Voluntary universal testing and treatment is unlikely to lead to HIV elimination: a modeling analysis

Bradley G. Wagner, Sally Blower 1

David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California

Abstract

Recently Granich et al. at the World Health Organization (WHO) concluded, using mathematical modeling, that HIV epidemics could be eliminated within a decade. They assumed all individuals would be tested annually and every infected individual (regardless of stage of infection) would be put on treatment. Based on this modeling study the WHO is considering using universal testing and treatment as an HIV elimination strategy. Here we examine the study by Granich et al. and assess its validity. We present new analyses of their model by varying assumptions and parameter values. We find that under certain very optimistic assumptions HIV elimination would be (theoretically) possible, but it would take at least 70 years. To obtain this result we assumed ∼65% of symptomatic and ∼20% of asymptomatic individuals would be treated per year; ARVs would reduce infectivity of treated individuals a hundred fold, and only 5% of symptomatic individuals would give up treatment per year. Even under optimistic assumptions we find elimination to be unlikely. For example, we show if ∼65% of symptomatic individuals are treated per year and treated individuals are completely noninfectious, HIV will remain endemic with a prevalence of 34% and an incidence of 2% per year. We conclude that the model developed by Granich et al., when used with realistic parameter values, does not show HIV elimination is possible. However our modeling results show treatment could act as an effective prevention tool and significantly reduce transmission, even if only symptomatic individuals receive ARVs. Treatment should first, and foremost, be used for therapeutic purposes. Hence, we recommend when resources are limited - targeting those in need of treatment. Such a strategy would be ethical, feasible and epidemiologically sound. We advise that models used as health policy tools should be carefully evaluated and their results interpreted with caution.

I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide.

Daniel Bernoulli 1760.

1 Introduction

Recently Granich and colleagues at the World Health Organization (WHO) have used mathematical modeling to assess the potential impact of antiretrovirals (ARVs) on controlling HIV epidemics [1]. On the basis of their modeling they concluded that universal testing and treatment with antiretrovirals (ARVs) could - within a decade - lead to HIV elimination. This finding is now being considered by the WHO as the basis for making global health policy decisions. However we propose, before the WHO assume the results from the Granich et al. study are correct, the modeling methodology be carefully examined to determine its validity. Here, we conduct such an examination. We also present new results and compare these with those obtained by Granich et al. We conclude by discussing the implications of our results for using ARVs to eliminate HIV.

The Granich et al. study builds on many previous modeling studies of HIV and treatment. It was first shown, nearly a decade ago, in a modeling study by Blower et al. that widespread use of ARVs could be expected to substantially reduce HIV incidence rates (as well as death rates) [2]. To make their predictions Blower et al. assumed that highly active ARV regimens, by suppressing viral loads, would reduce the infectiousness of treated individuals and consequently decrease transmission [2]. Notably, they also showed that if risky behavior increased by only ~10% this could overcome the effectiveness of ARVs on reducing transmission and result in incidence increasing [2]. Blower and Farmer were the first to suggest, in the modeling literature, that ARVs should be considered as prevention tools (abeit as an unconventional tool) because of their effect on reducing transmission [3]. Since then, many others (e.g., Lima et al.) have used modeling to show that widespread use of ARVs could substantially reduce HIV transmission and argued that ARVs should be considered as prevention tools [4]. The idea that ARVs could potentially be used to eliminate
HIV epidemics was first proposed by Velasco-Hernandez and colleagues in 2003 [5]. They conducted a modeling study to address the question: Could widespread use of combination antiretroviral therapy eliminate HIV epidemics? They concluded that ARVs can function as very effective HIV prevention tools; even if drug-resistant strains emerge and are transmitted. However they found elimination would only be likely if widespread usage of ARVs was accompanied by substantial reductions in risk behavior [5].

2 Basic Reproduction numbers

Mathematical modelers use the concept of the Reproduction Number \( R_0 \) to characterize infectious disease dynamics [6]. The Basic Reproduction Number \( R_0 \) is defined as the average number of new infections one infected individual generates during their lifetime; assuming the entire population is susceptible and no biomedical and/or behavioral interventions are in place. Given that \( R_0 \) is greater than one, an epidemic can be expected to occur. The Control Reproduction Number \( R_C \) is similar to the \( R_0 \) however it is calculated based on the assumption that biomedical and/or behavioral interventions are available. If interventions can reduce the value of \( R_C \) to below one it can be concluded that - theoretically - it is possible to eliminate the disease. Mathematical expressions that specify the \( R_0 \) and the \( R_C \) can be derived from epidemiological models that reflect disease transmission dynamics. Specific values of \( R_0 \) and \( R_C \) can then be calculated by using estimates of the models parameters.

Based on their modeling, Granich and colleagues concluded that the value of \( R_C \) for HIV epidemics could be reduced to below one (i.e., HIV could - theoretically - be eliminated) if almost all individuals were tested annually and every HIV-infected individual (regardless of their stage of infection) was immediately put on treatment [1]. To reach this conclusion they also assumed that: only 10% of individuals would give up treatment per year, and ARVs (by reducing viral load) would be able to reduce infectivity to 1% of the pretreatment value [1]. Modeling results are always dependent on the structure of the model and the parameter values that are chosen. Therefore both the model structure and the parameter values used in the Granich et al. study need to be carefully evaluated to assess the validity of the results.

We derived an analytical expression for the \( R_C \) of a three stage version of the Granich et al. model (see Supplementary Information (SI) for technical details); the three stages correspond to primary infection, asymptomatic with a CD4 count above 350 cells/µL and symptomatic with a CD4 count below 350 cells/µL. We then used the expression of \( R_C \) to assess the sensitivity of the results obtained by Granich et al. to a range of parameter values. Specifically, we determined what treatment rates and treatment-induced reduction in infectivity would be necessary to (theoretically) achieve HIV elimination (i.e., to reduce \( R_C \) below one).

3 Structure of the Granich et al. model

Simple models can yield important insights into transmission dynamics; however overly simplistic models can produce misleading results. Findings should always be assessed in terms of the assumptions that have been made to construct the model. The structure of the Granich et al. model is shown in terms of a flow-diagram in Figure 1. The model is deterministic and specifies the transmission dynamics of an HIV epidemic in a location where ARVs are widely available. It was constructed using the following assumptions:

- Individuals can only become infected with HIV through sexual transmission; vertical transmission is not included.
- The probability/risk of male-to-female transmission is equal to female-to-male transmission.
- After infection an individual progresses through four stages before dying of AIDS.
- Viral load (and hence infectivity) is the same in each of the four stages.
- Individuals can be treated in any of the four stages.
- The model is homogeneous (i.e., every individual in the model is assumed to be at the same risk for acquiring
HIV regardless of their gender, age and/or level of sexual activity).

- The earlier an individual receives treatment the longer they will survive. The “survival benefit” begins immediately after infection and individuals who go on treatment immediately after infection receives the greatest survival benefits. For example (using the parameter values chosen by Granich et al.) an individual who is put on treatment immediately after they become infected will gain (on average) an additional 11 years, but an individual who is put on treatment after they have been infected for 6 years will only gain (on average) an additional 5 years.

- Immediately after universal testing and treatment becomes available all infected individuals (whether treated or not) decrease their risk behavior.

- Individuals who become sexually active after treatment is introduced are less sexually active than individuals who were sexually active before treatment was introduced.

- It is not possible for treated individuals to either develop or transmit drug-resistant strains.

The results obtained by Granich et al. are based on these assumptions; if these assumptions are not satisfied then the results do not hold. It is very important to note that the model developed by Granich et al. cannot show anything but a beneficial impact of ARVs as the model does not include the possibility of drug resistance emerging, nor risk behavior increasing. Previous modeling studies have found that: (i) even if only 25% of all of the HIV-infected individuals in Sub-Saharan African receive ARVs the number of drug-resistant infections, after 5 years, could potentially be as high as ~850,000 [2] and (ii) if risk behavior increases by only 10% the benefits of ARV on reducing transmission are overcome and incidence remains constant [2].

4 How infectious are treated individuals?

As well as assessing the validity of the results in terms of the structure of the model, the parameter values that were used in the modeling should also be closely examined. Granich et al. assumed ARVs would reduce the infectivity of treated individuals a hundred fold (i.e., infectivity would be reduced to 1% of their pretreatment infectivity level) [1]. They use the term relative infectivity to express reductions in infectivity; where relative infectivity is defined as the ratio of the infectivity of a treated individual to the infectivity of an untreated individual. Consequently a relative infectivity of 0.01 corresponds to a hundred fold reduction in infectivity.

Treatment with ARVs reduces viral load. However, the degree to which treatment-induced reductions in viral load decrease infectivity is unknown. Clinical trials designed to assess the effect of ARVs on reducing infectivity, and hence transmission, are currently underway. However data from completed studies that have estimated transmission as a function of viral load can potentially shed some light on the effect of ARV-induced viral load reduction on decreasing infectivity.

Quinn et al. [7], Gray et al. [8] and Wawer et al. [9] have estimated transmission per coital act as a function of viral load for untreated, heterosexual, discordant couples in Rakai Uganda. Quinn et al. [7] identified a significant dose-response relation of increased transmission with increasing viral load. Specifically, they determined that each log increment in the viral load was associated with a rate ratio of 2.45 for seroconversion (95 percent confidence interval, 1.85 to 3.26). Smith and Blower [10] formulated a model (based on the dose-response relationship) that can be used to estimate the potential effect of ARV-induced viral load reduction on decreasing per act infectivity. This model, relating viral load to (per act) infectivity, is shown as Equation 1 and plotted in Figure 2:

$$\delta(\nu) = \delta_0 2.45^{10 \log_{10}(\nu)}$$

(1)

In Equation 1 $\delta$ and $\nu$ respectively represent per act probability of transmission (i.e., per act infectivity) and plasma viral load. The parameters $\delta_0$ and $\nu_0$ are baseline infectivity and viral load which are set equal to 0.0018 and 12,500 copies/mL respectively based on data obtained from the Quinn et al. study [7].

![Empirical relationship between viral load and per coital act infectivity derived by Quinn et al.](image)

Fig. 2. Empirical relationship between viral load and per coital act infectivity derived by Quinn et al. [7] (Eq. 1). The dashed blue line represents extrapolation of the curve below the detectable limit of the study data (i.e., 400 copies/mL).

Granich et al. assume that if ARVs reduce the viral load a 100 fold that infectivity will also be reduced a hundred fold [1]. However there are no data to support their assumption. In fact the available empirical data (see Figure 2) show that a 100 fold decrease in viral load results in only a six fold decrease in per act infectivity. Using the statistical relationship shown in Equation 1, we calculated (see technical details in the SI) that to reduce the relative infectivity to 0.01 it would be necessary for treatment to reduce viral load 150,000 fold (i.e., to essentially eliminate virus within an individual). We also calculated, that if ARV cause a four hundred fold reduction in viral load the infectivity of treated individuals will only be reduced 10 fold (i.e., the relative infectivity will be 0.10) (Figure 2).

It is possible that the relationship between viral load and in-
fectivity (shown in Equation 1 and Figure 2) may not hold at low viral loads and/or a viral load threshold may exist at which transmission risk becomes negligible [11]. In two studies of heterosexual discordant couples (that included patients on ARVs) transmission was not observed from individuals with viral loads less than 400 copies/ml [11]. This could imply a viral load transmission threshold, however (within a 95% confidence interval) the results are also consistent with one transmission event per 79 person years [11]. Additional empirical studies have also indicated that a threshold effect may occur at low viral loads. In six studies of untreated individuals with viral loads less than 400 copies/mL it was estimated that a mean of only one transmission event occurred per 625 person years; although (within a 95% confidence interval) these results are also consistent with one transmission event per 88 person years [11]. Further empirical studies need to be conducted to determine whether a viral load transmission threshold exists, as well as to quantify the relationship between ARV-induced reductions in viral load and transmission risk.

ARV regimens, when used by fully adherent individuals, may reduce infectivity below a certain threshold at which individuals become essentially noninfectious. However the regimens are extremely unlikely to be equally effective in reducing infectivity in all treated individuals. To eliminate HIV it is necessary for the ARV regimens to be effective at the population level, not just at the individual level. Effectiveness at the population-level will depend on the potency of the regimens, the level of adherence and the presence of co-factors (e.g., other sexually transmitted infections). Hence, even if regimens are extremely potent, a certain proportion of treated individuals will remain infectious. This is illustrated in Figure 3 which shows the relative infectivity in a population of treated individuals where there is incomplete adherence. It can be seen that under these conditions, even if the potency of regimens is such that individuals become noninfectious, the relative infectivity at the population level may be as high as 0.3 (Figure 3). Under these conditions, \( R_C \) would remain above one and elimination would be impossible.

5 Differential treatment (and drop-out) rates

In the modeling conducted by Granich et al. they assumed that infected individuals, regardless of their stage of infection, would be equally likely to accept treatment. We examined the consequences of this assumption on the probability of achieving elimination. To conduct this examination we made the acceptance rate of treatment a function of an individuals stage of infection. Specifically, we assumed that symptomatic individuals (with CD4 counts < 350 cells/microL) would be more likely to accept (and remain) treatment than asymptomatic individuals (with CD4 counts > 350 cells/microL).

The results of our analysis are shown in Figure 4. This Figure shows the conditions that would be necessary to eliminate HIV; the Y-axis shows the treatment rate for symptomatic individuals with CD4 counts < 350 cells/microL. The dashed black curve in Figure 4 delimits the threshold at which \( R_C \) equals one; above the curve elimination is (theoretically) possible and below the curve elimination is not possible. Figure 4 is based on two assumptions. Firstly, symptomatic individuals would be five times more likely than asymptomatic individuals to be treated. Secondly, asymptomatic individuals would be four times more likely to give up treatment than symptomatic individuals. It can be seen that elimination would be (theoretically) possible only if ARV regimens are able to reduce infectivity 10 fold (i.e., so the relative

Fig. 3. Probability density histogram for the relative infectivity of symptomatic individuals (CD4 < 350 cells/microL) undergoing treatment assuming realistic levels of adherence and co-factor prevalence. Relative infectivity is defined as the ratio of the infectivity of a treated individual to the infectivity of an untreated individual.

Fig. 4. Dependence of the Reproduction Control number \( (R_C) \) on treatment rates for symptomatic (CD4 < 350 cells/microL) individuals (Y-axis) and relative infectivity (X-axis) for an HIV epidemic with \( R_0 = 2 \). Relative infectivity is defined as the ratio of the infectivity of a treated individual to the infectivity of an untreated individual. Consequently a relative infectivity of 0.01 corresponds to a hundred fold reduction in infectivity. We assume symptomatic individuals are 5 times as likely to begin (and 4 times less likely to drop) treatment per year than asymptomatic individuals. The dropout rate for symptomatic individuals is 5% per year. The dotted black curve represents the theoretical threshold for elimination \( R_C = 1 \).
infectivity is less than or equal to 0.10) and 95% of symptomatic individuals with CD4 counts < 350 cells/microL are treated per year. As we have shown even if regimens are extremely potent, given realistic levels of adherence, relative infectivity is very unlikely to be less than 0.10.

6 Estimating the time to eliminate HIV epidemics

It is essential to note that even if elimination is shown to be theoretically possible (i.e., $R_C$ can be reduced to below one), the necessary conditions would have to be maintained for at least several decades in order to ensure incidence did not increase.

Figure 5 shows the results of numerical simulations calculated using the Granich et al. model [1]. The annual HIV incidence is shown as a function of time from the initiation of a universal test and treatment program. The curves terminate at the point at which incidence falls below the WHO elimination threshold of 1 case per thousand per year [1].

The black curve in Figure 5 is generated using the parameter values of Granich et al. [1] to define their universal test and treat strategy; to construct this simulation we assumed (as did they) that infectivity is reduced a 100 fold (i.e., the relative infectivity is 0.01) and the dropout rate is 1.5% per year. Under these conditions, it would take ~20 years to reduce incidence to the WHO elimination threshold. However, it is very important to note that after twenty years, when the incidence reaches the elimination threshold, a significant proportion of the population (14%) would still be on treatment. Consequently, these individuals would have to remain completely virologically suppressed for at least another decade in order to keep incidence below the threshold level.

The blue curve in Figure 5 is generated assuming more realistic, but still very optimistic, assumptions. To construct this simulation we assumed ~65% of symptomatic individuals (with CD4 counts < 350 cells/microL) and ~20% of asymptomatic individuals (with CD4 counts > 350 cells/microL) are treated per year. In addition we assumed the relative infectivity of treated individuals would be 0.03, and only 5% of symptomatic (and 20% of asymptomatic) individuals would give up treatment per year. Under these optimistic assumptions, it can be seen that HIV elimination would be (theoretically) possible, but it would take over 70 years.

The green curve in Figure 5 is generated assuming ~65% of symptomatic individuals (with CD4 counts < 350 cells/microL) would be treated and treated individuals become completely noninfectious. In this simulation asymptomatic individuals are not treated. Notably, in this case, even if treatment is completely effective at preventing transmission, HIV will remain endemic in the population with a prevalence of 34% and an incidence of 2% per year.

It should be noted that none of the simulations presented in Figure 5, because they are derived using the Granich et al. model, show the effect of the emergence and transmission of drug-resistant strains on the incidence of HIV. The emergence of drug resistant strains will significantly increase the time it will take to eliminate HIV.

7 Targetting ARVs

Public health interventions designed for controlling sexually transmitted diseases (STDs) often aim to target treatment to individuals in behavioral core groups, because these individuals disproportionally contribute to transmission. It was first shown in modeling studies conducted by Hethcote and Yorke that strategies based on targeting core groups have the potential to cause a substantial reduction in transmission of sexually transmitted diseases [12].

We surmise that it may soon be suggested that if ARVs are going to be used for HIV prevention purposes (and resources are limited) that ARVs should be targeted to behavioral core groups. Modeling studies will definitely show targeting ARVs will be the most effective strategy for reducing transmission and for using ARVs as a prevention tool. However we argue strongly that ARVs should not be used in the same manner as conventional prevention tools and target behavioral core groups.

A strategy using conventional prevention tools directly benefits uninfected individuals in the core group, but is not likely to lead to any significant “loss of benefit” to individuals who are outside the core group. ARVs should be regarded as an unconventional prevention tool because they provide at least two “benefits”: (i) a potential preventive benefit for uninfected individuals in the community and (ii) most im-
important, a survival benefit for the infected individuals who receive treatment. If ARVs are regarded as a conventional prevention tool and behavioral core groups are preferentially targeted the number of prevented infections will be maximized. However, such a strategy will ensure that infected individuals outside the core group will suffer a substantial “loss of benefit” as they will not receive the therapeutic benefits of ARVs. Hence targeting ARVs to behavioral core groups would be the most effective way to reduce transmission, but would be extremely unethical in terms of treatment equity. We suggest that targeting the sickest AIDS patients (as has been done in Haiti [13]) would optimize both therapeutic and preventive goals. This targeting strategy would be ethical, feasible and epidemiologically sound.

Fig. 6. Dependence of the Reproduction Control number ($R_C$) on treatment rates for symptomatic (CD4<350 cells/microL) individuals (Y-axis) and relative infectivity (X-axis) for an HIV epidemic with $R_0 = 2$. Relative infectivity is defined as the ratio of the infectivity of a treated individual to the infectivity of an untreated individual. Consequently a relative infectivity of 0.01 corresponds to a hundred fold reduction in infectivity. Only symptomatic individuals are treated. The dropout rate is 5% per year.

8 Conclusion

ARVs should be made widely available in resource-constrained countries as they will significantly increase survival of HIV-infected individuals. ARVs will also reduce transmission from infected individuals and hence, indirectly, save lives. Consequently, treatment will function as an effective prevention strategy.

Treatment should first, and foremost, be used for therapeutic purposes. Since treatment in many resource-constrained countries is limited it should be provided first to those who are most in need of treatment. Targeting ARVs to those most in need is the most ethical strategy. Notably, this strategy could also significantly reduce transmission (Figure 6). The treatment rate of symptomatic individuals with CD4 cell counts less than 350 cells/microL is show on the Y-axis in Figure 6; in the absence of treatment the $R_0$ equals 2. Figure 6 shows the higher the treatment rate of symptomatic individuals and the greater the potency of the ARV regimen in reducing infectivity the greater the reduction in the $R_C$.

For example, if 80% of symptomatic individuals are treated and treatment reduces infectivity ten fold the value of the $R_C$ will be 1.3. To put this result in context, this will result in a reduction in transmission of 35% (see SI for technical details). It can be seen that achieving a very high treatment rate (~95%) would reduce transmission substantially, but not enough to achieve elimination (Figure 6).

We conclude that the model developed by Granich et al., when used with realistic parameter values, does not show that HIV is (theoretically) possible. We recommend that any modeling results that are used as a foundation for health policy decisions should always be carefully examined. Sensitivity analysis should be used to determine the robustness of results [14]. In addition, assumptions that are made to construct health policy models should be made transparent enough to permit policy makers to understand them. Modeling results should always be interpreted with caution. We recommend that models should never be used as the sole basis for making health policy decisions; many other, often more important factors that are not included in the modeling framework, need to be considered [15].

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