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HIV Transmission Rate Modeling: A Primer, Review, and Extension

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Abstract

Several mathematical modeling studies based on the concept of “HIV transmission rates” have recently appeared in the literature. The transmission rate for a particular group of HIV-infected persons is defined as the mean number of secondary infections per member of the group per unit time. This article reviews the fundamental principles and mathematics of transmission rate models; explicates the relationship between these models, Bernoullian models of HIV transmission, and mathematical models based on the concept of the “reproductive rate of infection”; describes an extension of existing transmission rate models to better incorporate the positive impact of HIV treatment; and discusses the limitations of the transmission rate modeling approach. Results from the extended transmission rate model indicate that approximately 51.6% of new sexually-transmitted infections in the US are due to the transmission risk behaviors of infected persons who are unaware of their infection, including 10.9% due to persons in the acute phase of HIV infection. Findings from this study suggest that significant reductions in HIV incidence likely will require a combination of increased antibody testing, enhanced early detection of acute HIV infection, appropriate medical care and antiretroviral medicine adherence counseling, and behavioral risk reduction interventions.

Keywords

HIV transmission; transmission rate model; acute infection; serostatus awareness

Introduction

Several mathematical modeling studies based on the concept of “HIV transmission rates” have recently appeared in the literature. The transmission rate for a particular group of HIV-infected persons is defined as the mean number of secondary infections per member of the group per unit time. (1,2) To illustrate, an estimated 1,178,350 persons were living with HIV in the US at the end of 2008 (3) and approximately 56,300 persons acquire HIV each year. (4) The overall annual HIV transmission rate in the US is therefore $56,300 / 1,178,350 = 4.8\%$ That is, on average, each person living with HIV (PLWH) in the US transmits the

virus to about 0.05 previously-uninfected persons per year. (5) The annual transmission rate for any particular group of PLWH could be larger or smaller than this overall rate.

Transmission rate models have been used to estimate: (a) the proportion of new infections in the US that are due to transmission by infected persons who are aware of their HIV status versus unaware (6) or by persons with acute HIV infection (7,8); (b) the number of infections prevented as a result of increases in the serostatus awareness rate among PLWH in the US from 2001 to 2004 (9); (c) the potential impact of further increasing HIV serostatus awareness in the US through more aggressive testing strategies (2); (d) the potential burden of HIV in the US under different intervention scenarios (10); (e) the cost-effectiveness of pooled nucleic acid amplification testing for acute HIV infection (11); and (f) the cost-effectiveness of the US AIDS Drug Assistance Program. (12) They also have been used to generate recommendations for the prioritization of HIV prevention services for persons living with HIV (13) and to explore the potential of a “test and treat” strategy to control the US HIV epidemic. (14)

This article reviews the fundamental principles and mathematics of transmission rate models; explicates the relationship between these models, Bernoullian models of HIV transmission, and mathematical models based on the concept of the “reproductive rate of infection”; describes an extension of existing transmission rate models; and discusses the limitations of the transmission rate modeling approach.

Transmission Rate Modeling Examples

The most common application of transmission rate modeling is to estimate the transmission rates for particular subgroups of PLWH and then to use these estimates to determine the proportion of an epidemic due to secondary transmission from these population subgroups, or to assess the potential impact of interventions that “move” PLWH from one subgroup to another. Examples of these modal applications are described below.

As an example of the first type of application, Marks and colleagues developed a transmission rate model to estimate how many secondary infections in the US are due to sexual transmission by PLWH who are unaware of their HIV status. (6) In their model, the annual incidence of infection in the US consists of two components: infections due to transmission by HIV-status unaware persons and those due to transmission by HIV-status aware persons. In symbols,

$$\text{Annual incidence: } I = \gamma_0 N_0 + \gamma_1 N_1, \quad [1]$$

where N_0 and N_1 are the numbers of HIV-status unaware and aware PLWH, respectively, and γ_0 and γ_1 are the corresponding annual transmission rates for PLWH in these two groups (i.e., the expected number of secondary infections, per year per PLH who is either unaware or aware of his or her HIV status). Suppose that $\gamma_1 = \mu \gamma_0$ where μ indicates how much less likely HIV-status aware PLWH are than unaware PLWH to transmit the virus. Equation 1 can then be rewritten $I = \gamma_0 N_0 + \mu \gamma_0 N_1$, from which we derive,

$$\gamma_0 = I / (N_0 + \mu N_1). \quad [2]$$

The most recent CDC estimates indicate that there were 1,178,350 persons living with HIV in the US at the end of 2008, 20% (236,400) of whom were unaware of their HIV infection. (3) Consequently, $N_0 = 236,400$ and $N_1 = 941,950$. The incidence of sexually-transmitted infection in the US has been estimated at 56,300 new infections per year (4), including approximately $I = 47,207$ sexually-transmitted infections (8). Marks and colleagues estimated that $\mu = 1 / 3.4555$. From Eq. 2 we derive $\gamma_0 = 0.0927$, hence $\gamma_1 = \mu\gamma_0 = 0.0268$. The total number of secondary infections due to the transmission risk behaviors of unaware persons is then $\gamma_0 N_0 = 21,914$, or 46.4% of the annual number of sexually-transmitted incident infections.

This finding—that one-fifth of PLWH account for about half of all HIV transmission events—has been widely cited in support of more intensive HIV testing efforts (e.g., 15–19). One implication of this finding is that increasing serostatus awareness among PLWH could have important consequences for the ongoing HIV epidemic in the US. For example, using a somewhat different model than Marks and colleagues, Pinkerton and colleagues (9) estimated that the increase in HIV serostatus awareness in the US—from 70.5% in 2001 to 74.2% in 2004—can be credited with preventing nearly 6000 incident HIV infections during the corresponding 3-year period.

The above transmission rates, $\gamma_0 = 0.0927$ and $\gamma_1 = 0.0268$, suggest that 0.0659 sexually-transmitted infections could be prevented, per PLWH, by making unaware PLWH aware of their HIV status one year earlier. (Notably, many PLWH remain unaware of their HIV status until very late in the course of infection. (3)) These considerations form the basis for estimating the potential impact of increasing serostatus awareness among PLWH. (2) For example, an intervention that reduced the number of unaware persons by 10%, from 236,400 to 212,760, would be expected to prevent 1558 sexually-transmitted infections during the first year.

Transmission Rate Mathematics

In general, HIV transmission rate models are refined by subdividing groups for which transmission rates previously have been determined. For example, subdividing PLWH into HIV status aware and unaware groups, or subdividing unaware PLWH into those with acute HIV infection versus persons living with chronic infection.

Disaggregating the number of secondary infections due to a particular group, γN , into a 2-group equivalent, $\gamma N = \gamma_0 N_0 + \gamma_1 N_1$, requires knowing the ratio of the subgroup transmission rates, $\mu = \gamma_1 / \gamma_0$, as well as the number of persons in N_0 and N_1 (note that $N = N_0 + N_1$). Then, $\gamma N = \gamma_0 N_0 + \gamma_1 N_1$ implies that $\gamma N = \gamma_0 (N_0 + \mu N_1)$, so $\gamma_0 = \gamma N / (N_0 + \mu N_1)$ and $\gamma_1 = \mu \gamma_0$.

More generally, the overall population incidence (e.g., the incidence of infection in the US) can be written:

$$I = \gamma_0 N_0 + \gamma_1 N_1 + \dots + \gamma_n N_n. \quad [3]$$

The proportion of incident infections attributable to a particular group k then equals $\gamma_k N_k / I$, or equivalently,

$$\% \text{due}(\text{group } k) = \gamma_k N_k / (\gamma_0 N_0 + \gamma_1 N_1 + \dots + \gamma_n N_n). \quad [4]$$

To calculate the transmission rates for the individual groups, assume that the ratios of successive transmission rates are known and let $\mu_k^{k+1} = \gamma_{k+1} / \gamma_k$ represent the ratio of the $k+1$ st to the k th transmission rate. Because $\mu_0^1 \mu_1^2 \dots \mu_{k-1}^k = (\gamma_1 / \gamma_0)(\gamma_2 / \gamma_1) \dots (\gamma_k / \gamma_{k-1}) = \gamma_k / \gamma_0$, the k th transmission rate, γ_k , equals $\gamma_0 (\mu_0^1 \mu_1^2 \dots \mu_{k-1}^k)$. Consequently, the overall incidence of new infections can be expressed as:

$$I = \gamma_0 N_0 + \sum_{k=1..n} \gamma_k N_k, \\ = \gamma_0 (N_0 + \sum_{k=1..n} (\mu_0^1 \mu_1^2 \dots \mu_{k-1}^k) N_k), \quad [5]$$

And therefore,

$$\gamma_0 = I / (N_0 + \sum_{k=1..n} (\mu_0^1 \mu_1^2 \dots \mu_{k-1}^k) N_k), \quad [6]$$

If the incidence and the values of the μ 's and N 's are known, Eq. 6 together with the relationship $\gamma_{k+1} = \mu_k^{k+1} \gamma_k$ allows complete specification of the transmission rates $\gamma_0, \gamma_1, \dots, \gamma_n$.

Transmission Rate Models and Other Models

One way to estimate the transmission rate for a particular subgroup is to use a Bernoullian model of HIV transmission. (20,21) For example, suppose that the average number of sex partners, per year, for members of the subgroup equals m and the average number of unprotected vaginal intercourse acts, per partner, equals n . Then the transmission rate can be estimated as

$$\gamma = m[1 - (1 - \alpha)^n], \quad [7]$$

where α is the probability of HIV transmission, per act of unprotected vaginal intercourse. (Multiple sexual risk activities—such as anal intercourse and condom-protected vaginal or anal sex—can, of course, be incorporated into the Bernoullian modeling framework, as can individual-level sexual behavior variability. (22)) A similar model applies to secondary transmission through the sharing of HIV-contaminated syringes (23).

The HIV transmission rate also is closely related to the “reproductive rate of HIV infection,” which is defined as the expected number of secondary infections, per person living with HIV, over the course of his or her infection. In its simplest form, the reproductive rate is

equal to the product βcD , where β is the per-partnership risk of HIV transmission, c is the average number of partners per unit time, and D is the duration of infection. (24) The main difference between the transmission rate and reproductive rate formulations is that the former nominally assesses the number of secondary infections over a 1-year time period rather than over the duration of infection. (25) (Other time periods are, of course possible. For example, Pinkerton (6) estimated the daily transmission rate for persons with acute HIV infection.)

An Update and Extension

The following extension of existing transmission rate models builds upon Pinkerton (7) and Prabhu and colleagues (8) and is implicit in the model proposed by Marks and colleagues. (6) Both of the former models have 3 compartments, corresponding to acutely-infected PLWH who are presumed to be undiagnosed (i.e., unaware of their infection status) (N_0); PLWH with non-acute infection who are unaware of their serostatus (N_1); and PLWH who are aware of their HIV-positive serostatus. Here we subdivide the final group into 2 subgroups: Serostatus-aware PLWH who are not receiving medical care for their HIV (N_2) and those in care (N_3).

Marks and colleagues estimated that 60% of serostatus-aware PLWH are in treatment and that 54.5% of PLWH in treatment have CD4 cell counts below 500 cells/mL, hence were assumed incapable of transmitting HIV to sex partners. Consequently, $N_2 = 0.4(N_2 + N_3)$, $N_3 = 0.6(N_2 + N_3)$, and $\mu_2^3 = 1 - 0.545 = 0.455$. They also estimated that, as a consequence of behavioral risk reduction changes, serostatus-aware PLWH are 57% less likely to transmit HIV to their sex partners than are unaware PLWH, hence, $\mu_1^2 = 1 - 0.57 = 0.43$.

Table I summarizes the results for the 4-compartment model, as well as providing updated results for previous 3-compartment and 2-compartment models. Results from the 4-compartment model indicate that approximately 51.6% of new sexually-transmitted infections in the US are due to the transmission risk behaviors of PLWH who are unaware of their infection, including 10.9% due to PLWH in the acute phase of infection.

Increasing serostatus awareness is a cornerstone of the “test and treat” approach which, for optimal effectiveness, requires that all PLWH know their HIV status (26). Serostatus-aware PLWH are less likely to transmit HIV due both to behavioral changes (27) and due to reduced infectiousness as a consequence of effective antiretroviral therapy (28). The transmission rate modeling approach quantifies this reduction in HIV transmission, as described above. It also suggests that, unless more effective methods are developed to increase PLWH’s entry and retention in care and adherence to ART, substantial residual transmission will remain (14).

Limitations of the Transmission Rate Modeling Approach

The main limitation of the transmission rate modeling approach is that justifiable estimates of subgroup sizes and transmission rate ratios are required. This limitation suggests a research agenda to better determine the number of PLWH who fall into different categories (e.g., serostatus-aware, in treatment, in treatment with undetectable viral load) and to

estimate how these categorical distinctions affect the relative magnitudes of the corresponding HIV transmission rates. Figure 1 illustrates some of these potential distinctions. As the factual knowledge base increases, so should the number of groups included in transmission rate models. It is reasonable, in the interim, to make use of the best available evidence in constructing smaller transmission rate models.

Importantly, the transmission rate for a particular group is a point estimate that, presumably, represents the mean value of an unknown distribution of individual transmission rates. Transmission rate estimates do not take into account heterogeneity in the likelihood of HIV transmission among members of the group. Heterogeneity in transmission rates could arise as a consequence of either biological variance (e.g., viral load levels) or behavioral differences (number of partners, condom use, serosorting). Increasing the number of groups is one means of reducing within-group heterogeneity.

Another limitation is that most transmission rate models have built upon the pioneering study of Marks and colleagues (6) and have utilized their transmission rate ratios. Following Marks and colleagues, these models focus specifically on sexually-transmitted HIV and do not take injection-related transmission into account. (Exceptions include Pinkerton and colleagues (9) who estimated group-specific US transmission rates for 2001 to 2004 based on historical epidemiological data and Holtgrave (1,5) who examined changes in the overall transmission rate for the US.) There is a critical need to review existing transmission rate ratios and to undertake the research necessary to refine these estimates as necessary.

Summary

The transmission rate modeling approach has proved fruitful and appears promising for future exploitation. The limitations of this approach, such as limited information about the values of some parameters, are common to new—and often to existing—mathematical modeling frameworks.

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References

1. Holtgrave DR. Estimation of annual HIV transmission rates in the United States, 1978–2000. *J Acquir Immune Defic Synd.* 2004; 35:89–92.
2. Holtgrave DR, Pinkerton SD. Can increasing awareness of HIV seropositivity reduce infections by 50% in the United States? *J Acquir Immune Defic Synd.* 2007; 44:360–363.
3. Centers for Disease Control and Prevention. HIV surveillance—United States, 1981–2008. *Morbidity and Mortality Wkly Rep.* 2011; 60:689–693.
4. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA.* 2008; 300:520–529. [PubMed: 18677024]
5. Holtgrave DR, Hall HI, Rhodes PH, et al. Updated annual HIV transmission rates in the United States, 1978–2006. *J Acquir Immune Defic Synd.* 2009; 50:236–238.

6. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS*. 2006; 20:1447–1450. [PubMed: 16791020]
7. Pinkerton SD. How many sexually-acquired HIV infections in the US are due to acute-phase HIV transmission? *AIDS*. 2007; 21:1625–1629. [PubMed: 17630558]
8. Prabhu VS, Hutchinson AB, Farnham PG, et al. Sexually acquired HIV in the United States due to acute-phase HIV transmission: An update. *AIDS*. 2009; 23:1792–1794. [PubMed: 19684485]
9. Pinkerton SD, Holtgrave DR, Galletly CL. Infections prevented by increasing HIV serostatus awareness in the U.S., 2001 to 2004. *J Acquir Immune Defic Syndr*. 2008; 47:354–357.
10. Hall HI, Green TA, Wolitski RJ, et al. Estimated HIV prevalence, incidence, and potential infections averted in the United States: A multiple scenario analysis. *J Acquir Immune Defic Syndr*. 2010; 55:271–276.
11. Hutchinson AB, Patel P, Sansom SL, Farnham PG, Sullivan TJ, Bennett B, et al. Cost-effectiveness of pooled nucleic acid amplification testing for acute HIV infection after third-generation HIV antibody screening and rapid testing in the United States: A comparison of three public health settings. *PLoS Med*. 2010; 7:e1000342.10.1371/journal.pmed.1000342 [PubMed: 20927354]
12. Pinkerton SD, Kibicho JW, Galletly CL. Is the US AIDS Drug Assistance Program cost-effective?. Under review.
13. Holtgrave DR, Anderson T. Utilizing HIV transmission rates to assist in prioritizing HIV prevention services. *Int J STD AIDS*. 2004; 15:789–792. [PubMed: 15601483]
14. Holtgrave DR. Potential and limitations of a ‘test and treat’ strategy as HIV prevention in the United States. *Int J Clin Pract*. 2010; 64:678–681. [PubMed: 20518946]
15. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *Morbidity Mortal Wkly Rep*. 2006; 55(RR-14):1–16.
16. Fenton KA. Changing epidemiology of HIV/AIDS in the United States: implications for enhancing and promoting HIV testing strategies. *Clin Infect Dis*. 2007; 45(suppl 4):S213–S220. [PubMed: 18190289]
17. El-Sadr W, Affrunti M, Gamble T, Zerbe A. Antiretroviral therapy: A promising HIV prevention strategy? *J Acquir Immune Defic Syndr*. 2010; 55(suppl 2):S116–S121.
18. Lansky A, Brooks JT, DiNenno E, et al. Epidemiology of HIV in the United States. *J Acquir Immune Defic Syndr*. 2010; 55(suppl 2):S64–S68.
19. Millett GA, Crowley JS, Koh H, et al. A way forward: The National HIV/AIDS Strategy and reducing HIV incidence in the United States. *J Acquir Immune Defic Syndr*. 2010; 55(suppl 2):S144–S147.
20. Pinkerton SD, Abramson PR. An alternative model of the reproductive rate of HIV infection: Formulation, evaluation, and implications for risk reduction interventions. *Evaluation Review*. 1994; 18:371–388.
21. Pinkerton SD, Abramson PR, Kalichman SC, et al. Secondary HIV transmission rates in a mixed-gender sample. *Int J STD AIDS*. 2000; 11:38–44. [PubMed: 10667899]
22. Pinkerton, SD.; Abramson, PR. The Bernoulli-process model of HIV transmission: Applications and implications. In: Holtgrave, R., editor. *Handbook of Economic Evaluation of HIV Prevention Programs*. New York: Plenum Press; 1998. p. 13-32.
23. Allard R. A mathematical model to describe the risk of infection from sharing injection equipment. *J Acquir Immune Defic Syndr*. 1990; 3:1010–1016.
24. Anderson RM, May RM. Epidemiological parameters of HIV transmission. *Nature*. 1988; 333:514–519. [PubMed: 3374601]
25. Holtgrave DR. Is the elimination of HIV infection within reach in the United States? Lessons from an epidemiologic transmission model. *Public Health Rep*. 2010; 125:372–376. [PubMed: 20433031]
26. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA*. 2009; 301:2380–2382. [PubMed: 19509386]

27. Marks G, Crepaz N, Senterfitt W, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States. *J Acquir Immune Defic Synd.* 2005; 39:446–453.
28. Cohen MS. HIV treatment as prevention: To be or not to be? *J Acquir Immune Defic Synd.* 2010; 55:137–138.

Figure 1.

Potential compartments (groups) in a comprehensive transmission rate model. Following Marks and colleagues (6), this schematic assumes that PLWH with CD4 cell counts less than 500 cells per mL are incapable of transmitting HIV to sex partners. Alternative models might substitute undetectable viral load for $CD4 < 500$ cells per mL or otherwise distinguish potential transmitters from non-transmitters.

Table 1

Summary and update of transmission rate modeling results

	2-compartment model (model 1) ^a	3-compartment model (model 2) ^b	4-compartment model (model 3) ^c
Incidence of sexually-transmitted infection, I	47,207 ^d	47,207 ^d	47,207 ^d
PLWH with (undiagnosed) acute HIV infection on any given day, N ₀		7558 ^e	7558 ^e
PLWH with undiagnosed HIV (non-acute in models 2 and 3), N ₁	236,400 ^f	228,842 ^f	228,842 ^f
PLWH with diagnosed HIV infection (not in treatment in model 3), N ₂	941,950 ^f	941,950 ^f	376,780 ^{f,g}
PLWH with diagnosed HIV infection (in treatment), N ₃			565,170 ^{f,g}
Transmission rates ^h			
Acute HIV infection, γ_0		.6796	.6796
Undiagnosed HIV infection (non-acute in models 2 and 3), γ_1	.0927	.0839	.0839
Diagnosed HIV infection (not in treatment in model 3), γ_2	.0268	.0243	.0361
Diagnosed HIV infection (in treatment), γ_3			.0164
% of sexually-transmitted epidemic in US due to			
Acute HIV infection		10.9	10.9
Undiagnosed HIV infection (non-acute in models 2 and 3)	46.4	40.7	40.7
Diagnosed HIV infection (not in treatment in model 3)	53.6	48.4	28.8
Diagnosed HIV infection (in treatment)			19.7

^aUpdated from Marks et al. (6)

^bUpdated from Pinkerton (7) and Prabhhu et al. (8)

^cNovel 4-compartment model described in text.

^dSum of infections acquired through heterosexual and male-male sex (45,500), plus a portion of the MSM-IDU transmission category attributed to male-male sex (1707 infections). (8)

^eCalculated as $T / 365 * 56,300$, where $T = 49$ is the average duration of the acute phase of HIV infection (7) and 56,300 is the overall annual incidence of HIV infection in the US. (4)

^fAssumes 236,400 PLWH—including acutely-infected PLWH—are unaware of their HIV status and total of 1,178,350 PLWH in the US. (3)

^gAssumes 60% of serostatus-aware PLWH are in treatment. (6)

^hThe following transmission rate ratios were used in the analyses: $\mu_0^1 = 1 / 8.1$ (models 2 and 3; ref. 7); $\mu_1^2 = 1 / 3.4555$ (models 1 and 2; ref. 6); $\mu_1^2 = 0.43$ (model 3; ref. 6); and $\mu_2^2 = 0.455$ (model 3; ref. 6).