EDITORIAL COMMENTARY

Antiretroviral Therapy as Prevention: Linking the Mainframe to Main Street

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(See the brief report by Charlebois et al, on pages 1046–1049.)

Dr Charlebois and colleagues [1] address the most compelling question in human immunodeficiency virus (HIV) infection prevention research today: Can antiretroviral therapy (ART)-based interventions reduce HIV infection incidence and prevalence sufficiently to justify their cost? To investigate the potential impact of different modes of expanding ART to populations broader than those included in current treatment guidelines, the authors use deterministic models that make simple assumptions regarding sexual mixing. Such models require estimation of a large number of parameters, such as those that characterize degree of risk-taking, probability of transmission, and the proportion of populations willing to be tested and that will adhere to treatment. The authors correctly describe their work as a "thought experiment informed by data," and as such, it serves a useful purpose: exploring the feasibility of different consequences of different types of interventions. This and several other modeling exercises have performed a valuable service in providing some plausible ranges for the impact of the expansion of ART [2, 3].

Despite recent glimmers of hope in HIV vaccine and microbicide research, only the most sanguine of scientists believe that either is on the fast track to success [4, 5]. Thus, as the epidemic expands, it is not surprising that new ideas such as "test and treat" have attracted great attention. In addition to providing uncertainty estimates (the interpretability of predictions in the abstract would benefit from the provision of intervals of uncertainty), modeling exercises can suggest which parameters' results are most sensitive—in this case, the impact of ART on the risk of transmission—and can help guide research. However, such exercises cannot tell us what will and will not be cost-effective in different regions of the world. To determine that information, we need to perform real research in actual communities. We believe that the time has come to raise the bar for expectations regarding future research—both for studies in the field and for those in the computer lab.

In the real world, we should consider a range of different methods for getting quicker answers about whether a package of interventions shows promise. Although large-scale, community-level randomizations will provide the highest level of validity and the greatest power for detecting modest effects, such studies are expensive, and probably the world will be willing to do only a very small number. To mount appropriate large studies, we need more information on how to design them and which interventions to consider. Achieving this goal requires the equivalent of phase I/II studies but conducted at the community, rather than the individual, level. Such studies are both faster and less expensive to mount; they can provide valuable evidence regarding the impact of prevention interventions that would be of interest in itself and useful for designing larger-scale intervention research.

Part of such research needs to be focused on the extent to which local conditions drive outcomes. Phase I/II studies make use of end points that reflect activity but are not intended to provide definitive proof of efficacy. To extend this idea to the community setting, one might start by reviewing the work of Brenner et al [6] and Smith et al [7], who demonstrated the value of genetic clustering for making inferences about epidemic dynamics. For example, Brenner et al [6] demonstrated that approximately half of the viral genotypes

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from those diagnosed with primary HIV infection in Quebec clustered with at least one other from this group, implying an important role for patients with primary infection in transmitting HIV; it may be naive to develop models that ignore this feature of the epidemic. Such clustering can be useful in relatively short studies of prevention interventions that would provide early evidence of an impact—much as viral load monitoring guided therapeutic research efforts after 1996, leading to clinical trials that demonstrated the cost-effectiveness of the broad provision of ART [8, 9].

Another important issue is raising the bar for modeling exercises. It is reasonable to start with models in which subjects mix preferentially within compartments defined by factors such as risk and sex and, to a lesser extent, across them. But these models are not based on any genuine attempt to understand the true nature of sexual and transmission networks and, therefore, may not produce reliable results. Progress in this area requires development of agent-based models of epidemics that propagate along more realistic sexual networks. An important open question is how to identify the most network features that have the highest impact on efficacy of intervention packages and therefore need to be included in models. Morris et al [10] have shown concurrency to be highly relevant for HIV propagation, but other network features also may be important epidemic drivers, such as the tendency for people who have many partners to choose others who do as well [11]. At the very least, there needs to be assessment of whether results that are obtained from theoretical models with different sexual network topologies produce results similar to those used by Charlebois et al [1], which do not consider network features of this type.

Another major concern about modeling exercises is communication of the true range of uncertainty. Charlebois et al [1] consider the uncertainty in important parameters, such as the proportion of subjects who fully suppress virus on treatment or who are at high risk, and rates of treatment cessation, mortality, and testing. But many other important sources, such as those described above, are not considered. A crucial question for modelers is which features of an epidemic can safely be ignored. Finding the appropriate middle ground between grossly simplistic models and truly accurate representation of sexual or other networks is critical. Complete accuracy is neither possible nor, in all likelihood, necessary; what we require instead is an understanding of the level of accuracy sufficient for producing useful results. An analogy is the use of population genetic sequencing for guiding therapy. Population genetic sequences hardly constitute a realistic representation of the true genetic diversity of an evolving viral swarm. There are many theoretical reasons to believe that population sequencing should not be adequate for guiding therapy; one is that it is not informative about minority species that may rebound under drug pressure. Yet, both randomized and observational research confirm the value of population sequences in selecting drug combinations. Nonetheless, population sequences are not adequate for all research purposes; for example, research on genetic lineages requires deep sequencing that is more expensive but provides more complete information about viral populations. Similar principles apply for models intended to characterize how viruses spread through communities. There may be no use in continuing with models that ignore potentially important realities, such as the impact of network topologies.

It is essential to avoid drawing premature conclusions about what may or may not be cost-effective from oversimplified models. Thought experiments are of great value but must lead to actual experiments for this value to be realized. The range of uncertainties is large; reducing them requires the right studies conducted as efficiently as possible. Crucial to cost evaluation is assessment of practicality from both the operational and fiscal perspective. If the HIV infection epidemic could be controlled by one tenofovir a day for all those at risk in the world, that would be theoretically interesting but not helpful for devising practical solutions. On the other hand, providing that one tenofovir pill per person per day to the subpopulation disproportionately driving the epidemic now might lead to a much larger reduction in the number of pills required to treat a community in the future. The public health question is not how to provide therapy to everyone with HIV infection (as in the current "brute force" test and treat paradigm) but rather how to identify and to recruit for therapy those whose transmission risk over time and whose position in networks make treating them particularly valuable. Ultimately, the goal is to reduce the average number of new infections derived from each incident infection (termed the R_0) to <1 [12]. Concentrating on those most likely to contribute to this goal is analogous to considerations that traditionally drive decision making in the clinical setting: those most likely to benefit move to the front of the line.

Urgently needed is coordinated support from government, industry, and foundations for research to advance two goals: (1) developing appropriate public health responses to the HIV infection epidemic and (2) investigating mechanisms by which interventions do and don't work—pathogenesis at the community level. Early success with nucleoside analog therapy whetted our appetites in the latter half of the 1980s, but lags in therapeutic progress reflected lags in understanding mechanisms that drove empirical results [13]. Strategies such as large simple trials—successful in fields like cardiology—could not, in HIV research, provide generalizable answers to questions such as when to start therapy and how to combine and to

sequence drugs. Chief among the many reasons for this is that evolution of microbes within individuals and communities produces moving targets not reachable by fixed strategies. Just as therapeutic success in the mid-1990s followed better understanding of mechanisms of disease and drug action [14], so might success in prevention research follow improved understanding of mechanisms that drive disease spread. Prevention studies should be designed to foster such knowledge, and modeling can be a helpful tool in this regard. But to be useful, models must permit higher levels of representation of reality and must have a stronger basis in evidence to provide information about which factors drive the success or failure of prevention efforts. Such knowledge will depend on both theoretical and field research. We could not have learned both the value and the limits of genetic testing from viral dynamic and evolutionary models alone; but without such models and the intellectual frameworks that underlie them, we could not know where and how to apply results of studies. Turning HIV infection from a death sentence into a manageable disease resulted when an organized multidisciplinary research community capably executed an integrated scientific agenda in which laboratory and clinical research were mutually reinforcing. Such coordination of theoretical and clinical researchers is likewise essential for prevention based on ART to move from mainframe to Main Street.

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