What can modeling tell us about the threat of antiviral drug resistance?
Sally Blower\textsuperscript{a} and Paul Volberding\textsuperscript{b}

Purpose of review
Currently, antiviral resistance is a major public health concern. Here, we review how mathematical models have been used to provide insights into the emerging threat of antiviral resistance. We focus mainly on the problem of drug resistance to HIV.

Recent findings
We review how antiviral models of HIV have been used: (1) to understand the evolution of an epidemic of drug-resistant HIV, (2) to predict the incidence and prevalence of drug-resistant HIV, (3) to conduct biological 'cost–benefit' analyses, and (4) to make public health policy recommendations. We also briefly discuss antiviral resistance for HSV-2 and influenza. Recent studies indicate that for HSV-2 and influenza drug resistance is not likely to become a major public health problem. However, for HIV the situation is very different. Results from several studies predict that a high prevalence of drug-resistant HIV will be an inevitable consequence of more widespread usage of antiretroviral therapies (ART). However more widespread usage of ART will save a substantial number of lives, and could even result in epidemic eradication.

Summary
Models have been used in many ways to provide insight into the emerging threat of antiviral resistance, particularly for HIV. At this stage in the HIV epidemic the most important future use of models may be that they will force the goals of public health policies to be clearly defined. Once goals have been defined it can then be decided whether a high prevalence of drug-resistant HIV is a threat or simply a justified means to an end.

Keywords
antiviral, drug resistance, mathematical model

Introduction
Along with our increasing ability to treat viral infections is our fear that resistance to these new drugs will become as limiting a barrier as has already occurred for some bacterial pathogens. HIV drug resistance already limits treatment success and many share the concern that drug resistance will occur for other viral infections like herpes simplex virus type 2 (HSV-2, the cause of genital herpes) and hepatitis B virus. Here, we discuss a variety of ways in which mathematical models have been used as tools for providing insights into the emerging threat of antiviral resistance. Mathematical models of epidemic dynamics consist of a series of equations that describe the specific transmission processes of a particular pathogen; hence models can be used to predict population-level outcomes such as incidence or prevalence. They are useful tools for predicting the epidemiological consequences of medical (and behavioral) interventions, because the model contains explicit mechanisms that link the effects of individual behaviors with transmission dynamics. Mathematical modeling was first used for analyzing how to control smallpox in 1760 [1]. Since then a wide variety of infectious diseases have been modeled including tuberculosis, malaria, trachoma, and influenza.

The first epidemic models of HIV that included the effects of treatment were used to assess the potential epidemiological consequences of monotherapy (with zidovudine); these studies predicted that widespread usage of monotherapy (under the assumptions that zidovudine would substantially increase survival time but would only slightly reduce infectivity) could increase the incidence rate [1–7]. These early modeling analyses of monotherapy did not include the possibility of either increases in risky behavior or of the emergence (and subsequent transmission) of drug-resistant strains. The introduction of combination antiretroviral therapies (ART) in the mid-1990s was accompanied by the rapid emergence of antiviral resistance and also (in high-risk communities) by increases in risk behavior. Thus predicting the epidemiological consequences of these new therapies became a more complex problem, and led to the development and analysis of new models [8,9\textsuperscript{**},11\textsuperscript{**},12\textsuperscript{**},13\textsuperscript{**}]. These new HIV models were similar in structure to earlier epidemic models of antibiotic resistance [14–17], as they allowed drug-resistant strains to emerge during treatment and to be transmitted.
The new HIV models were used to predict the effects of widespread usage of ART in the San Francisco gay community, under both optimistic and pessimistic assumptions concerning changes in risky sex and the rate of emergence of drug resistance [8]. It has been shown that – even in the presence of high rates of emergence and transmission of drug resistance – a high usage rate of ART would significantly decrease the AIDS death rate and prevent a substantial number of new HIV infections [8,9**]. Thus, treatment can act as an effective prevention tool [8,9**,10**]. The models have also been used to evaluate the trade-off between decreasing transmission (due to ART) and increases in transmission (due to increases in risky sex). An increase in the average level of risky sex of only 10% in the San Francisco gay community would be enough to counter-balance the benefits of a high usage of ART in decreasing transmission and would result in an increase in the incidence rate [8]. Similar results have been found for the gay community in Australia [12*].

**Modeling antiviral resistance**

To date, relatively few epidemic models have been used to analyze problems relating to antiviral resistance; resistance to HIV has been the main focus of attention. A few models of antiviral resistance have also been developed for HSV-2 [18,19] and influenza [20]. Here we review these analyses and discuss what they tell us about the threat of antiviral resistance. We organize our review under four topics describing how models have been used (1) to understand the evolution of an epidemic of drug-resistant HIV, (2) to predict the incidence and prevalence of drug-resistant HIV, (3) to conduct biological ‘cost–benefit’ analyses, and (4) to make public health policy recommendations. Finally, we briefly discuss HSV-2 and influenza.

**To understand the evolution of an epidemic of drug-resistant HIV**

Analyses of antiviral epidemic models have revealed interesting insights into the evolution of epidemics of drug-resistant HIV. The growth and dynamics of an epidemic of drug-resistant strains have been shown to be fundamentally different from the growth and dynamics of an epidemic of drug-sensitive strains [9**]. These differences are due to the ecological competitive dynamics between drug-resistant and drug-sensitive strains for ‘resources’ (i.e. high-risk individuals to infect), and to the differences in the number of processes that fuel the epidemic [9**]. Drug-sensitive epidemics are fuelled by only one process (transmission); however drug-resistant epidemics are fuelled by two processes: (1) transmission and (2) the conversion of treated drug-sensitive infections to drug-resistant infections (acquired resistance). Since the rate of increase in drug-resistant infections is not rate-limited by transmission, the rate of increase in drug-resistant infections can be much faster than the rate of increase in drug-sensitive infections; hence a high prevalence of drug resistance can be reached very quickly [8,9**,11**,21]. Computational analysis of antiviral models has been used to determine which process is most important in fuelling the epidemic of drug resistance: acquired resistance or transmitted resistance [9**]. The vast majority of new cases of drug-resistant HIV will be the result of acquired resistance; transmitted resistance will only account for a relatively small percentage of the new cases of drug resistance [9**].

Sensitivity analyses of antiviral epidemic models have been used to identify which factors are important in increasing both the transmission and the prevalence of drug-resistant strains of HIV [9**]. Transmission and prevalence of drug resistance increases as treatment rates increase, and/or as the rate of development of acquired resistance increases. In addition, transmitted resistance has been shown to be very dependent upon the transmissibility of the drug-resistant strains (drug-resistant strains that have a high relative fitness generate a high transmission rate) and the degree of treatment-induced reduction in viral load of drug-sensitive strains [9**]. Prevalence of drug resistance increases as the average duration of time that a drug-resistant patient spends on ineffective therapy increases. Uncertainty and sensitivity analyses of epidemic models have revealed how treatment changes the competitive dynamics between the drug-sensitive and the drug-resistant strains. High treatment rates (ranging from treating 50 to 90% of HIV-infected individuals) significantly decrease the percentage of drug-sensitive infections, but substantially increase the percentage of drug-resistant infections (Fig. 1); this effect increases over time. The treatment rate also determines the level of transmitted resistance [9**].

There has been considerable variation in the reported prevalence of HIV drug resistance in the ‘real-world’ [22,23]; these empirical results may initially appear surprising. The theoretical results, however, enable us to understand the observed heterogeneities in the data sets from different geographical regions. The modeling results (Fig. 1) show (not surprisingly) that drug resistance is a function of time and treatment rate [9**]. Therefore, prevalence of resistance is expected to be low in regions with limited drug access and use. Also, cities where early treatment was available and where patients were provided with the less potent regimens that were then in vogue are expected to have a serious problem with community HIV drug-resistance prevalence. Populations (in the ‘real world’) also vary with respect to levels of medication adherence that is related to drug-resistance...
To predict the incidence and prevalence of drug-resistant HIV

Scenario analysis (i.e., one single computer simulation of a model) is useful for predicting the emergence of drug resistance if the values of each parameter in the model can be precisely estimated. Data, however, are often sparse. For example, the values of many of the parameters (such as the transmissibility of drug-resistant strains) are only imprecisely known; therefore scenario analysis has limited utility [24]. Models can still be analyzed (even if parameter estimates are only imprecisely known), however, by using uncertainty analysis [25–27]; uncertainty analysis is a technique developed in the field of risk assessment and engineering in order to predict the probability of adverse events occurring [28,29]. Uncertainty analysis can be used to predict the future (with a degree of uncertainty) by including uncertainty in estimating the specific values of each of the models’ input parameters [24,25]. By using uncertainty analysis antiviral epidemic models can be used as predictive tools [8,9*,10*,18,19]. An uncertainty technique based upon Latin hypercube sampling [28,29] has previously been applied in infectious disease modeling to predict the future of HIV epidemics [8,9**,10**,24], the potential epidemiological consequences of HIV vaccines [30] and the emergence of antiviral-resistance [8,9**,18,19,21].

Uncertainty analysis of an antiviral epidemic model has been used to predict both the prevalence and transmission of drug-resistant HIV in the gay community in San Francisco [9**,21]. Using both optimistic and pessimistic assumptions concerning the rate of increase in risky sex and the emergence of drug-resistant HIV, a high prevalence of drug resistance has been predicted [21]. It has been predicted (using the pessimistic assumptions) that 42% of the HIV-infected cases in San Francisco will be infected with drug-resistant strains by 2005 [9**]. The time of exponential increase for transmitted resistance, however, is likely to be rather short due to the effect of the competition between drug-resistant and drug-sensitive strains for ‘resources’ (i.e. high-risk individuals to infect) [9**]. These competitive dynamics ensure that transmitted resistance in San Francisco (defined in terms of the percentage of new HIV infections that are drug resistant) will remain fairly low and is expected to stabilize in the next few years. Even by 2005, only 15.6% (median value) of the new HIV infections are predicted to be drug resistant [9**]. Recent empirical studies [23] show that these theoretical predictions are in close agreement with the levels of drug resistance that have actually been observed.

Goudsmit and colleagues [13**] have recently analyzed the impact that therapy failure had on the transmission of zidovudine-resistant strains of HIV in a cohort of gay
men in Amsterdam. They used a model to calculate the number of cases of zidovudine resistance that were expected to have occurred (as a result of transmission) in this cohort from 1990 through to 1998. They estimated the necessary parameter values for their model using empirical data. The model predictions were then compared with cohort data on temporal trends in AZT resistance in newly infected men. Over the 8-year study period 43 individuals in the cohort were recently infected, but only three of these primary infections were due to the transmission of zidovudine-resistant strains. Model predictions, and the empirical data, showed that the transmission and prevalence of zidovudine-resistant strains rose and fell over the study period as the usage of AZT rose and fell. The prevalence of AZT resistance initially rose to 22% due to the large number of patients receiving zidovudine monotherapy, but then prevalence fell rapidly (after 1996) as patients were switched to more effective therapies. The model revealed that very few (n=3) cases of transmitted AZT resistance were expected as the prevalence of AZT resistance quickly fell to zero. Thus the high (but temporary) prevalence of AZT resistance in the Amsterdam cohort was almost completely driven by acquired resistance.

To conduct ‘biological cost–benefit’ analyses

Medical interventions are designed to benefit individual patients, but can sometimes lead to detrimental epidemic-level effects; for example, HIV epidemics will worsen if moderately effective HIV vaccines are accompanied by an increase in risky behavior [31,32]. Models can be coupled with economic analyses to perform cost–benefit and cost-effectiveness analysis [11**]. Modeling, however, can also be used to conduct ‘biological cost–benefit’ analyses; these analyses have two stages. First, the epidemic-level benefits and costs of a particular control strategy are quantified, and then a treatment evaluation criterion is defined and used to determine whether the benefits outweigh the costs. Models can be used to calculate ‘real-world’ treatment evaluation criteria such as the annual (or cumulative) death rate, and the annual (or cumulative) incidence rate. Also, models can be used to define theoretical treatment evaluation criteria [14,15,18]. For example, in the ‘real world’ the treatment failure rate is often used as a treatment evaluation criterion for evaluating tuberculosis control programs. The treatment failure rate, however, is only a measure of the direct effect of treatment in generating resistance; the indirect effect of treatment in generating resistance is not assessed within this treatment evaluation criterion. A theoretical treatment evaluation criterion was defined (by analyzing a model of antibiotic resistance) to assess both the direct and the indirect effects of treatment in generating antibiotic resistance [14]. This treatment evaluation criterion was used to calculate the number of cases of acquired plus transmitted drug resistance that emerged during the treatment of a single case of drug-sensitive tuberculosis [15]. Applying this treatment evaluation criterion to data from developing countries it was determined that (due to high treatment failure rates) control programs could actually make the epidemic worse by generating (on average) 1.7 drug-resistant cases per treated drug-sensitive tuberculosis case [15].

Antiviral models have been used to perform biological ‘cost–benefit’ analyses (1) by assessing whether the epidemic-level benefit of ART (i.e. reduction in transmission of drug-sensitive strains) outweighs the epidemic-level cost of ART (i.e. increase in transmission of drug-resistant strains) [8,9**], and (2) by calculating the cumulative number of HIV infections prevented per prevalent case of resistance [9**]. These analyses have shown that the reduction in transmission of drug-sensitive strains (due to widespread usage of ART) substantially outweighs any increase in new infections due to transmitted resistance. It has also been shown that the high usage of ART in San Francisco has (and will continue to) significantly reduced the overall transmission rate [8,9**]; by 2005 approximately one HIV infection will have been prevented for each prevalent case of drug resistance that is present [9**].

To make public health policy recommendations

Models can be useful health policy tools as they can be used to identify how to design and improve epidemic control strategies. Certain epidemic control strategies can substantially reduce the morbidity and the mortality caused by drug-sensitive strains, but substantially increase the morbidity and mortality caused by drug-resistant strains. In order to design and improve epidemic control strategies, goals and evaluation criteria need to be clearly specified [15]. Many different goals can be specified, for example, disease eradication, stabilization (at a specific level) of drug resistance, or a specific reduction in incidence, prevalence, morbidity or mortality rates. Goals need to be defined in terms of an epidemiological measure (for both the drug-sensitive and the drug-resistant strains) and by a time frame in which the goal is to be attained [15]. The model can then be analyzed in order to determine how to achieve the particular goal(s) in the specified time frame. Eradication is an easy goal to specify theoretically, although it is a hard goal to achieve in the ‘real world’. Analysis of antiviral models has shown that it is theoretically possible to achieve eradication of HIV epidemics by using a combination of ART and risk reduction: even a high-prevalence (30%) epidemic could be eradicated if 70% of HIV-infected cases are treated and risky behaviors are reduced by 25% [10**]. When designing epidemic control strategies both short-term and long-term goals need to be specified, and the compatibility of these two goals needs to be carefully
resistance. Tchetgen adherence leads to a high rate of emergence of acquired important factor is patient adherence; a low rate of patient, the clinician and the drug regimen. One variety of factors that depend upon the virus, the resistance. These results have been used to suggest rational public health policies for controlling HIV epidemics. These theoretical analyses have shown that if the goal is to maximize the reduction in the AIDS death rate and incidence rate then the strategy should be to treat as many HIV-infected people as possible and to link treatment programs with effective behavioral intervention programs. If the goal is to minimize the transmission and prevalence of drug resistance then theoretical analyses have led to four health policy recommendations: (1) delay therapy as long as possible, (2) reduce as much as possible the rate of development of acquired resistance, (3) develop more effective therapies that will completely suppress resistant isolates, and (4) minimize the average length of time that a drug-resistant case is receiving ineffective treatment. These recommendations are in accord with the British guidelines and the US treatment guidelines that recommend delaying therapy.

Resistance to antiretroviral drugs develops due to a variety of factors that depend upon the virus, the patient, the clinician and the drug regimen. One important factor is patient adherence; a low rate of adherence leads to a high rate of emergence of acquired resistance. Tchetgen et al. have developed an epidemic model of treatment and antiviral resistance and have used their model to assess the effects of adherence on the emergence of resistant virus. Specifically, they have used their model in order to answer the question of whether clinicians should screen patients for adherence and choose to selectively treat patients in order to minimize the emergence of drug resistance. They combined an epidemic model with a probabilistic model that accounted for the frequency and accuracy with which physicians screen patients for adherence. The model was used to compare a policy of screening and treating only the patients that the clinicians believe are likely to adhere to a policy of treating all HIV-infected individuals. The results showed that, in general, screening and selective treatment would generate lower levels of resistance but a higher incidence of HIV and AIDS than a policy of treating all HIV-infected individuals.

Other diseases and antiviral resistance Genital herpes (caused by HSV-2) is the most prevalent sexually transmitted disease worldwide. In many developing countries, however, genital herpes is untreated, and in the United States only 10% (or less) of HSV infections are treated. An antiviral epidemic model of HSV-2 has been developed and used as a health policy tool to predict the levels of antiviral drug resistance that would emerge if treatment rates for genital herpes were substantially increased. The results showed that increasing treatment rates (in an immunocompetent population) would significantly decrease the incidence of HSV-2 infections, and that (in contrast to HIV) the prevalence of drug-resistant viral strains (even after several decades) would remain low. The same model was also used to determine the probability of eradicating herpes epidemics by using antivirals, and to quantify the effect of increasing antiviral usage on decreasing HSV-2 prevalence. Further analyses were performed to calculate the effect of antiviral usage on individual patients in terms of the decrease in the average number of infectious days per year, and an individual's lifetime probability of acquiring permanent drug resistance.

Stilianakis et al. developed a mathematical model to track the emergence of drug-resistant influenza viruses during an influenza epidemic. They fitted their model to data from an influenza A epidemic that occurred in 1978 in a boarding school. They used their model to evaluate several treatment and chemoprophylaxis strategies during both an outbreak in a school and an epidemic. Three strategies were evaluated: treating only infected persons with clinical symptoms, mass chemoprophylaxis for all uninfected persons, and chemoprophylaxis plus treatment. Their results showed that chemoprophylaxis of susceptible individuals (without treatment of those who are infected and symptomatic) would be the best strategy for reducing transmission and would generate only low levels of drug-resistant viruses.

Conclusion The effects of ART at the epidemic level are complex. Models allow us to focus on the big picture and to evaluate simultaneously all aspects of the epidemic. Models of antiviral resistance have many uses. They can be used to predict how much antiviral resistance is to be expected and over what time scale resistance will emerge. They can also be used to identify which biological, behavioral or treatment factors contribute to the emergence and transmission of drug-resistant strains. The results of these analyses can be used to suggest how to prudently use existing (and new) treatment regimens
to control viral epidemics whilst simultaneously maximizing the public health benefit. The models have shown that for HSV-2 and influenza, drug resistance is not likely to become a public health problem. For HIV, however, the situation is very different. Analyses indicate that (not surprisingly) a high prevalence of drug-resistant HIV will be an inevitable consequence of more widespread usage of ART. More widespread usage of ART, however, will save a substantial number of lives, and could even result in epidemic eradication. At this stage we need to determine what are the desired epidemic-level goals for controlling HIV epidemics. When these goals have been defined we can decide whether a high prevalence of drug-resistant HIV should be perceived as a threat or simply as a justified means to an end.

Acknowledgements
S.B. acknowledges the financial support of NIH/NIAID (RO1 AI41935). P.V. acknowledges the financial support of the USCF-GIVI Center for AIDS Research (P30 AI27763-11).

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
** of special interest
** of outstanding interest

11 Tchetgen E, Kaplan EH, Friedland GH. Public health consequences of screening patients for adherence to highly active antiretroviral therapy. JAIDS 2001; 26:118–129.