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Mathematical Models for HIV Transmission Dynamics:

Tools for Social and Behavioral Science Research

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Summary

HIV researchers have long appreciated the need to understand the social and behavioral determinants of HIV-related risk behavior, but the cumulative impact of individual behaviors on population-level HIV outcomes can be subtle and counterintuitive, and the methods for studying this are rarely part of a traditional social science or epidemiology training program. Mathematical models provide a way to examine the potential effects of the proximate biologic and behavioral determinants of HIV transmission dynamics, alone and in combination. The purpose of this article is to show how mathematical modeling studies have contributed to our understanding of the dynamics and disparities in the global spread of HIV. Our aims are to demonstrate the value that these analytic tools have for social and behavioral sciences in HIV prevention research, to identify gaps in the current literature, and to suggest directions for future research.

Keywords

AIDS; microsimulation; prevention

The basic routes of HIV transmission between persons are now well understood and widely known, but the determinants of the disparities in HIV prevalence and trends among populations remain an area of debate and intense scientific research. These disparities have their roots in the transmission system; thus, understanding that system—its components and its dynamics—is key to understanding the disparities. Mathematical models of HIV transmission dynamics are an important research tool in this endeavor.

The HIV transmission system has biologic and social determinants. Biologic determinants include characteristics of the pathogen, the host, and biomedical interventions. Social determinants include individual-level, pairwise, and community-level processes that affect behavior, and thus the structure and dynamics of the transmission networks. This covers a wide range of factors: knowledge, attitudes, beliefs, power differentials, cultural norms,

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population mobility and mixing patterns, and the larger social context that gives rise to all these.

HIV researchers have long appreciated the need to understand the social and behavioral determinants of HIV-related risk behavior, and the methods for this type of analysis are well established. The cumulative impact of individual behaviors on population-level HIVoutcomes can be subtle and counterintuitive, however, and the methods for studying this are rarely part of a traditional social science or epidemiology training program. The purpose of this article is to help make these connections, and to show how mathematical modeling studies have contributed to our understanding of the dynamics and disparities in the global spread of HIV.

MATHEMATICAL MODELS FOR HIV

The primary purpose of a mathematical model of HIV transmission is to project population-level outcomes from individual-level inputs. There are many possible outcomes that can be examined with a model, for example, the incidence of infection, the prevalence of infection, or the doubling time of the epidemic. The most basic outcome, however, is simply the likelihood of an epidemic occurring—whether there is sufficient transmission potential for a chain of infection to be sustained. In classic epidemic theory, this outcome is captured by a simple summary statistic: the reproduction number of the infectious process, R_0. In a susceptible population, R_0 represents the expected number of secondary infections generated by the first infected individual. If R_0 is 1 or greater, an epidemic is expected. At an $R_0 < 1$, the infection is expected to die out.

R_0 is a function of biologic and behavioral factors. For a simple homogeneous population, it is defined as:

$$R_0 = \beta c D$$

where the terms on the right-hand side are the average probability of transmission per sexual contact (β), the average number of sexual partnerships formed per unit time (c), and the average duration of infectiousness of an infected individual (D). If R_0 is >1, disease transmission typically persists and the magnitude of R_0 determines the speed, scale, and spread. Each component of R_0, in turn, unfolds into more detailed behavioral and biologic determinants, and the factors that influence R_0 also influence the other epidemic outcomes of interest. As in a laboratory, mathematical studies often vary one of these components of R_0, holding the others constant, to understand its effects. These 3 components thus provide a natural outline for our review of the literature.

Mechanically, there are many different ways to construct a model. There are 2 basic dimensions, however, and these define 4 classes of models with similar strengths and limitations. First, the underlying processes can be represented in a deterministic or stochastic form. The difference is analogous to using the mean as a prediction summary versus using the full probability distribution of outcomes. Second, the dynamics over time can be explored analytically or using computational methods. Analytic, or “closed-form,” solutions isolate the outcome on the left-hand side of an equation, with all the determinants on the right-hand side; thus, it is clear how the outcome depends on the inputs. Not all processes can be represented this way, however. Computational, or “numeric,” solutions must be used if there are nontrivial feedback loops in the process, so that the outcome ends up on both sides of the equation. Models of this sort are said to be “analytically intractable.” This happens quickly as simplifying assumptions are relaxed; thus, most models that attempt to build in realistic heterogeneity need to be solved computationally.

All models divide the population into states (eg, susceptible, infected) and define the process and rate of movement between those states. Deterministic models are usually built on group aggregates or macrolevel states, whereas stochastic simulation models are usually built to reflect the microlevel states occupied by discrete individual persons. The primary difference between deterministic and stochastic models is how they define the movement between states. Deterministic models define the dynamics using the average rate of transition between states. Stochastic models define the dynamics using the probability that an individual makes the transition from one state to another.

Analytic models of both sorts (deterministic and stochastic) are typically regarded as the ideal because they reveal a process in terms of simple cause and effect. Many infectious processes are not simple in that way, however, and the assumptions made to gain tractability often come at the cost of ignoring important parts of the process, and thus failure to project the outcomes of interest properly. As computing power has become more widely available, the need for tractability has declined and computational-deterministic models have become the workhorse of mathematical epidemiology. Their use has led to substantial insight into the population dynamics of HIV and other sexually transmitted infections (STIs) as well as a wide range of other infectious diseases. Increasingly, the limitations of deterministic models are leading to the adoption of computational-stochastic or “microsimulation” methods. These methods are better for representing heterogeneities in the transmission process, behavioral or biologic, and they are the only way to represent accurately something as simple as a person having multiple ongoing (“concurrent”) partnerships. The advantages of microsimulation are discussed in detail by van Imhoff and Post.[1] The primary disadvantages are that it requires richer inputs and may require significantly more computational capacity.

In the review that follows, we group studies by topic (the component of the process that is the focus of interest) and note the classes of models used.

β: TRANSMISSION PROBABILITY PER CONTACT

The first component of the basic reproductive number R_0 is β, the probability of transmission per contact. This single parameter actually represents 2 components of transmission: the infectivity of the HIV-positive partner and the susceptibility of the HIV-negative partner. Both components may, in turn, depend on a wide range of demographic, behavioral, and biologic factors. Most of the studies discussed here use computational-deterministic models.

Demographic Heterogeneity

For many years, it was assumed that the probability of HIV transmission by means of heterosexual sex from the male to female partner was higher than from the female to male partner. The most recent evidence from an empiric study of discordant couples in Uganda, however, suggests that there may be little asymmetry in transmission by gender.[2] Population-level outcomes can differ dramatically given different assumptions of HIV transmission probabilities by gender. The kind of impact can be seen in the modeling study by Goodreau et al[3] reviewed in the contact rate section in this article: in general, asymmetric transmission lowers the rate of spread through a population, and therefore lowers prevalence.

High rates of infection among young women in many countries of sub-Saharan Africa also led to theories that susceptibility might vary with age. Recent empiric work, however, suggests that the pattern of sexual mixing by age rather than by some biologic mechanism may be responsible.[4] Mathematical models of the impact of mixing by age are reviewed in the contact rate section in this article as well.

Stage of Disease

There is now compelling evidence that for HIV-infected individuals, infectivity is not constant over time but varies by stage of infection and viral load.[2,5] Most studies agree that the probability of transmission peaks at the early (acute) stage of infection, decreases during the latent stage, and then increases again during the symptomatic stage.

At the population level, however, there are 2 reasons that might explain why individuals in the primary stage of infection contribute the highest proportion of secondary infections: heightened infectiousness during acute infection or a period of higher contact rates that leads to infection and secondary transmission in short succession. Biology and behavior can be confounded here, and they may both contribute.

Jacquez et al[6] were the first to use mathematical models to emphasize the importance of primary stage transmission. Using a computational-deterministic model, they showed that an interval of high contagiousness during primary infection followed by a large decline in infectiousness was consistent with the pattern of epidemic spread seen in cohorts of men who have sex with men (MSM) in the early years of the epidemic. These findings depend on many assumptions: that people have serially monogamous relationships, that there is random mixing by activity levels, on population prevalence, and on the distribution of persons in each stage of infection. Changes in any of these assumptions would change the findings. A recent modeling study reanalyzed these data and pointed out that the time spent in each stage (the duration component) is an equally important factor in determining the impact of infection stage on transmission. Given the much longer time spent in stages after primary infection, it is argued that the impact of primary stage infection on overall incidence declines dramatically as an epidemic matures.[7] Thus, an individual-level effect (higher primary stage infection) may not drive the population-level outcome (incidence).

Coinfection With Other STIs

Coinfection with HIV and other pathogens is believed to have strong implications for infectivity and susceptibility. For instance, herpes simplex virus type 2 (HSV-2) is associated with a 2- to 4-fold increased risk of HIV-1 acquisition.[8]

Mathematical models have been used to estimate the cofactor effect of various STIs on the risk of HIV transmission, and thus population-level prevalence. Blower and Ma[9] used a deterministic mathematical model to predict that HSV-2 epidemics can more than double the peak HIV incidence and that biologic heterogeneity in susceptibility and transmission induced by an HSV-2 epidemic can cause HIV incidence to vary nonlinearly. The implication was that STI treatment would be useful for preventing HIV transmission. The empiric findings of a large randomized community trial of STI treatment in Uganda (for bacterial STIs like gonorrhea, syphilis, trichomoniasis, and bacterial vaginosis), unfortunately, showed no effect on HIV incidence.[10] Mathematical models were then used to help understand why. These stochastic-computational models suggested that 2 population level factors, STI prevalence and HIV epidemic maturity, play a determining role. STI management may be an effective HIV prevention strategy in populations with a high prevalence of curable STIs, particularly in an early HIV epidemic, but epidemic maturity reduces the effectiveness of STI treatment.[11,12] Work is continuing on the potential impact of treating viral STIs such as HSV-2.

Circumcision

Male circumcision recently has been shown to reduce annual susceptibility to infection with HIV by approximately 60%.[13–15] The first randomized controlled trial was quickly followed by a mathematical model of the potential impact of male circumcision as a public health

intervention.[16] The investigators used a deterministic simulation model and found that male circumcision could lower the rate of transmission by nearly 40% after the intervention is in place for at least 10 years but that it was unlikely to bring transmission rates down lower than the reproductive threshold.

Vaccines

No HIV vaccine has been successfully produced, and the current candidates are all expected to be less than perfect at preventing infection. Mathematical models can show the population level effects of imperfect vaccines, in what scenarios they might be effective, and what other prevention strategies need to be coupled with imperfect vaccines to reduce transmission to lower than the reproductive threshold.

There are several ways in which a vaccine can work. A “sterilizing” vaccine protects everyone completely against infection, and no current candidates are of this sort. A “leaky” vaccine protects everyone partially, and an “all-or-nothing” vaccine protects a fraction of the population completely.[17] A vaccine can also lower infectiousness or lower susceptibility (or both).[18] Finally, a “therapeutic vaccine” may increase the symptom-free period, establishing a longer duration in a less infective state. The population-level effects of a vaccine depend entirely on these differences. With any nonsterilizing vaccine, the protective effect could be overwhelmed by an increase in risky behavior, a phenomenon called “behavioral disinhibition,” or by an increase in life expectancy that is proportionally greater than the decrease in infectivity. In general, the effect is determined by the combined impact on the 3 components of secondary transmission: the probability of transmission (presumably lowered by means of infectivity or susceptibility), the rate of contact (which could rise because of behavioral inhibition), and the duration of infection (which would rise under a therapeutic vaccine). Recent models have predicted that eradication of HIV using a vaccine alone is unlikely unless the vaccine is combined with considerable reductions in risk behavior.[18–20]

C: CONTACT RATE

The component c in the basic reproduction number denotes the average rate of sexual partner change, or the contact rate. This is an area in which social scientists have much to contribute, and the recent progress in modeling the nature and impact of the contact network on HIV transmission has been substantial.[21]

Core Group Theory

This was the first theory to address the heterogeneity in contact rates explicitly. Studies of STI clinic patients in United States in the late 1970s found that 3% to 7% of the infected persons accounted for approximately 30% of the caseload; these were people with high contact rates who would be reinfected quickly after treatment.[22,23] Mathematical models then demonstrated that even if the rest of the population had contact rates too low to sustain transmission, a small “core” group like this could have enough partners to keep the disease circulating.[24,25] The idea of a core group of transmitters was seen as a driving force behind sustained STI transmission, and therefore a clear target for intervention strategies.

Selective Mixing

Early studies of core groups assumed that the members of the core group selected their partners at random (ie, without regard to the activity level of their partners), but researchers soon realized that this assumption might be inappropriate. Mathematical models introduced selective (or heterogeneous) mixing and showed that the degree of mixing between groups had a major influence on the pattern and spread of STIs and HIV. In general, assortative mixing by activity level was shown to lead to more rapid but constrained spread, whereas

disassortative mixing led to slower but more pervasive spread.[26–28] Other simulation studies have shown that these effects can be strong and highly variable[29] and that they can bias other model estimates if they are not taken into account.

Social scientists and demographers have approached the question of assortative mixing differently. Starting from the question of how people identify and choose "appropriate" partners, they focus on social attributes that influence the partner selection process. This generates mixing between groups by attributes such as age, race, and sexual preference as well as by "bridge populations" that form links between otherwise unconnected groups. It may also induce assortative mixing by degree if demographic groups vary in their activity levels and mix assortatively.

Assortative mixing by race and ethnicity may help to explain the large disparities in HIV infection rates across races; HIV infection is significantly higher among non-Hispanic blacks than it is among any other young adult racial or ethnic group in the United States.[30] Using a range of statistical models to summarize the "local network" mixing structure and drive a dynamic deterministic model for transmission through this structure, researchers have shown that assortative mixing by race, ethnicity, sexual preference, and sexual roles can have large population-level effects on transmission and prevalence disparities.[3,29,31]

Age mixing is another major behavioral determinant in individual risk of infection.[4,32] In the generalized epidemic in sub-Saharan Africa, it is almost universally the case that women are infected at a younger age (15 to 20 years old) than men. Gregson et al[4] find that having an older male partner is a significant determinant of infection in young women in Zimbabwe. This might suggest that we should encourage age-assortative mixing to reduce prevalence among the younger group by protecting them from the higher prevalence older population. A computational-deterministic study based on data from a longitudinal cohort of MSM found that if contact rates are sufficiently higher among the young, however, this could actually amplify the spread of infection.[33]

In some cases, selective mixing can lead to a complete lack of contact between spatially integrated groups, but indirect exposure may exist if there is a "bridge population" that links the 2 groups. A good example is men who have sex with female commercial sex workers (CSW) and non-CSW partners. Morris et al[34] used a simple deterministic-analytic model based on local network data collected in Thailand and showed that this male bridge population would play a key role for the spread of HIV into the general population.

Another mixing example is behavioral role patterns among MSM. Individual men can have the insertive or receptive role. Some men consistently perform one or the other, whereas others perform both. This yields 3 role subgroups of men—insertive, receptive, and versatile —as opposed to the 2-role categories of male and female partners in heterosexual intercourse. The impact on transmission dynamics depends on the prevalence of each role, the patterns of mixing among roles, and the relative transmission probabilities of insertive and receptive sex. In a recent data-driven simulation, Goodreau et al[3] show that a population of MSM with identical contact rates but complete role versatility would have had twice the HIV prevalence for the epidemic's first 3 decades. It also showed that versatility, although raising population prevalence, is not necessarily an individual risk factor; versatile men remain less at risk than receptive-only men. This is not true, however, if versatile men mix assortatively with other versatile men and role-segregated men mix selectively (but disassortatively) with role-segregated men.

In many of these mathematical modeling studies, deterministic-computational models were used. This is because the attribute classifications are few and easily translated into additional group states for the model. Mixing between classifications can then be controlled in an ad

hoc fashion (as in the early core group simulations) or by statistical estimates from data (as with the later demographic mixing simulations).

Timing, Sequence, and Concurrency

Another dimension of contact networks is governed by timing: the duration and sequencing of partnerships. One of the main issues explored here is the impact of concurrent (or overlapping) partnerships. Concurrency has a number of effects on a network that all work to amplify the dynamics of transmission.

The earliest studies of partnership timing and sequence focused on monogamy, using deterministic models; long-duration monogamy was shown to slow the rate of disease transmission and raise the number of contacts needed to reach the epidemic threshold.[35] The first model that considered the concept of partnership concurrency was a simple deterministic compartmental model, but it allowed for the possibility that an initially uninfected partner of a susceptible individual may become infected over the duration of their partnership.[36] This model found that an infection spreads more quickly with a high number of overlapping partnerships.

A handful of mathematical models in the late 1990s began to use stochastic models to examine the impact of concurrency on HIV transmission dynamics better.[37] These showed that concurrency can dramatically increase the size of an epidemic, even without increasing the total number of partnerships in the population (ie, keeping the mean contact rate the same). The effect is attributable to 3 things. First, concurrency destroys the protective effect of sequencing that serial monogamy confers; earlier partners in the sequence can now be exposed to infection that an index partner picks up from a subsequent concurrent partner. Second, concurrency reduces the waiting time between infections, because partnerships in which a transmission occurs do not have to end before the next one begins. Finally, small amounts of concurrency can have a dramatic nonlinear effect on the connectivity of a network and the robustness of that connectivity.[38,39] There is now growing evidence that concurrency may be part of the explanation for the generalized epidemics in sub-Saharan Africa[40,41] and that it may play a role in the racial disparities in HIV in the United States.[42] Thus, the prevention message of “1 partner at a time” is as important as promoting fewer partners.[41]

Social Influences on Behavior

Societal context can also influence individual behavior and the contact rate (c), and thus population-level outcomes of HIV. For instance, migration and travel, brothels, and bath-houses all structure contact rates. A study of HIV concordance and discordance in migrant couples suggested that migrant men are significantly more likely to be infected from outside their primary relationship than from inside compared with nonmigrant men.[43] A deterministic model demonstrated the key role that migration can play at different epidemic stages; early on, it has an impact on the propagation of HIV between communities, and, later on, it can have an impact on the scale of the epidemic.[44]

The population-level impact of these issues, or the importance for HIV prevention, has not been examined much through the use of mathematical models. The reason may be that the social structuring introduces a multilevel process with additional demands on the data needed for inputs. The growing interest in “venue-based” interventions is likely to lead to more emphasis on this type of modeling.

D: DURATION OF INFECTIOUSNESS

The duration of infectiousness is the last component of the basic reproduction ratio, R_0. HIV disease is defined by at least 3 stages that coincide with viral load and CD4 cell counts: primary (or acute) infection, defined by the initial spike in viral load and infectiousness, which can last from a few weeks to 6 months; the asymptomatic (or latent) stage, during which viral load and infectiousness stay low, which lasts approximately 10 years on average; and the symptomatic stage, which includes the onset of AIDS when viral load rises again. Without treatment this final stage lasts an average of 3 years until death,[45] but it can vary greatly if an individual receives antiretroviral therapy (ART), which extends the asymptomatic stage and life expectancy, and thus the duration of infection.

The primary focus of models that examine the impact of duration is the role of ART. The population-level effects of ART are similar to those observed with imperfect vaccines.[46] ART reduces viral load[47] and the probability of transmission by 50%.[48] It also reduces mortality and increase the life expectancy of infected individuals, however. These factors work in opposite directions. Increases in transmission-related behavior may occur if ART recipients perceive that treatment reduces their infectiousness or if the general population no longer fears HIV infection.[49] Boily et al[50] used a computational-deterministic model to examine the potential impact of disinhibition. They suggest that the impact of ART on HIV transmission dynamics depends on treatment coverage and efficacy. Whether or not ART is actually associated with behavioral disinhibition is still unclear.[51,52]

CONCLUSION AND DISCUSSION

For the behavioral scientist, mathematical models are the equivalent of a laboratory: a way to examine the potential effects of the proximate determinants of HIV transmission dynamics alone and in combination. These methods provide the tools for bridging the micro-macro gap in the study of HIV and STI population dynamics as well as in any complex biobehavioral system. As the models become more sophisticated and better able to capture observed heterogeneities in data, their role begins to change from “what if” scenarios designed to provide basic insights into population dynamics to design optimization for community trials of the range of prevention interventions that are becoming available. Modeling can help to ground the debate about the tradeoffs between treatment and prevention and can give behavioral scientists the tools to demonstrate the population impact of a well-designed social or behavioral intervention.

The key topics for future modeling can be drawn from the global and local disparities in the current burden of HIV infection. Why is there a generalized epidemic in sub-Saharan Africa? How much is behavioral (eg, concurrent partnerships), and how much is biologic (eg, circumcision, cofactor STIs)? Why are there such large racial disparities in HIV prevalence in industrialized countries? How much of this is attributable to simple immigration? How do we make progress in further reducing the epidemic among MSM? Should serosorting (ie, encouraging HIV-positive individuals to partner with other HIV-positive individuals) and other forms of risk network segregation be promoted? In all populations, what mix of imperfect treatment and prevention interventions might together bring transmission down to lower than the reproductive threshold? As more prevention interventions become available, the tools of mathematical modeling will become increasingly important for helping us to understand and maximize the population level impacts these interventions can have.

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