Eradicating HIV epidemics

Could widespread use of combination antiretroviral therapy eradicate HIV epidemics?

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Current combination antiretroviral therapies (ARV) are widely used to treat HIV. However, drug-resistant strains of HIV have quickly evolved, and the level of risky behaviour has increased in certain communities. Hence, currently the overall impact that ARV will have on HIV epidemics remains unclear. We have used a mathematical model to predict whether the current therapies: are reducing the severity of HIV epidemics, and could even lead to eradication of a high-prevalence (30%) epidemic. We quantified the epidemic-level impact of ARV on reducing epidemic severity by deriving the basic reproduction number ($R_0$). $R_0^{\text{ARV}}$ specifies the average number of new infections that one HIV case generates during his/her infectious lifetime in a community of susceptible individuals. $R_0$ can be reduced either through behavioural or medical interventions. If $R_0$ is reduced to below one then epidemic eradication occurs, because each infected individual (on average) will generate less than one new infection. Here, we have quantified the effect of ARV on $R_0$ (for both drug-sensitive and drug-resistant infections) and we have answered the question, “Could widespread usage of ARV eradicate HIV epidemics?”

We addressed this question by deriving an analytical expression for $R_0$ for HIV in a community where ARV is available and where both drug-sensitive and drug-resistant strains are co-circulating ($R_0^{\text{ARV}}$). We used clinical, virological, and behavioural data from the gay community in San Francisco to estimate numerical values for $R_0^{\text{ARV}}$ under three different assumptions: ARV plus decreases in risky sex, ARV with no change in risky sex, and ARV plus increases in risky sex. For each assumption, we then identified the key factors that substantially increase (or decrease) the value of $R_0^{\text{ARV}}$. Finally, we calculated the probability that a high usage of ARV could eradicate the current high prevalence (30%) HIV epidemic in San Francisco, and we also determined the time dynamics of eradication.

The concept of $R_0$ was first proposed by Macdonald in the 1950s and applied to malaria. The numerical value of $R_0$ indicates the severity of the epidemic; the greater the value of $R_0$ (above one) the greater the severity of the epidemic. By deriving an expression for $R_0$, and setting the value equal to one, the specific levels of treatment, vaccination, or reductions in risky behaviour that are necessary to achieve epidemic eradication can be determined for any infectious disease. The expression for $R_0$ based upon the transmission dynamics of sexually transmitted HIV in an untreated community is simple and is dependent upon only three parameters: $\beta$ (the probability that sexual transmission of HIV occurs during a sexual partnership), $c$ (the average number of new sexual partners per unit time), and $D$ (the average duration of infectiousness). However, the situation is more complex if one needs to compute a reproduction number for HIV where ARV is available, since ARV leads: directly to the emergence of drug-resistant strains.

**Introduction**

Current combination antiretroviral therapies (ARV) increase survival time of HIV-infected individuals, but do not lead to viral eradication within individuals and hence do not cure. These therapies are based upon three or more anti-HIV medications that typically combine a protease inhibitor (PI), or a non-nucleoside reverse transcriptase inhibitor (nRTI), with at least two nucleoside reverse transcriptase inhibitors (nRTI). However, to eradicate an epidemic it is not necessary to cure any individuals, but simply to reduce the transmission rate to below a certain threshold value that is specified by the basic reproduction number $R_0$; where $R_0$ is the average number of new infections that one infectious case generates during his/her infectious lifetime in a community of susceptible individuals.
drug-resistant strains during treatment,\(^7\)\(^8\) and indirectly to the transmission of drug-resistant strains.\(^7\)\(^8\)\(^9\)\(^10\) Under these circumstances it is necessary to calculate a reproduction number based upon the transmission potential of treated and untreated individuals infected with either drug-sensitive and/or drug-resistant strains of HIV.

Blower et al\(^12\)\(^13\) have previously defined a mathematical model of an HIV epidemic that includes the effects of ARV on the transmission dynamics of both drug-sensitive and ARV-resistant strains. The model is specified by five ordinary differential equations;\(^12\) a web version can be run at http://www.biomath.ucla.edu/faculty/sblower. Previously, this model has been used to assess the effect of ARV (over a 10 year period) on the incidence of HIV,\(^12\) the AIDS death rate,\(^11\) and also to predict the transmission and prevalence of drug-resistant strains.\(^13\)

Here, we have used this model to derive an analytical expression for \(R_{0,\text{ARV}}\); where we define \(R_{0,\text{ARV}}\) as the average number of new HIV-infections that one infected individual will generate during his/her lifetime in a community where ARV is available and where both drug-sensitive and ARV-resistant strains are co-circulating. Hence, \(R_{0,\text{ARV}}\) functions as a single outcome measure that provides a summary estimate of the overall epidemic-level impact of ARV. We calculate the values of \(R_{0,\text{ARV}}\) that are generated due to a variety of different treatment rates; hence we assessed whether ARV has an overall beneficial or detrimental impact at the epidemic-level.

**Methods**

We first calculated an analytical expression for \(R_{0,\text{ARV}}\). To calculate \(R_{0,\text{ARV}}\) we used the next-generation operator methodology.\(^14\) We set the right-hand side of the model differential equations (given in reference 12) to zero and made a standard change of variables to find the disease-free equilibrium in terms of the forces of infection of the resistant (\(H_{9261}^R\)) and sensitive (\(H_{9261}^S\)) strains. The problem was then reduced to a system of two nonlinear algebraic equations given in equation 1.

\[
\begin{align*}
    \frac{dH_{9261}^S}{dt} &= F(H_{9261}^S, H_{9261}^R), \\
    \frac{dH_{9261}^R}{dt} &= G(H_{9261}^S, H_{9261}^R)
\end{align*}
\]

The disease-free equilibrium of the original model can be recovered from the solution \((H_{9261}^S, H_{9261}^R)=(0,0)\) of equation 1.

Linearising the right-hand side of equation 1 around this equilibrium point we computed the dominant eigenvalue of the resulting Jacobian matrix, thus obtaining \(R_{0,\text{ARV}}\).

**Estimating the value of \(R_{0,\text{ARV}}\)**

Estimates of the value of \(R_0\) for HIV before the introduction of ARV in the San Francisco gay community ranged from 2 (lower bound) to 5 (upper bound) in the early 1990s;\(^15\) more recent data\(^12\)\(^13\) suggest that the value of \(R_0\) (in the absence of ARV) was approximately 1\(^\text{.43}\). ARV has been widely used in San Francisco since 1996.\(^12\)\(^13\)\(^16\) We determined the epidemic-level impact of ARV by estimating the value of \(R_{0,\text{ARV}}\) in the gay community (where the current prevalence of HIV is 30% \(^16\)) using clinical, virological, and behavioural data from San Francisco\(^12\)\(^13\)\(^16\) to set upper and lower bounds for parameter estimates, and then applied uncertainty analysis.\(^12\)\(^13\)\(^17\)\(^18\)\(^19\) These data are described in reference 12 and references therein. Uncertainty analyses were based upon Latin hypercube

![Figure 1. Results from three uncertainty analyses; all have high ARV usage (60–90% of cases receive treatment). Pink=no change in risky sex plus only 10% of treated cases develop ARV resistance per year; green=decreased risky sex plus only 10% of treated cases develop ARV resistance per year; blue=increases in risky sex plus 10–60% of treated cases develop ARV resistance per year.](http://www.biomath.ucla.edu/faculty/sblower)
For each of the three uncertainty analyses, LHS was used to randomly sample (without replacement) each PDF for each parameter 1000 times. For example, in the third analysis we included uncertainty in the rate of emergence of drug resistance during the treatment of drug-sensitive cases (r) using LHS to sample 1000 values of r from a uniform PDF (minimum=0, maximum=6). In this analysis, we also included uncertainty in the degree of increase in risky behaviour (I) using LHS to sample 1000 values of I from a uniform PDF (minimum=0–1, maximum=0–6). Hence, risky behaviour varied from no increase (I=0) to doubling (I=1–0). This sampling procedure produced 1000 different estimates of $R_{AV}$ for each of the three uncertainty analyses.

**Identification of key factors that decrease, and increase, $R_{AV}$**

We then did sensitivity analyses, using data generated from each of the three uncertainty analyses, to identify the key factors that substantially increase (and decrease) the value of $R_{AV}$. For these calculations we used our uncertainty analysis estimates of $R_{AV}$ and the PDFs that specified each of the virological, clinical and behavioural parameters (described previously in references 12 and 13) to calculate sensitivity coefficients; a partial rank correlation coefficient (PRCC) was calculated for each parameter. A parameter was identified as a key factor in increasing or decreasing the value of $R_{AV}$ if the absolute value of the PRCC was greater than 0·5. For each of the three sensitivity analyses, before calculating PRCCs we examined scatterplots of each model parameter versus the 1000 estimated values of $R_{AV}$.
$R_{0}^{\text{ARV}}$ to check for monotonicity and discontinuities. All relations in the scatterplots were non-linear, and monotonic; no interactions and no discontinuities were observed.

**Probability of epidemic eradication, and the time course**

We used the results from our three uncertainty analyses to calculate the probability that widespread usage of ARV could eradicate the HIV epidemic in San Francisco (ie, the probability that $R_{0}^{\text{ARV}} < 1$), using previously described methods. It should be noted, that these methods slightly underestimate the chance of eradication. Finally, we determined the time course of epidemic eradication using the LHS data generated for each of our three uncertainty analyses and numerically simulating the transmission model with each parameter set (of the 1000 parameter sets in the LH sample) that generated a value of $R_{0}^{\text{ARV}}$ less than one.

**Results**

The analytical expression for $R_{0}^{\text{ARV}}$ is very complex and hence is not shown.

**Estimated values of $R_{0}^{\text{ARV}}$**

Our calculations for the numerical values of $R_{0}^{\text{ARV}}$ for each of the three uncertainty analyses are shown as boxplots in figure 1A, and as frequency distributions in figure 1B. Since the value of the reproduction number is 1.43 if ARV is not used (ie, if ARV is not used then $R_{0}^{\text{ARV}} = R_0$), the results of all three of the uncertainty analyses reveal that a high usage of ARV (ie, 50–90% of cases receiving ARV) would significantly reduce the severity of the HIV epidemic in the gay community in San Francisco (figure 1). The median values (and interquartile range [IQR]) of $R_{0}^{\text{ARV}}$ for these three analyses are: 0.90 (0.85–0.96; data shown in green, assuming reductions in risky sex), 1.0 (0.94–1.05; data shown in pink, assuming no change in risky sex increases) and 1.16 (1.05–1.28; data shown in blue, assuming increases in risky sex) (figure 1A). The results clearly reveal that a high usage of ARV if combined with substantial decreases in risky sex (green data) could drive $R_{0}^{\text{ARV}}$ below one, and hence would eventually lead to epidemic eradication. Conversely, if risky sex increases (blue data), then even with a high usage of ARV, $R_{0}^{\text{ARV}}$ is highly likely to remain greater than one. If no change in risky sex (pink data) occurs then a high usage of ARV would reduce the severity of the HIV epidemic, but the value of $R_{0}^{\text{ARV}}$ would remain at just above or just below the critical threshold level for eradication.

**Identification of key factors that decrease, and increase, $R_{0}^{\text{ARV}}$**

Our sensitivity analyses identified two key factors that substantially decreased (PRCC < −0.5) the value of $R_{0}^{\text{ARV}}$. The value of $R_{0}^{\text{ARV}}$ decreased substantially as:

1. The ARV treatment rate increased from 50% to 90%,
2. The ARV-induced reduction in infectivity/transmissibility of HIV from treated patients increased.

Our sensitivity analyses also identified two key factors that were most important in substantially...
increasing (PRCC >0.5) the value of \( R_{\text{AV}} \). The value of \( R_{\text{AV}} \) increased substantially as: (1) the relative fitness (ie, the transmissibility relative to drug-sensitive strains) of ARV-resistant strains increased, and/or (2) the levels of risky sex increased (table). The evolution of ARV-resistant strains that were very transmissible (ie, very fit) significantly increased the value of \( R_{\text{AV}} \) (figure 2A). Reductions in risky sex (green data) significantly reduced \( R_{\text{AV}} \) (figure 2B), whereas increases in risky behaviour (blue data) significantly increased \( R_{\text{AV}} \) (figure 2B). Thus, changes in risk behaviour determine the effect of the value of fitness of ARV-resistant strains on increasing \( R_{\text{AV}} \) (figure 2A).

We calculated that if ARV was widely used (median value 70% of cases received ARV) and substantial reductions (median value 25% decrease) in risky sex occurred the probability of eradication of the HIV epidemic would be high (\( p=0.85 \)). We determined that if levels of risky sex remain stable the probability of eradication would be only 0.5, and if levels of risky sex increased (median value 50% increase) then epidemic eradication would be unlikely (\( p=0.13 \)).

Figures 3A and 3B show the frequency distributions (using only the simulations from the LHS that eventually lead to epidemic eradication) for the predicted HIV prevalence in San Francisco after 50 and 100 years of continuous ARV. These results clearly show that, although epidemic eradication is possible (with either high levels of ARV alone [pink data] or else high levels of ARV combined with risk reductions [green data]), it would be likely to take 100 years or more to achieve. These estimates of eradication times are upper bound estimates; clearly, if parameter values change over time (as is to be expected as new and more effective therapies are developed) then eradication will occur more quickly. An eradication strategy based upon current ARV will be slow as all patients with prevalent infections would have to die, and patients on ARV have a fairly long survival time. However, clearly any HIV epidemic-eradication strategy will take a long time; it has been shown that even widely deployed and highly effective HIV vaccines would take several decades to achieve eradication1.

Figure 3. Frequency distributions of the prevalence of HIV infection in the gay community in San Francisco after (A) 50 years and (B) 100 years of continuous high usage of ARV. Only simulations in which eradication of HIV from the population would occur are shown (ie, only if \( R_{\text{AV}} <1 \)). Results from the three uncertainty analyses are shown; all have high ARV usage (50–90% of cases receive treatment). Pink=no change in risky sex plus only 10% of treated cases develop ARV resistance per year (\( N=506 \)), green=decreased risky sex plus only 10% of treated cases develop ARV resistance per year (\( N=847 \)); blue=increases in risky sex plus 10–60% of treated cases develop ARV resistance per year (\( N=130 \)).

Discussion

Our findings have four significant clinical and public health implications. First, increasing the percentage of cases receiving ARV would substantially reduce the severity of the HIV epidemic (ie, the value of \( R_{\text{AV}} \)), even in the presence of high levels of ARV resistance and increases in risky behaviour. However, ARV should not be used as an epidemic control strategy to improve public health unless increasing usage rates would also produce clinical benefits for the treated individuals. Second, even fairly moderate reductions in the infectivity/transmissibility of treated cases will be extremely beneficial in reducing the severity of the HIV epidemic. Reductions in infectivity/transmissibility could be achieved either
Eradicating HIV epidemics

by developing new drugs and drug regimens that more effectively suppress virus, and/or by significantly increasing the use of condoms by treated cases. Third, if highly transmissible ARV-resistant strains emerge (even though they are less transmissible than the drug-sensitive strains), they will significantly reduce the beneficial overall impact of ARV on the HIV epidemic. Great efforts should be made to prevent cases of acquired resistance developing during treatment, because these cases can lead to cases of transmitted resistance. Fourth, the value of \( R_0^{ARV} \) is extremely sensitive to changes in risky sex. Our findings demonstrate unequivocally that it is imperative that the usage of ARV should be tightly coupled with effective risk-reduction strategies. It is imperative that levels of risky sex are substantially reduced. We have also shown that the impact of changes in risky sex on reducing the HIV epidemic will be very dependent upon the biological characteristics of the ARV-resistant strains that evolve. If levels of risky sex increase, then even ARV-resistant strains with a low transmissibility will increase epidemic severity; conversely, reducing the level of risky behaviours will significantly reduce the transmission rate even if highly transmissible ARV-resistant strains emerge.

High usage of ARV in San Francisco has substantially reduced the AIDS death rate,\(^{12,13}\) and it has been estimated that ARV has also decreased the transmission rate in this city.\(^{12,13}\) After the widespread use of ARV in 1996, incidence rates in San Francisco were predicted\(^{12}\) to first rise (due to increases in risky sex) and then to fall (when the beneficial effects of ARV on decreasing transmission outweigh the effects of increases in risky sex on increasing transmission). The first of these theoretical predictions has been confirmed by recent empirical studies: the incidence rate in the gay community in San Francisco has increased.\(^{14}\) Therefore, based upon current empirical data, it is unclear whether the overall impact of ARV on the HIV epidemic will be beneficial. Furthermore, the high usage of ARV in San Francisco has already led to a high prevalence of ARV-resistance;\(^{15}\) by 2005 42% of the HIV infections in San Francisco are predicted to be ARV-resistant.\(^{15}\) Here, we have shown by calculating a single summary outcome measure (\( R_0^{ARV} \)) that a high usage of ARV will substantially reduce the severity of the HIV epidemic in the gay community in San Francisco. This beneficial impact of ARV at the epidemic level occurs because widespread usage of ARV reduces (at the population level) the average viral load,\(^{16}\) and this reduction in average viral load translates into a reduction in the average level of infectivity\(^{16}\) that hence reduces transmission.\(^{2,13,14,27}\) Our results show that although the current therapies do not cure individuals they could be used to eradicate a high-prevalence (30%) HIV epidemic. However, we have shown that the probability of eradication is very sensitive to changes in the level of risky sex. Currently in San Francisco there are high rates of emergence of drug resistance\(^{13}\) and high rates of increase in risky sex,\(^{13,14}\) therefore our calculations (shown in blue in the figures) suggest that whereas high usage of ARV could result in epidemic eradication in this city it is quite unlikely under the current conditions. Elsewhere\(^{13}\) we have advocated the widespread usage of ARV in Africa and other developing countries, because of the beneficial effect of ARV on reducing HIV transmission and AIDS death rates.\(^{12,13}\) However, the beneficial impact of ARV on reducing transmission will be masked if risky behaviours increase;\(^{15}\) therefore, it becomes necessary to theoretically estimate the "true" impact of ARV on HIV epidemics by calculating a single summary outcome measure (\( R_0^{ARV} \)). The same key factors that substantially reduce the HIV-infection rate and the AIDS-death rate\(^{12,13}\) also decrease the value of \( R_0^{ARV} \) and hence increase the probability of eradication. Our current quantitative findings imply (by contrast with the position argued by others\(^{2,14}\)) that widespread usage of ARV in Africa and other developing countries would be extremely beneficial in reducing HIV epidemics. The methodology we propose is generalisable to other geographical locations. Hence, we suggest that estimates of \( R_0^{ARV} \) should now be calculated for HIV epidemics in other locations to predict and to quantify the effect of ARV on reducing the severity of HIV epidemics in these countries. Such analyses should reveal that a high usage of ARV would much more easily eradicate HIV epidemics that are less severe than the current high-prevalence epidemic in San Francisco. The development of more effective drugs and drug regimens that render patients completely uninfectious will obviously benefit the treated individuals, but will also result in a much more substantial reduction in the value of \( R_0^{ARV} \) than we have calculated for our current analyses. Hence epidemic eradication using ARV could then become significantly quicker and easier than we have calculated. However, our findings clearly show that a high usage of the currently available combination ARV therapies (as well as benefitting the individual patients receiving treatment) would also serve as an effective HIV-prevention tool.

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Conflicts of interest
None declared.
References


