

Forecasting the Future of HIV Epidemics: the Impact of Antiretroviral Therapies & Imperfect Vaccines

S. Blower^{1*}, E.J. Schwartz¹ and J. Mills²

¹AIDS Institute & Department of Biomathematics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

²Monash University Building, Alfred Hospital, Melbourne, Australia.

Abstract

Mathematical models can be used as health policy tools and predictive tools. Here we review how mathematical models have been used both to predict the consequences of specific epidemic control strategies and to design epidemic control strategies. We review how models have been used to evaluate the potential impact on HIV epidemics of (i) combination antiretroviral therapies (ART) and (ii) imperfect vaccines. In particular, we discuss how models have been used to predict the potential effect of ART on incidence rates, and to predict the evolution of an epidemic of drug-resistant HIV. We also discuss, in detail, how mathematical models have been used to evaluate the potential impact of prophylactic, live-attenuated and therapeutic HIV vaccines. We show how HIV vaccine models can be used to evaluate the epidemic-level impact of vaccine efficacy, waning in vaccine-induced immunity, vaccination coverage level, and changes (increases or decreases) in risky behavior. We also discuss how mathematical models can be used to determine the levels of cross-immunity that vaccines will need to attain if they are to be used to control HIV epidemics in countries where more than one subtype is being transmitted.

Key words

Antiretroviral therapy. Vaccines. HIV transmission. Drug resistance.

Introduction

Mathematical models are useful tools for understanding epidemic dynamics because epidemics are complex, nonlinear systems. Models are espe-

cially useful tools in assessing the epidemiological consequences of medical or behavioral interventions, because they contain explicit mechanisms that link individual behaviors with a population-level outcome such as incidence or prevalence. Mathematical models can be used as health policy tools and predictive tools by coupling models with time-dependent uncertainty and sensitivity analyses based upon Latin Hypercube Sampling¹⁻¹¹. Mathematical models are also extremely useful tools for designing epidemic control strategies, because they can be used to calculate the epidemiological consequences of

Correspondence to:

AIDS Institute & Department of Biomathematics
David Geffen School of Medicine at UCLA
10833 Le Conte Avenue
Los Angeles, CA 90095-1766, USA.
E-mail: sblower@mednet.ucla.edu

medical and behavioral interventions at the level of the community. An effective medical intervention will always benefit the individual patient, but may be detrimental at the level of the community. For example, mathematical modeling has been used to quantify the conditions under which low-efficacy HIV vaccines, if accompanied by an increase in risky behavior, would increase the severity of the HIV epidemic¹². Here we review how mathematical models have been used, both to predict the consequences of specific epidemic control strategies, and to design epidemic control strategies. In particular, we review and discuss how models have been used to evaluate the potential impact of combination antiretroviral therapies (ART) and imperfect vaccines on HIV epidemics.

Modeling combination antiretroviral therapies

Predicting the impact of ART on transmission & incidence

ART has dramatically reduced viral loads in infected individuals, often to levels less than 50 copies of HIV RNA/ml of plasma, and these benefits have been sustained for long periods of time in some patients. For all modes of HIV transmission, the single most important attribute determining the likelihood of transmission is HIV viral load. This relationship has been shown most elegantly for heterosexual^{13,14} and vertical (mother-to-child)¹⁵⁻¹⁷ transmission, but is undoubtedly true for other modes of transmission as well. Given this relationship, one would expect that factors that decrease HIV viral load, such as antiretrovirals¹⁸, would decrease transmission risk. This relationship has formally been shown only in the setting of antiretroviral therapy to reduce mother-to-child transmission¹⁵⁻¹⁷, but almost certainly must be true in other contexts.

Mathematical models have been useful tools for predicting and evaluating the effects of ART, by reducing viral load in individual patients, at the epidemic-level^{8-10,19,20}. Modeling predictions have been made for the San Francisco gay community of the potential epidemic-level effects of ART in terms of HIV infections prevented and AIDS deaths averted⁸. These analyses have shown that a high usage of ART (treating 50 to 90% of HIV-infected persons) substantially decreases the annual AIDS death rate, by increasing survival, and also substantially reduces the transmission rate, by reducing average viral load⁸. It has been calculated that these high usage rates of ART, over a 10-year period, have reduced the AIDS death rate by 18-33%, and have prevented a substantial number (40%) of HIV infections occurring⁸. Modeling analyses have shown that the higher the usage of ART, the greater the reduction in the annual AIDS death rate, and the greater the number of infections prevented^{8,19,20}. Furthermore, it has been shown

that a high usage of ART, treating 50-90% of HIV-infected individuals, coupled with reductions in risky behavior could result in the eradication of HIV epidemics¹⁰, even those of high prevalence (30%). However, epidemic eradication would take many decades¹⁰.

The modeling analyses have shown that a high usage of ART lowers the transmission rate, but may not decrease the incidence rate; in fact the incidence rate may actually increase^{8,20}. The effect of ART on the incidence rate depends upon whether the levels of risky behavior increase. If levels of risky behavior stay constant then incidence rates will decrease. However, if levels of risky behavior increase then incidence rates may increase. Models have been used to quantify the trade-off between the effect of ART on decreasing transmission and the effect of increases in risky behavior on increasing transmission⁸. It has been calculated that an increase in risky behavior of only 10% would be enough to counterbalance the benefits of even a high level (50-90% of HIV-infected cases treated) of ART in decreasing transmission⁸. Therefore, increases in risk behavior of greater than 10% result in the incidence rate increasing and the effect of ART on decreasing transmission would be masked⁸. Decreasing incidence rates, due to ART, have not been observed in population-based empirical studies in the "real-world", either because an increase in risky behavior has masked the effect and/or treatment rates have been low. Current practice guidelines recommend that a substantial proportion of patients with HIV infection, primarily those with CD4 counts above about 350/ μ l, remain untreated for many years²¹.

Predicting the evolution of drug resistance (incidence & prevalence)

Conventional wisdom suggests that transmission of drug-resistant strains will always tend to increase. However, by modeling the evolution of epidemics of drug-resistant pathogens, it has been shown that, in fact, transmitted drug resistance does not always continuously increase^{5,8,9,21-26}. This effect occurs because drug-resistant strains have to "compete" with an epidemic of drug-sensitive strains that are already in place. Hence, if the prevalence of the drug-sensitive strains is high, transmission of drug-resistant strains can be forced to stabilize at fairly low levels. Thus, in order to predict the evolution of an epidemic generated by drug-resistant strains, it is necessary to understand the competitive dynamics that occur between the drug-sensitive and the drug-resistant epidemics. In order to predict the epidemic of drug-resistant HIV, it is also necessary to understand the time scale over which it will unfold. Epidemics can operate over very different time scales; for example, one cycle of an influenza epidemic occurs over a few weeks or months while one cycle of a tuberculosis epidemic can

take many decades or even several hundred years^{3,6}. HIV epidemics unfold fairly slowly, as transmission is limited by the rate of acquisition of new sex partners; hence, HIV epidemics can take several decades to reach equilibrium. Thus, it could take several decades for drug-resistant strains (that are sexually transmitted) to reach their maximum (equilibrium) levels.

Several factors affect the development of drug resistance in patients being treated with antiretrovirals. The key element in all of these factors is failure to markedly suppress HIV replication (currently defined as achieving HIV viral loads < 50 copies of HIV RNA/ml). Continued HIV replication in the presence of the selective pressure of antiretroviral therapy selects drug-resistant virus strains, which are a major cause of treatment failure^{27,28}. The rate at which resistance develops appears to depend on several factors, but the principal ones are the rate of virus replication in the patient (roughly equivalent to the viral load) and the genetic mechanism mediating drug resistance (single codon changes mediating high-level resistance, as with nevirapine, permit rapid development of clinically-evident resistance)^{29,30}. In the clinic, resistance may result from treatment with suboptimal drug combinations; for example, one or two antiretrovirals instead of three or more, or the use of inappropriate combinations (drugs which antagonize each other²⁹, or combinations including one or more drugs to which the infecting HIV strain is already resistant^{31,32}). Patients receiving a well-designed treatment regimen may fail to completely suppress virus replication because of poor absorption, drug interactions, or poor adherence to the treatment regimen³³⁻³⁵. In addition, patients who begin therapy with very high viral loads may be more difficult to suppress completely than patients with lower initial values³⁵.

The incidence and prevalence of HIV strains resistant to antiretrovirals has not been assessed in epidemiologically-rigorous studies. However, over 5-10 years a substantial proportion of patients treated with well-designed antiretroviral regimens will either fail to completely suppress virus replication, guaranteeing the development of resistant strains, or will ultimately fail therapy due to resurgence of drug-resistant virus^{28,29,32}. The mechanism in at least some of these patients appears to be poor adherence to treatment regimens, resulting in increased HIV replication and ultimately worsened clinical outcomes and selection of drug-resistant HIV strains^{31,34,36,37}, although only one study has directly correlated the decreased drug levels caused by poor adherence with an increased prevalence of drug-resistant HIV strains²⁷.

Mathematical models, coupled with uncertainty analyses, have been used to understand, and to predict, the evolution of the epidemic of drug-resistant HIV in San Francisco from 1996 (when ART first began to be widely used in that city) to 2005^{8,9}. To make these predictions, the relative

fitness of the ART-resistant strains, as specified by the transmissibility of the ART-resistant strain relative to that of a drug-sensitive strain, was varied over a wide range: it was assumed that an ART-resistant strain could be almost as transmissible (maximum relative fitness), to only 1% as transmissible as the drug-sensitive strain (minimum relative fitness). Predictions were made under both optimistic and pessimistic assumptions regarding the magnitude of increase in risky behavior and the rate of emergence of acquired resistance^{8,9}. Optimistically, it was assumed that there would be no increase in risky behavior and that only a low rate of acquired resistance would occur (i.e., only 10% of treated drug-sensitive cases per year would become ART-resistant)⁸. Pessimistically, it was assumed that the average level of risky behavior would increase (anywhere from no increase to double the current level) and that the rate of development of acquired resistance would be high (anywhere from 10 to 60% of treated ART-sensitive cases per year would become ART-resistant)^{8,9}; this range is based upon recent data from clinical and community-level studies of ART resistance⁹.

The predicted prevalence of ART resistance expected in San Francisco under both the optimistic (Fig. 1A) and pessimistic (Fig. 1B) assumptions is shown. These predictions show that the prevalence of ART resistance, and hence the clinical burden of ART resistance, quickly rose, is already high, and will continue to increase substantially, to reach 42% in San Francisco (Fig. 1B) by 2005^{8,9}. Sensitivity analysis has revealed that three key factors significantly increased the prevalence of drug resistance: (i) the treatment rate, (ii) the average duration of time that an ART-resistant patient spends on ineffective therapy, and (iii) the rate of development of acquired resistance⁹. High treatment rates significantly decreased the percentage of drug-sensitive infections but substantially increased the percentage of drug-resistant infections⁹.

HIV strains resistant to one or more antiretroviral drugs can be transmitted to others³⁸, and there is some evidence that the proportion of patients with primary HIV infection due to the transmission of drug-resistant strains is increasing³⁸⁻⁴², although studies in some locations have not seen this effect^{43,44}. Mathematical models have been useful tools for predicting the extent of transmission of ART-resistant strains⁹. It has been calculated that transmission of ART-resistant strains has so far been low, relative to the transmission of the wild-type drug-sensitive strains, and that, over the next few years, transmitted resistance is only likely to gradually increase⁹ (Fig. 2A). By 2005, only a relatively low percentage (median 15.6%) of the new HIV infections in San Francisco are predicted to be ART-resistant⁹ (Fig. 2A). Thus, the modeling analyses have shown that transmitted resistance has only accounted for a relatively small proportion of the new infections that have occurred in

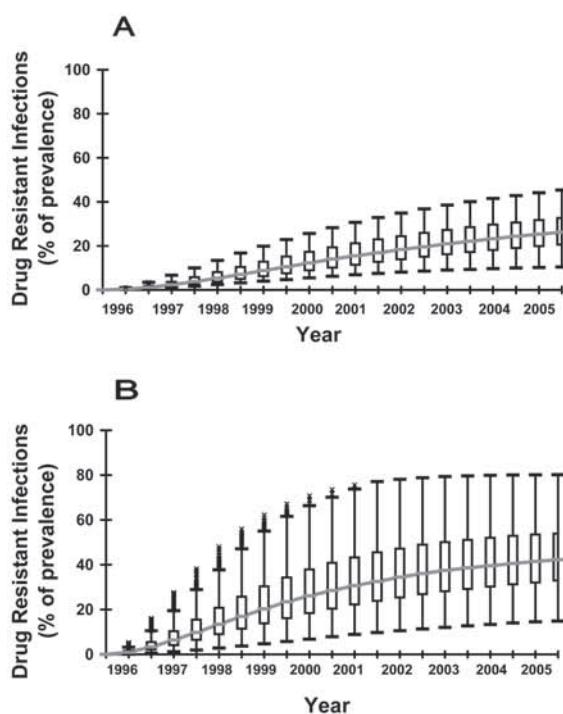


Figure 1. Results of optimistic (A) and pessimistic (B) time-dependent uncertainty analyses on the effect of combination anti-retroviral therapy (ART) on the HIV epidemic in San Francisco. A mathematical model (described elsewhere)^{8,9} that tracks the transmission dynamics of drug-sensitive and drug-resistant strains was used to generate these results. For each graph, every six months, 1,000 computer simulations are plotted as a frequency distribution in the form of a box-plot. These box-plots show the median value (horizontal gray line), the upper and lower quartiles, and the outlier cutoffs. The effect of a high usage rate of ART (i.e., treating 50-90% of HIV-infected individuals) on HIV prevalence of infection is plotted.

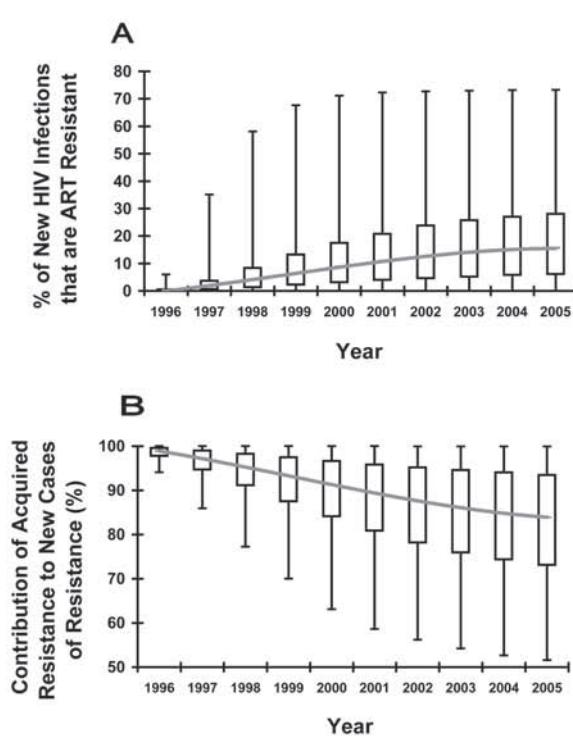


Figure 2. Temporal predictions of ART resistance in San Francisco from 1996 to 2005, calculated using the model^{8,9} and time-dependent uncertainty analyses. Gray lines show median values. A) Newly HIV-infected patients can be infected by either drug-sensitive or drug-resistant virus. Shown here is the proportion of new infections that are drug-resistant. B) New cases of drug resistance can be either transmitted or acquired during treatment of drug-sensitive cases. Shown here is the proportion of new cases of drug resistance that are acquired during treatment.

Table 1. Characteristics of some current vaccines

Target disease or pathogen	Type of vaccine ²	From natural infection:		Vaccine mechanism:		From Vaccine Administration:	
		Protection ³	Duration	Prevents infection ³	Prevents disease ³	Protection, %	Duration, Yrs
Smallpox	LA	+++	Lifelong	?+	+++	70-90	10-20
Polio	LA	++	Lifelong	++	+++	>99	>30
Polio	IN	++	Lifelong	+	+++	>90	10-20
Measles	LA	+++	Lifelong	0	+++	>95	>20
Mumps	LA	+++	Lifelong	0	+++	>95	>20
Varicella	LA	+++	?Lifelong	0	+++	>90	>10
Hepatitis B	S	++	Lifelong	+	+++	>95	>10
Influenza	S	++	?2-10 yrs	+	++	30-90	1-5
Yellow Fever	LA	+++	Lifelong	+	+++	>95%	>20
Diphtheria	T	+++	?Lifelong	0	+++	≥90	10-20
Tetanus	T	0	—	0	+++	>98	>10
Pertussis	IN	++	?	0	++	80-95	>10
Pertussis	S	same	same	0	++	80-95	>10
HIB ¹	S	++	?	0	+++	>95	?
<i>Pneumococci</i>	S	++	?	0	++	>50	>5
<i>S. typhi</i>	LA	++	?	+	+++	60-80	3-7
Tuberculosis	LA	++	?Lifelong	?++	+++	0-80	>20

1: *Hemophilus influenza B*; 2: LA - live attenuated, IN - inactivated whole pathogen, S - subunit (purified or recombinant), T - toxoid (inactivated toxin); 3: + - low, ++ - intermediate, +++ - high. Material taken from numerous primary and secondary sources, especially Plotkin, et al.⁵⁰.

San Francisco; the vast majority of new HIV infections each year have been, and will remain for the near-future, drug-sensitive⁹ (Fig. 2A). These theoretical predictions have recently been "tested" against newly collected empirical data⁴⁰ on transmitted resistance in San Francisco and found to be valid⁴⁵.

Modeling analyses have revealed that it is possible, under certain conditions, for extremely high rates of transmitted resistance to occur⁹. These analyses have shown that transmitted resistance will increase as: (i) treatment rates increase to high rates (from treating 50 to 90% of HIV-infected cases), or (ii) the rate of acquired resistance is high (from 10 to 60%), or (iii) ART-resistant strains evolve that have a very high relative fitness (i.e., are very transmissible) or (iv) the degree of treatment-induced reduction in viral load in drug-sensitive patients is low⁹. However, it is important to note that the modeling analyses have shown that the majority of new cases of ART-resistance that are occurring are the result of acquired resistance rather than transmitted resistance (Fig. 2B)⁹. These results therefore suggest that public health efforts should be focused on trying to minimize the rate of acquiring resistance (from treating drug-sensitive cases) rather than trying to prevent the transmission of ART-resistant strains.

Modeling analyses can also provide important insights into the expected transmission of ART-resistant strains in developing countries. Since treatment rates in developing countries will be far lower than the treatment rates in developed countries, both the prevalence and the transmission of

ART-resistant strains can be expected to be far lower than has been observed, and predicted to occur, in San Francisco⁴⁶.

Modeling HIV vaccines

Vaccines have been a highly successful means of controlling many infectious diseases (Table 1). The eradication of smallpox, the near-eradication of poliomyelitis and the dramatic reductions in measles, tetanus and other infectious diseases can be attributed in large measure to immunization with effective vaccines. However, effective vaccines have not yet been developed against a number of other important pathogens, including hepatitis C virus, respiratory syncytial virus, *Neisseria gonorrhoea*, and *Treponema pallidum*. No HIV vaccine has yet been shown to protect humans from HIV infection; numerous candidate vaccines are in various stages of development^{47,48}. These include subunit vaccines (primarily HIV envelope proteins), formulated subunits (e.g. virus-like particles), DNA vaccines (DNA plasmids expressing HIV proteins), and various recombinant vectors also expressing HIV proteins (e.g. poxviruses, adenoviruses, flaviviruses, *Salmonella*). These vaccines are frequently employed in combination in a prime-boost strategy⁴⁹.

The mechanism of protection by, and efficacy of, existing vaccines against infectious diseases varies widely (Table 1). At one mechanistic extreme are the bacterial toxoid vaccines and some viral vaccines, which permit infection with wild-type pathogen whilst effectively preventing dis-

ease. At the other extreme are immunogens, such as the live-attenuated poliovirus, which substantially inhibit both infection (through production of intestinal IgA neutralizing antibody) and disease (via serum neutralizing antibody, preventing virus from reaching the nervous system) (Table 1). Some vaccines (e.g. influenza vaccine) induce excellent protection against life-threatening disease, less protection against mild disease, and little or no protection against asymptomatic infection. The degree of protection also varies widely by vaccine (Table 1) and by geographic location; e.g. measles and live-attenuated polio vaccines are less effective in the tropics than in developed countries.

HIV presents an extraordinary obstacle to vaccine development, as it uses numerous means to avoid neutralization by antibodies or attack by CTL⁵¹. Although at least some of these immune evasion strategies are employed by other pathogens, the capacity of HIV to destroy immune responses by killing CD4 lymphocytes is unique, and this latter property of HIV is of substantial concern to the HIV vaccine development effort. Most vaccines for other infectious diseases (Table 1), and many HIV vaccines^{47,52}, appear to permit infection and exert their protective effect by markedly reducing viral replication (as measured by viral load in the case of HIV) and thereby preventing disease (e.g. for HIV, slowing the decline in CD4 lymphocyte numbers) or by blocking access of the virus to sites critical for production of disease (e.g. hepatitis B and polio viruses). However, studies with an attenuated strain of HIV have shown that even low levels of HIV replication over long periods of time can still result in clinically-significant CD4 lymphopenia⁵³. These data would argue that vaccines that permit any ongoing replication by HIV might not provide lasting protection against AIDS.

Despite these caveats, there is some hope that a vaccine against HIV may be possible. HIV infection generates a vigorous immune response, both humoral and cellular^{52,54-56}. The efficacy of this response is most clearly shown by the fact that HIV mutates to avoid the response in infected patients⁵¹. The efficiency of HIV transmission (sexually) is relatively low, and many patients are infected initially by a single virion⁵². Consistent with these data, humans infected with HIV appear to be relatively resistant to superinfection⁵⁷⁻⁵⁹, and prior infection with HIV-2 (simplistically an imperfectly-attenuated live HIV-1 vaccine) appears to offer some protection against HIV-1⁶⁰, although not all studies support this conclusion⁶¹. Further, live-attenuated SIV vaccines have to date prevented SIV infection of macaques better than other immunization strategies⁶², and numerous other vaccination strategies have been at least partially protective in the macaque-SIV model^{48,52,55,56}.

Prophylactic vaccines: vaccine efficacy

Mathematical models can be developed and analyzed in the absence of data. Therefore, even

though there are no HIV vaccines yet available, the potential epidemiological impact of HIV vaccines can be assessed. A decade ago, Blower and McLean designed the first transmission model of HIV vaccines to assess the potential epidemic-level impact of imperfect vaccines (i.e., vaccines that had an efficacy level significantly less than 100%)^{12,63-66}. Their results showed that even imperfect vaccines could substantially decrease prevalence and incidence in a high (30%) prevalence HIV epidemic^{12,63}, and even result in eradication¹². They also derived an analytical expression (given in equation 1) that could be used to determine the critical vaccine efficacy levels (e_c) and the vaccination coverage levels (p) that would be necessary to eradicate any HIV epidemic^{12,63-66},

$$e_c = \left(\frac{1}{pf} \right) \left(1 - \frac{1}{R_0} \right) \quad (1)$$

where f specifies the fraction of vaccinated individuals in whom the vaccine does not wane during the time period when they are selecting new sex partners, and R_0 specifies the basic reproduction number (which determines the severity of the epidemic). It is currently unknown what efficacy levels HIV vaccines will actually achieve. However, equation 1 is an extremely useful public health tool for assessing how effective these vaccines would have to be, and what coverage levels would need to be attained in order to eradicate HIV epidemics. For example, if R_0 is 2 (as has been estimated for the gay community in San Francisco¹²), if the vaccine coverage rate is 80% ($p = 0.8$) and if the vaccine protects 80% of people during the length of their sexual life span (i.e., during the time when they are selecting new sex partners; $f = 0.8$), then it can be calculated (from equation 1) that the efficacy of the vaccine would have to be 78% effective in order to eradicate. It can be seen (from equation 1) that the vaccine efficacy level that is necessary for eradication will decrease as vaccination coverage levels, and/or the duration of vaccine-induced immunity, increases.

Blower and McLean also showed that the efficacy (e) of an HIV vaccine can best be understood by evaluating vaccine efficacy in terms of two components^{12,63-66}: *take* (ε) and *degree* (ψ); thus vaccine efficacy (e) equals $\varepsilon \psi$. *Take* specifies the fraction of vaccinated individuals that show a protective immunological response to the vaccine. *Degree* specifies the degree of vaccine-induced protection against HIV infection experienced by the individuals in which the vaccine takes. For example, if a HIV vaccine induced an immunological response in 80 out of 100 vaccinated individuals (i.e., *take* was 0.80), and these 80 individuals were protected against infection in 50% of their risky encounters, then the vaccine efficacy (e) would equal 40% (0.8 x 50%). Mathematical models have also been used to under-

stand and evaluate the epidemiological significance of the mechanism of action (*take* and *degree*) on the epidemiological impact of HIV vaccines^{12,63-66}. For example, two vaccines could both have a 50% efficacy level, but one vaccine could have a 50% *take* and 100% *degree* effect, whilst the other vaccine could have a 100% *take* effect and a 50% *degree* effect. Modeling analyses have shown that these vaccines could have very different epidemiological impacts, and the differences in the epidemiological impact between these two vaccines would be exacerbated by changes in risky behavior^{12,66}. In general, the analyses indicate that *take* vaccines will be more useful than *degree* vaccines in controlling HIV epidemics, especially in the presence of increases in risky behavior^{12,63-66}. Thus, it is essential that clinical trials of HIV vaccines determine the two components of efficacy.

Prophylactic vaccines: vaccine effectiveness

The effectiveness of HIV vaccines in reducing transmission in the "real-world" depends upon the average duration of vaccine-induced immunity, the achieved coverage level (i.e., the fraction of the susceptible population that receive the vaccine), and any changes (increases or decreases) in risky behavior that may occur.

Live attenuated vaccines, especially viral vaccines, generally have been found to induce long-term immunity (Table 1). The resistance of HIV-1- and HIV-2-infected humans to HIV-1 superinfection⁶⁰ presumably persists for life, and live-attenuated SIV or SHIV vaccines have induced long-term protection in the SIV/SHIV-macaque model⁶², albeit with the risk of causing disease themselves^{53,67}. However, the duration of immunity to any HIV vaccine, other than to a live, attenuated vaccine that induces lifelong infection, is unclear. CTL responses to other viral infections tend to be relatively short-lived, and this appears to be the case with some of the candidate HIV vaccines as well⁵². Mathematical models have been used to investigate the epidemiological impact of imperfect HIV vaccines that vary in *take* and *degree* and also wane over time. The rate of waning of vaccine-induced immunity has been shown to be a crucial factor in determining the epidemiological impact of HIV vaccines^{12,63-66}. Blower and McLean showed that the epidemic-level impact (ϕ) of an HIV vaccine is the product of vaccine efficacy (ϵ) multiplied by the proportion of vaccinated individuals in whom the vaccine does not wane (f ; $f = [\mu / (\mu + \omega)]$ where $1/\mu$ specifies the average timespan during which an individual selects new sex partners, and $1/\omega$ specifies the average duration of vaccine-induced immunity). Thus $\phi = \epsilon \psi [\mu / (\mu + \omega)]$; if the vaccine-induced protection is life-long then the epidemic-level impact (ϕ) is simply equal to the vaccine efficacy (ϵ). The critical duration of vaccine-induced immunity ($1/\omega_c$) that an HIV vac-

cine must induce in order to achieve epidemic eradication can be calculated from equation 2 (equation 2 is obtained simply by rearranging equation 1):

$$\frac{1}{\omega_c} = \left(\frac{1}{\mu} \right) \left[\frac{1 - \frac{1}{R_o}}{p\epsilon\psi - \left(1 - \frac{1}{R_o} \right)} \right] \quad (2)$$

The interactions among the vaccination coverage level (p), the vaccine efficacy ($\epsilon \psi$) and the critical average duration of vaccine-induced immunity ($1/\omega_c$) can be calculated from equation 2 and are shown in figure 3A. The duration of vaccine-induced immunity that is necessary to achieve epidemic eradication increases as vaccine efficacy decreases (Fig. 3A). For example, assuming that 80% of the susceptible population is vaccinated, if the vaccine is 100% effective then vaccine-induced immunity would have to last, on average, for 17 years. However, if the vaccine is 75% effective then the vaccine-induced immunity would have to last, on average, for 50 years (Fig. 3A). The critical average duration of vaccine-induced immunity that is necessary to achieve epidemic eradication also increases as vaccination coverage decreases (Fig. 3A). For example, assuming that an 80% effective vaccine is used, if 90% of the population was vaccinated, then the vaccine-induced immunity would have to last, on average, for 23 years. However, if only 80% of the population received the 80% effective vaccine, then the vaccine-induced immunity would have to last, on average, for 36 years (Fig. 3A).

The effectiveness of HIV vaccines in the "real-world" will be very dependent upon the achieved coverage level (i.e., the fraction of the susceptible population that receive the vaccine). If an effective HIV vaccine is developed, it is likely that it will be used widely at the population level. If reasonable resources are supplied, high levels of immunization are likely to be achieved, even in difficult situations such as poor, highly-dispersed populations lacking public health infrastructure and living in conflict zones. Poliomyelitis has been eradicated in all except about 10 countries by achieving very high levels of population immunity to poliovirus through vaccination with live-attenuated or inactivated polio vaccine⁶⁸. Measles immunization campaigns in Africa have achieved coverage rates of over 90%^{69,70}, and a nationwide measles-rubella immunization campaign in Costa Rica reached over 95% of persons aged 15-39 years, the group likely to be considered for a candidate HIV vaccine⁷¹. The critical coverage levels (p_c) that would have to be attained in order to achieve HIV eradication can be calculated from equation 3 (equation 3 is obtained simply by rearranging equation 1):

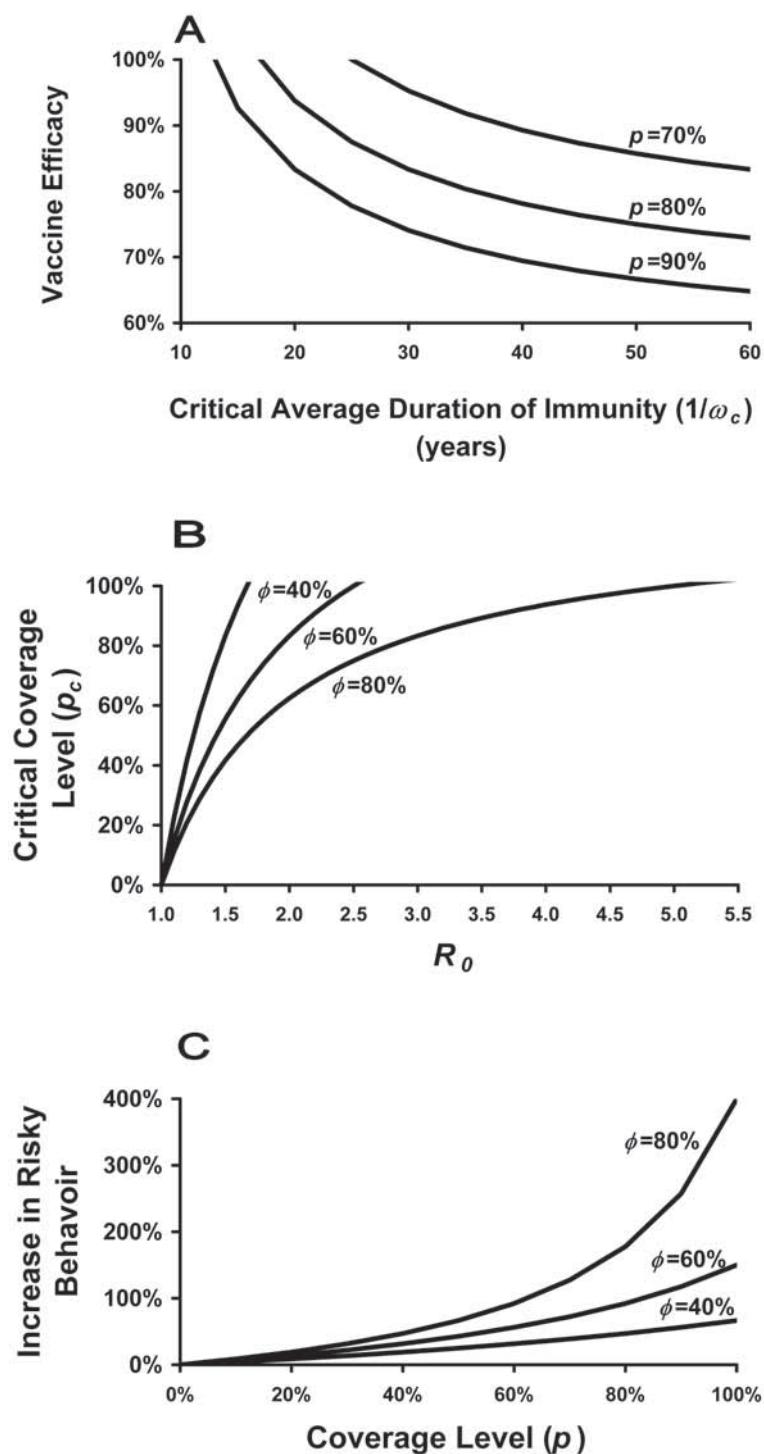


Figure 3. A) Vaccine efficacy (ψ) is shown as a function of the critical average duration of immunity ($1/\omega_c$), according to equation 2 (given in the text), with $R_0 = 2$ and $1/\mu = 10$ years. Vaccine coverage levels (p) of 70, 80, and 90% are shown. B) The critical vaccination coverage level required for eradication (p_c) is shown as a function of the severity level of the epidemic (R_0), as in equation 3 (given in the text). Vaccine impact levels (ϕ , or ϵ_f) of 40, 60, and 80% are shown. C) The critical degree by which risk behavior is increased (D_c), shown as a function of varying vaccine coverage levels (p); the plotted curves delineate whether a mass vaccination program would have a harmful (above the curve) or beneficial (below the curve) public health impact. Vaccine impact levels (ϕ) of 40, 60, and 80% are shown. The equation for the critical degree by which risk behavior is increased¹² is $D_c = 1/(1 - \phi p)$.

$$p_c = \left(\frac{1}{ef} \right) \left(1 - \frac{1}{R_0} \right) \quad (3)$$

The critical coverage levels (p_c) for three different impact levels of HIV vaccines ($\phi = ef = 40, 60$ and 80%) are shown in figure 3B. The critical coverage level increases as the severity of the epidemic (as specified by the basic reproduction number [R_0]) increases⁶³ (Fig. 3B). For example, for a low severity epidemic (i.e., $R_0 = 1.5$) and a 60% effective vaccine, 56% of the population would need to be vaccinated in order to achieve epidemic eradication. However, for a more severe epidemic (i.e., $R_0 = 2.5$), 100% of the population would have to be vaccinated with the same vaccine in order to achieve epidemic eradication (Fig. 3B). The critical coverage level decreases as the impact of the vaccine increases (Fig. 3B). The Blower and McLean model included *take*, *degree* and *duration*^{12,63-66}. More complex HIV vaccine models have been developed that allow for altered pathogenesis in vaccinated individuals who become infected; under these conditions the critical coverage level (p_c) can be calculated using more complex equations given elsewhere⁶⁴⁻⁶⁶.

Blower and McLean also used their model to derive an evaluation criterion to quantify the trade-off between vaccination with an imperfect HIV vaccine and potential changes (increases and decreases) in risky behavior^{12,66}. Their results showed that it would be unlikely that imperfect vaccines would be able to eradicate HIV in San Francisco, unless they were combined with considerable reductions in risky behaviors. Furthermore, their results showed that, under certain conditions, mass vaccination could have the perverse outcome of increasing the severity of the HIV epidemic^{12,66}. They showed that, if low impact vaccines are used and coverage levels are low, relatively low increases in risky behavior would make the epidemic worse (Fig. 3C). For example, if the vaccine impact was only 40%, and 50% of the population were vaccinated, an increase in risky behavior of 25% would make the epidemic worse (Fig. 3C). However, if vaccines of moderate-to-high impact are used, and coverage levels are high, then even substantial increases in risky behavior will not increase the severity of the epidemic (Fig. 3C). For example, if the vaccine impact was 80%, and 100% of the population was vaccinated, the average level of risky behavior would have to increase five-fold (i.e., 400%) in order to increase the severity of the epidemic (Fig. 3C).

Risky vaccines: live-attenuated HIV vaccines

Live-attenuated vaccines have been the dominant successful vaccine type for control of other infectious diseases, especially viral infections (Ta-

ble 1). Despite this history, the fact that a live-attenuated HIV-1 vaccine (HIV-2 infection) appears to protect humans against HIV-1 infection⁶⁰, and that live-attenuated SIV vaccines have been highly effective in preventing SIV infection of macaques⁶², research on live-attenuated HIV vaccines has faltered because of understandable concerns about the long-term safety of such vaccines^{53,67,72}. Blower, et al. developed and analyzed a mathematical model in order to assess the potential public health impact of live-attenuated HIV vaccines; this model has been used to assess the potential impact of mass vaccination campaigns using live-attenuated HIV vaccines in Thailand and Zimbabwe¹¹. This analysis has shown that such vaccines, due to their high efficacy, could substantially reduce transmission of wild-type strains of HIV in both countries, and result in epidemic eradication. The model was also used to evaluate the trade-off between vaccine efficacy (in terms of preventing new infections with wild-type strains) and safety (in terms of vaccine-induced AIDS deaths). Results of uncertainty analyses showed that these risky vaccines could have either a beneficial or a detrimental impact at the epidemic level, and that a threshold transmission rate exists that determines whether any specific live-attenuated HIV vaccine will have either a beneficial or a detrimental impact. The model was used to define and quantify the threshold at which a live-attenuated HIV vaccine causes a detrimental public health impact by increasing the number of AIDS deaths. This threshold was called the Vaccine Perversity Point and was defined in terms of the safety effect of the vaccine. Hence, this modeling analysis, by determining the trade-off between vaccine efficacy and safety, determined exactly how safe live-attenuated vaccines would have to be in order to be used to control HIV epidemics. The results also clearly showed that such risky vaccines should only be used in countries that have high incidence rates¹¹.

Therapeutic vaccines

ART dramatically improves the survival of patients with HIV infection⁷³⁻⁷⁵. Unfortunately, long-term ART is associated with numerous side effects, including the consequential ones of peripheral neuropathy and myopathy, acceleration of atherosclerosis and an increased risk of diabetes^{76,77}. ART also comes at a cost of at least US \$10,000 per year. It has been proposed that augmenting the immune responses of HIV-infected subjects prior to the development of profound immunodeficiency ("therapeutic" vaccination) may improve immune control of HIV infection and thereby permit either intermittent cessation of therapy (so-called structured treatment interruptions, or STIs^{78,80}) or possibly even complete cessation of ART. Although there are only rare examples of other chronic infections that have been controlled by *post hoc* immunization⁸¹,

there are macaque studies with SIV that do suggest that therapeutic immunization improves control of immunodeficiency virus infection following treatment interruption⁸⁰.

A variety of immunogens have been considered as HIV therapeutic vaccines, but most of them are also being considered as prophylactic vaccines⁵⁴. An exception to that generalization is the Tat and IFN α vaccine being proposed by Gallo, et al.⁸². Preliminary data on therapeutic immunization of humans have not been encouraging. Although most studies have shown that immune responses can be augmented, at least to some degree^{79,80,83,84}, none of the vaccines evaluated have had a salutary effect on viral load or CD4 lymphocyte numbers⁸⁵⁻⁸⁷. Whether other therapeutic immunization strategies will have a discernable beneficial effect on the course of HIV infection remains to be determined. However, mathematical modeling of hypothetical therapeutic HIV vaccines has shown that therapeutic vaccines could have substantial public health benefits by decreasing transmission⁸⁸.

HIV subtypes & vaccines

As a result of the high mutability and high replication rate of HIV, many strains of HIV-1 are now circulating globally⁸⁹. Three main groups of HIV strains are recognized: M (Main; representing > 95% of global HIV-1), O (Outlier) and N (Non-M, Non-O). The majority of HIV-1 subtypes (formerly "clades") are in the M group, which includes subtypes A-G as well as a number of circulating recombinant forms (CRFs) that represent recombination between subtypes (e.g. the Thai A/E CRF). HIV-2 also causes AIDS, although it is substantially less pathogenic than HIV-1, as HIV-2 viral loads are lower, CD4 lymphocyte numbers decline more slowly in HIV-2-infected subjects, and transmissibility is less than with HIV-1⁹⁰. The relevance of this viral diversity to immunization against HIV infection is unclear, as the HIV-1 subtypes, which are defined on the basis of sequence relatedness, do not have clear immunologic correlates^{91,92}. There is some evidence that HIV-2 infection may protect against subsequent HIV-1 challenge, although the protection is imperfect^{60,61}. HIV-1 and HIV-2 differ by about 50% overall, but envelope sequences, especially relevant to antibody neutralization, are substantially less well conserved^{90,93,94}. In contrast, env amino acid sequences within subtypes usually differ by $\leq 20\%$ and between subtypes by $\leq 35\%$ ⁸⁹. Given that genetic differences of a few percent can virtually eliminate neutralization by antibodies to the influenza hemagglutinin⁸⁹, it seems likely that HIV subtype differences will be relevant, at least to neutralizing antibodies. Three of the four reported cases of HIV superinfection have been instances of superinfection with a different subtype, suggesting that subtype differences are relevant to protective immunity. However, some investigators

have identified both antibodies and CTL that neutralize across HIV subtypes, at least to some degree^{89,95-97}.

Because of uncertainty about the relevance of HIV subtypes for vaccine development, most investigators are developing vaccines specific to the subtypes present in the population being immunized⁸⁹. The only Phase III vaccine trials currently underway are using the two HIV gp120 protein vaccines developed by VaxGen. One of the two VaxGen vaccines is based upon a combination of B and AE gp120s, and is being tested in Thailand, where B and AE (the Thai CRF) co-circulate⁴⁷; the other vaccine is a monovalent B gp120 being tested in the USA. Mathematical models have been used to assess the potential effects of vaccine-induced cross-immunity on the ability of vaccines to control HIV epidemics that are generated by more than one subtype^{98,99}. Blower and Porco have developed transmission models and used them to calculate (by deriving analytical expressions) the vaccination coverage levels, the vaccine efficacy levels, and the degree of vaccine-induced cross-immunity that would be necessary to control an HIV epidemic that is generated by two subtypes. Their results show that it is necessary that the vaccines induce very high levels of cross-immunity^{98,99}.

Conclusions

Epidemics are non-linear complex systems; the epidemiological impact of ART and imperfect vaccines is complex, and the epidemiological outcomes are difficult to predict using intuition alone. Furthermore, even when the epidemiological effects of interventions are intuitive, intuition cannot be used to assess the magnitude and/or the speed of the effect. For example, ART decreases the transmission and prevalence of drug-sensitive strains, and ART increases the transmission and prevalence of drug-resistant strains. However, only by modeling these interventions is it possible to predict how much drug resistance is to be expected, and over what time-scale it will occur. A very timely question "What will happen if we use imperfect vaccines to control HIV epidemics, and risky behavior increases?" can only be answered by using mathematical modeling analyses. Mathematical models can be used to evaluate explicit assumptions, and to determine the specific conditions under which ART and imperfect vaccines will have a beneficial, or detrimental, public health impact. Mathematical models are therefore extremely useful tools for making public health policy recommendations. So far a variety of different models^{8,9,19,20,88,100,101} have been analyzed and obtained similar results; these analyses have all shown that ART, and even imperfect HIV vaccines, would have very beneficial effects in controlling HIV epidemics. We suggest that, in the future, HIV modelers

work more closely with "real-world" experts in order to test the modeling predictions against empirical data sets¹⁰².

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