci et al., Proc. Natl. Acad. Sci. USA 95, 14 (1998)]. The total population size \(N = X + Y_s + Y_d + Y_r = Y_s + Y_d + Y_r\). As shown in Eq. 1, susceptible individuals can become infected with either drug-sensitive or drug-resistant strains at a rate \((\beta X_t)/N\) when using ART and behavior \(t\) that is less than or equal to 0.1; 0.12 years, c = 1.7 new risky sex partners per year, \(t = 2133\) gay men per year, and \(1/t = 30\) months. We assumed that ART can increase the average survival time of untreated drug-resistant cases \((1/\tau_{dR})\) by using sampling constraints during LHS to ensure that \(1/\tau_{dR} = 1/\tau_{dS}\) (25).

10. The average survival of cases can range from 12 to 36 months for both treated \((1/\tau_{dS})\) and untreated \((1/\tau_{dR})\) drug-resistant patients. Sampling constraints that ensured for all of the cases: \(1/\tau_{dR} = 1/\tau_{dS}\) (25). To model uncertainty in the impact of ART on reducing infectiousness in treated drug-resistant cases \((s_i)\), we used LHS to sample 1000 values of a multiplier \((u\alpha)\) from a uniform pdf \((0.0 \text{ to } 1.0)\). 1000 values of \(\alpha d_{R,dS}\) were then calculated by \(\alpha d_{R,dS} = \alpha d_{S,dS} - \alpha d_{R,dR}\). We modeled uncertainty in the average survival time of untreated drug-resistant cases \((1/\tau_{dR})\) by using sampling constraints during LHS to ensure that \(1/\tau_{dR} = 1/\tau_{dS}\) (25).

27. Uninfected and treated drug-resistant individuals could transmit drug-resistant strains with probability \(p_t\) and \(p_s\), respectively; we used LHS to sample 1000 values each of \(p_t\) and \(p_s\) from a uniform pdf \((0.0 \text{ to } 1.0)\). We modeled uncertainty in the average time before reversion \((1/\tau_{dR})\) by using LHS to sample 1000 values from a triangular pdf \((\text{min} = 2\text{ weeks}, \text{max} = 6\text{ months, peak at 6 weeks})\) (17).

28. We modeled differential response to therapy by using two assumptions. First, we reduced the per capita treatment rate of drug-resistant strains \(1/\tau_{dR}\) in comparison to that of drug-sensitive strains by an efficacy parameter \(e\); where \(1/e = 0\) (thus, the per capita effective treatment rate of drug-resistant strains equals \(e\)). Second, we assumed that ART could increase survival \((1/\tau_{dR} > 1/\tau_{dS})\) (to some uncertain degree) in drug-resistant patients, but that this effect would be reduced in drug-resistant cases in drug-sensitive cases. We operationalized this assumption by using sampling constraints during LHS. We assumed that the average survival times could range from 12 to 36 months for both treated \((1/\tau_{dS})\) and untreated \((1/\tau_{dR})\) drug-resistant patients. Sampling constraints that ensured for all of the cases: \(1/\tau_{dR} = 1/\tau_{dS}\) (25). To model uncertainty in the impact of ART on reducing infectiousness in treated drug-resistant cases \((s_i)\), we used LHS to sample 1000 values of a multiplier \((u\alpha)\) from a uniform pdf \((0.0 \text{ to } 1.0)\). 1000 values of \(\alpha d_{R,dS}\) were then calculated by \(\alpha d_{R,dS} = \alpha d_{S,dS} - \alpha d_{R,dR}\). We modeled uncertainty in the average survival time of untreated drug-resistant cases \((1/\tau_{dR})\) by using sampling constraints during LHS to ensure that \(1/\tau_{dR} = 1/\tau_{dS}\) (25).

29. These data are available on Science Online at www.sciencemag.org/feature/data/1044287.shl.

30. Over the 10-year time period the value of the PRCC for effectiveness and the parameter \(t\) (which specifies the rate at which drug resistant strains emerge) remained between zero and \(0.2\).


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