Reversibility of HIV Drug Resistance

Using a mathematical model, Blower et al. (1) predicted the impact of antiretroviral therapy (ART) on future trends in the sexual spread of human immunodeficiency virus (HIV). The model employed Latin hypercube sampling to allow for the high degree of uncertainty in the estimation of many model parameters.

The authors incorporated into their model the assumption that patients with drug-resistant virus who cease treatment ($Y_{R,U}$ in the model) will revert to being drug sensitive ($Y_{S,U}$) within a short period (2 weeks to 6 months). Existing data do support the notion of a conversion from a predominantly resistant to sensitive virus detectable in the blood following cessation of treatment (2), and the subsequent transmission of drug-sensitive virus (3). Blower et al. included in their model a probability ($p_{R,U}$) that patients with drug resistance may transmit drug-sensitive virus.

However, although studies suggest that drug-sensitive virus may reemerge in patients’ blood following cessation of therapy, there is no evidence that patients become “sensitive” to further treatment with the same ART regimen. Clinical practice with such patients affirms that reinstitution of drug therapy rapidly selects again for resistant virus, and the patient once again becomes unresponsive to the ART regimen. The model of Blower et al. assumed that drug-resistant patients are able to revert to drug sensitivity and complete another round of identical therapy, as if they were drug naïve. Indeed, it was assumed that they do so at a high rate.

As a result, in the model, very few patients remained drug resistant and untreated. Because this group is expected both to have a high death rate (relative to all treated groups) and to exert an influence on the spread of resistant virus, their absence is significant. In addition, because this group kept cycling back into the drug-sensitive group, they then benefited from the long survival time and low transmission rates of drug-sensitive, treated patients.

The transmission of drug-resistant HIV is a major public health issue. As Blower et al. illustrate, increases in risk behavior related to optimism over the benefits of drug therapy may increase in the overall burden of HIV. The model offered by Blower et al. provides an important framework for future analysis of the HIV epidemic, and it is essential that such models accurately reflect our current understanding of the infection. In the case of both individual patients and the community as a whole, once antiretroviral drug resistance is present, there is no turning back the clock.

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Response: Mathematical models are important tools to guide decision-making in public health, particularly in evaluating how to control antibiotic (1) and antiviral (2, 3) resistance. Our mathematical model (3) is the first theoretical framework for future analysis of the HIV epidemic that incorporates the effects of combination ART, changes in risk behavior, and the emergence of drug-resistant strains of HIV. To develop our model, we applied Occam’s razor to the current biomedical understanding of the transmission dynamics of drug-sensitive and drug-resistant HIV strains in San Francisco. We assumed that some patients who are infected with drug-resistant HIV strains who cease treatment could revert (at rate q) to being drug sensitive, an assumption based on existing data (4). Davenport points out that if these patients are then re-treated, they will not respond to therapy in exactly the same manner as drug-naïve patients. We agree that this is a likely outcome and one that has indeed been shown to occur (4, 5). Our intention was to develop and analyze a first, simple model to provide general insights; as such, our model was an abstraction of reality, not a mirror of reality.

The principal insight from our analysis was that increasing ART usage rates would decrease both the death rate from acquired immunodeficiency syndrome (AIDS) and the number of new HIV infections, even if risky behavior increased and the rates of emergence of drug resistance were high (3). One of us (Blower) is now using this simple model as the foundation for building a more detailed version that explicitly includes re-treatment failure rates and salvage therapy. In this more complex model, re-treated patients can respond differently to therapy than drug-naïve patients; specifically, the two groups can differ in their rate of acquiring drug resistance, their viral load, and their survival time. Results from this more detailed model are still under study, however, the time-dependent sensitivity analyses even for our simple model can provide some preliminary insight into the potential impact of re-treatment and salvage therapy (3). In these analyses, we varied the rate of emergence of drug resistance, r, for treated drug-sensitive patients. We assumed that this rate of acquired (or reacquired) resistance could vary from a low of 10% to a high of 60% of treated patients per year (3). This range encompasses virological failure rates that have been observed in those with previous drug-resistant infection who re-initiate therapy after a period of treatment interruption (4).

Interestingly, the results revealed that neither a very high rate of acquired (or reacquired) resistance, r, nor a very high reversion rate, q, significantly affected the two main outcome variables of interest: the cumulative number of HIV infections prevented and the cumulative number of AIDS deaths averted over the next 10 years (3). Our results did reveal, however, that a high rate of acquired (or reacquired) resistance would lead to a high prevalence of drug-resistant infections (6). Thus, on the basis of these analyses, we agree with Davenport that every effort should be made to prevent the emergence of drug-resistant strains in treated individuals.

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6. These data are available at www.sciencemag.org/featuredata/1044287.shtml.

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