PHI and Transmission Risk (Part 1): The Contribution of Mathematical Modeling

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WITHOUT A DOUBT, PUBLIC HEALTH INITIATIVES SURROUNDING PHI—whether it's aggressive testing and counseling of acutely infected individuals, stepped-up contact tracing efforts, or the use of HAART—need to be considered carefully in the larger context of HIV/AIDS prevention efforts. Yet our understanding of the public health consequences of "unchecked" viremia and risky sexual behavior during PHI is still in its infancy, and even less is known about the cost-effectiveness of intervention programs, particularly when pricey diagnostic tests and antiretroviral therapies are involved.

Skepticism surrounding the utility of expensive early intervention programs is definitely warranted, especially when one considers that only a minority of transmissions occur during PHI and that only a few of these individuals are diagnosed early and treated. But as Dr. Koopman argues, taking advantage of this window of opportunity may end up having large effects on population infection levels. "In order to understand this," he says, "we need to analyze the transmission system that disseminates infection. Undoubtedly, we don't have enough information currently for such an analysis, so the first task is to figure out which studies we need to conduct to assess the effectiveness of such programs."

Transmission systems involve all of the contacts that can spread infection, as well as the specific interactions between HIV and its human hosts that affect the natural history of infection. More simply put, transmission systems are what sustain the circulation of HIV and facilitate its spread to different parts of the host populations. As explained by Dr. Koopman, "These are dominant determinants of population infection levels and offer several opportunities for infection control that epidemiologists commonly miss when they use standard individual risk-based methods. Unfortunately, it has been difficult to get data needed for transmission system analysis. But nucleotide sequence-based phylogeny data hold great promise of moving us forward."

What this all boils down to is mathematical modeling. Given that there are numerous difficulties associated with empirically measuring the impact of intervention programs as they relate to HIV—whether it be behavioral, social, or medical intervention—current impact and cost-effectiveness information is terribly limited. What information does exist generally comes from randomized controlled trials. Yet these studies are expensive and, in turn, are unlikely to be conducted in a broad range of settings.

Mathematical modeling, Dr. Koopman argues, plays a vital role in the development and implementation of epidemiological studies and infection-control programs that will likely yield the most worthwhile and cost-effective results. For example, specialists responsible for the control of infections, such as anthrax in the postal system and other potentially more elaborate outbreaks of bioterrorism, employ a variety of barrier techniques to prevent the spread of transmissible pathogens. These techniques are extrapolated from models that describe our understanding of the processes of transmission. "Modeling should tell us a lot about what's going on in the transmission of HIV and, more importantly, what we might be able to do about it."

Early Diagnosis and Treatment of PHI: Four Mechanisms of Indirect Transmission Benefit

Until recently, the bulk of PHI treatment research has involved two central aims: first, to understand the individual health benefits of treatment, and second, to evaluate the direct transmission benefit—that is, the reduction in an infected individual's risk of transmitting the virus to his or her sexual or drug-injecting partners while he or she is acutely infected. "The direct transmission benefit is important, but it oversimplifies things," Dr. Koopman said. "It's only a small part of the total population benefit." Dr. Koopman is particularly interested in the indirect transmission benefit of early diagnosis and treatment, which focuses on the benefits of intervention because of changed transmission dynamics. "This I think is where we'll see the majority of expected benefits."

To appreciate the potential population benefits of early intervention programs, it is necessary to step back and examine some of the mechanisms that can cause transmission occurring during PHI to amplify transmission in populations.

The first mechanism, originally discussed in a cutting-edge paper published in the *Journal of Acquired Immune Deficiency Syndromes* in 1994, involves the observation that early transmission epidemic chains grow quickly (Jacquez, 1994). Dr. Koopman, a coauthor of the paper, noted that this work "helped explain that early infection transmission best accounts for population patterns of HIV infection." For example, the pattern of high infectiousness during PHI, followed by a large drop in contagiousness, may explain the pattern of epidemic spread seen in male homosexual cohorts in the early years of the epidemic. "Some modelers remain skeptical," Dr. Koopman admitted. "At present, data to assess the role of early infection or to estimate transmission probabilities are still lacking."

The second mechanism discussed by

Dr. Koopman involves fluctuating high-risk behaviors in high-risk settings that can extend or expand the transmission tree. The fluctuating risk factors, he pointed out, advance the hypothesis that individuals in an early stage of infection are more likely to transmit to those who also have a high likelihood of transmitting during their own early stage of infection (Koopman, 1997).

Two types of fluctuations are worth mentioning: age fluctuations and transient fluctuations. Dr. Koopman suggests that most people become infected during a period of indiscretion in their lives, when they are having more sexual encounters in risky environments than during other periods. There are a number of possible reasons for this: It might be a life stage when young people are coupling with other young people; it might be an even more transient life stage than youth; it might be a period of relationship instability; it might be a period of mobility with movement into unsupportive social environments that provide many sexual outlets. Such mobility might result in either adventurism or needs for relationship that lower one's guard.

It's also important to recognize that such fluctuations are almost always a "group thing"—The individuals one encounters sexually or through needle contact are also likely to be in such periods of their own lives. Consequently, the individuals to whom one transmits are in turn more likely to transmit during early HIV infection than those one encounters during other life stages. "These fluctuations need to be taken into account," Dr. Koopman stated. "Most modelers don't account for such transient behavior, which may be quite significant in acutely infected individuals."

The third mechanism discussed by Dr. Koopman involves long-term contact patterns, specifically inter- and intra-risk-group mixing. The HIV epidemic depends on this mixing—that is, the extent to which high-risk individuals engage in sexual activity only with other high-risk partners (assortative mixing) or also with low-risk partners (disassortative mixing).

To examine the significance of mixing patterns, Dr. Koopman and his colleagues constructed a model with 5% of the population in a high-risk group and 95% in a low-risk group; prevalence by group was 15% and 3%, respectively. A mixing scale was included in the analysis that went from "completely assortative"—meaning no contact between the two groups—to "maximally disassortative"—in which all contacts from one group were only with individuals from the other—on opposite ends of the range.

"What we found was really quite interesting," Dr. Koopman reported. "Only a 5% reduction in contagiousness of infection in the 5% of the population in the high-risk group could decrease the total infection in the population by 28% if the mixing is not very assortative. The effect decreases as the mixing becomes more assortative, but still remains large. This shows that infection detection and treatment programs focusing on high-risk groups are indicated, which would certainly include acutely infected individuals."

A final mechanism discussed by Dr. Koopman comes about when chance raises or lowers the level of infection in a population. The models to capture such mechanisms are called "stochastic" models and are more difficult to analyze than the "deterministic" models that can be used to assess the first three mechanisms. One way these stochastic effects arise is that groups of individuals remain free of infection by chance for a prolonged period of time, when suddenly, a chance infection sets off a large tree of spreading infection. While this mechanism has the potential to be quite important for some factors spreading infection widely in a community, which was Dr. Koopman's observation during previous work involving contaminated water spreading Cryptosporidia, it is not yet known how important the mechanism might be for HIV.

The Hope of Phylogenetics

While Dr. Koopman firmly believes that his hypothesis that HIV transmissions during PHI are increased by transmission systems, he is also the first to point out that no studies have actually been conducted to confirm or refute any of the amplification mechanisms described above. Because Dr. Koopman and his colleagues hope to assess the potential effects of early treatment intervention on populations of people, not just individual transmission probabilities, a vast amount of data will be needed for modeling purposes. "We don't want just a random sample of individuals and their partners," Dr. Koopman explained. "We want contact patterns. We want to see what happens in an individual and his partners and his partner's partners, connecting everyone across many links." This, he argues, will help illustrate how transmission interruption (e.g., therapeutic intervention), even in just a small percentage of patients with PHI, might have a protective ripple effect.

The problem is that data pertaining to contact patterns across links are not available, and manual contact tracing would likely be incredibly laborious and expensive to conduct. A potential solution might be the use of nucleotide sequencing. "We wouldn't seek to link individuals to each other, as is often done in phylogenetic analysis," Dr. Koopman said. "We only need to know the pattern of phylogenetic distances between the HIV of different classes of individuals infected at different times. Infected individuals need to be classified by their contact history. The places where partners meet is particularly useful."

Phylogenetic analysis is useful to analyze transmission because transmission is one of the "bottlenecks" that can impact viral diversity. Bottlenecks exist in both the transmission of HIV and the natural history of HIV once established in a human host. For example, the use of antiretroviral agents can narrow the variation of HIV quasispecies. These bottlenecks that fix variation in a population make the measurement of HIV phylogenetic distances particularly useful for assessing population transmission patterns. They also present a challenge, however, as they mean that more sophisticated phylogenetic analysis methods are needed. But Dr. Koopman remains undeterred: "We should be able to meet the challenge of identifying the right time scale for studying transmission and the right sequence changes that reflect that scale."

Mathematical Supermodel?

As discussed above, individual mathematical models have their strengths and weaknesses. Deterministic models, for example, are relatively simple in their execution, but they abstract reality in limited ways. Stochastic models are more realistic, as they account for the randomness that occurs in real life, yet they are complex and must be run a number of times to produce probability distribution of possible outcomes. Both model types should play a role in the analysis of transmission systems.

Instead of selecting one modeling approach over another, Dr. Koopman's team

is working with a new strategy called Model Transition Sensitivity Analysis (MTSA). As its name implies, MTSA calls for the adaptation of specific models so that they can be linked together. This helps to grease the wheels when shifting from easier to more complex models and increases confidence in model validity. In this particular case, Dr. Koopman will need to utilize deterministic compartmental models, stochastic compartmental models, and individual network models. Shifting between these models would be quite difficult without MTSA.

Biomedware Inc. has patented the MTSA and is developing software to implement this methodology by way of funding from a Small Business Innovative Research grant from the National Institutes of Health. "It's currently in the first phase and will be moving into the second phase of development soon," Dr. Koopman remarked. "This is very exciting for epidemiologists; shifting from one model to another can be done with a click of the mouse."

Conclusions

When it comes to the significance of acute HIV infection, multiple lines of reasoning converge to suggest that it truly is a dynamic window of opportunity, not only to achieve certain therapeutic goals, but also to curtail the continual growth of the HIV/AIDS epidemic. However, reasoning alone does not justify sweeping changes in clinical care guidelines, especially when costly diagnostic tools and antiretroviral agents are involved. Only data from well-designed clinical trials—whether the goals are medical, epidemiological, or a combination of both—will settle some of the complexities and controversies that continue to prevent clinicians from stepping up their efforts toward more aggressive diagnosis and treatment of individuals in this earliest stage of HIV disease.

As illustrated by Dr. Koopman, a great deal of foundational work has been completed or is currently under way, which certainly paves the way for future efforts, both in research and in the clinic. "There really is quite a bit of data to suggest major public health implications of primary HIV infection," commented Dr. Koopman. "Now is the time to figure out how to move forward and to design studies that will evaluate how significant it really is and the most cost-effective ways to implement control strategies."

KEY POINTS

- The possible benefits of detecting and treating PHI are threefold: 1) a direct medical benefit for the individual being treated; 2) a direct transmission benefit for the infected individual's sexual partners; and 3) an indirect transmission benefit because of changed transmission dynamics (i.e., reduced transmission in the population in general, resulting in fewer exposures to infection at all of its stages.)
- Although only a small fraction of transmissions would be prevented by programs oriented at detecting PHI, the indirect transmission benefits of these few directly prevented transmissions could be large.
- More data are needed to solidify inferences about the potential population effects of programs to detect and treat PHI. Mathematical models should be used to design studies to assess transmission probabilities by infection stage and the potential of early treatment to stop transmissions.
- Model transition sensitivity analysis (MTSA), employing phylogenetic data, may provide better model analysis of potential treatment effects and help design efficient studies.

References

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