Reconciling Different Infectivity Estimates for HIV-1

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Summary: In our article, “HIV-1 Epidemics Driven by Late Stage Disease,” we conclude that the probability of transmission of HIV through promiscuous or casual sexual contacts is significantly higher in the third or symptomatic stage of the disease. Our results differ greatly from those of the current literature. The primary stage or first stage has been reported to be the most infectious based on an article by Jacquez et al. More recently, the Wawer et al study of monogamous heterosexual couples in Rakai, Uganda found that the transmission of HIV was most likely to occur in the first 5 months after infection. We describe how the findings of the Wawer et al study might be compatible with our results. We also respond to a response by Koopman and Simon, who seem to criticize their own paper severely and choose not to defend it against our remarks.

Key Words: effective contact rate, HIV, infectiousness, mathematical model, transmission dynamics

In the article by Rapatski et al, we focused on measuring the infectivity of gay men. By the “infectivity” of a person, we mean the fraction of his susceptible “contacts” that he infects, which may also be stated as the probability of transmission between an infected individual and a susceptible individual in a single sexual contact. For HIV, we interpret a contact to be a single isolated encounter involving the type of sexual contact that causes most infections for gay men, namely, receptive anal intercourse. Infectivity varies as the individual progresses through 3 distinct stages of disease. (All our discussions are for infected individuals who are not undergoing antiretroviral treatment.) The primary stage lasts 2 to 6 months, the second or latent stage typically has a mean duration of around 7 years, and the third or symptomatic stage typically lasts around 3 years and includes people who are just beginning to develop symptoms and are still quite sexually active as well as those debilitated individuals with AIDS. In the article by Rapatski et al, we analyzed the San Francisco City Clinic Cohort (SFCCC) data, the only high-resolution data set documenting the onset of HIV in a population, and modeled how many contacts there are at each point in time between susceptible and infected individuals as well as what stages of infection those men are in. We now conclude that the symptomatic stage is more infectious than the primary stage, likely at least 5 times as infectious, although the precise factor is not critical. The literature is unanimous in concluding that the asymptomatic stage has low infectivity and we concur, but whether the third stage is as infectious remains in doubt. Resolving this question is essential for developing effective strategies to combat spread. The third stage (not counting AIDS) is usually estimated to be about 2 years, whereas the first stage is 2 months, a factor of 12 shorter.

ACQUIRED PARTIAL IMMUNITY?

The paper by Wawer et al is an interesting heterosexual transmission study of monogamous couples in Rakai, Uganda. It estimates per contact infectivities for monogamous heterosexual couples having frequent sexual contacts. The authors find that if the susceptible partner does not become infected in the first 5 months, it is most likely that he or she is not going to become infected. This does not refute our claims. We believe the Rakai study’s transmission rates are the results of the uninfected partners acquiring partial immunity (or “resistance”) that is regularly reinforced by frequent contacts with their infected partners. Our paper already addresses this general point, saying: “We remark that in the study by Peterman et al there is a (slightly) negative correlation between the number of contacts a couple has and the probability that the disease is transmitted. For couples with more contacts, it was reported less likely for the susceptible partner to become infected.” Kaplan shows that data like those of Peterman et al cannot be used for computing per contact infectivities.

There are other papers suggesting that people having many contacts with infected individuals can acquire a temporary immunity. This phenomenon was apparently observed in sex workers in Nairobi, Kenya. Shearer and Clerici have suggested that a sufficiently small dose of HIV virions can generate immunity to HIV mediated by cytotoxic T lymphocytes (CTLs) without resulting in infection. A direct precedent for such immunity is found in macaques, a simian immunodeficiency virus (SIV) animal model studied by Clerici et al. McKeagney suggests that at least some of the seronegative Nairobi sex workers acquired a partial resistance. Pinto et al presented evidence for an immunity mediated by CTLs in health care workers exposed to HIV-contaminated body fluids, primarily through needle punctures. These investigators

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conclude that a single exposure can induce a CTL immunity response. We believe that the article by Wawer et al\textsuperscript{21} can help in determining the extent of the acquired resistance.

**A RESPONSE BY KOOPMAN AND SIMON**

Jacquez et al\textsuperscript{16} wrote an influential article that reported estimates of how infectious the 3 stages are. These investigators concluded that the first stage of infectivity was at least 5 to 100 times more infectious than the third stage. We began our investigation of the infectivities of gay men because of apparent shortcomings of the article by Jacquez et al.\textsuperscript{16} Our paper criticized their methodology as follows: “...they say without giving any details that the symptomatic stage infectivity was estimated using previous partner studies\textsuperscript{17,19} and in most cases heterosexual partner studies. It is unclear how those stage estimates were obtained, since those studies do not differentiate infectivity per stage.” It is impossible to obtain stage information from those papers.

Two of the authors of that paper published a response (Koopman and Simon)\textsuperscript{20} attacking our conclusions but in no way addressing our assertion that there was no basis for their third-stage infectivity estimate. It is curious that most of their criticisms of our paper apply equally to their 1994 paper.\textsuperscript{16} For example they criticize our model because there is “no [consideration of] clustering of contacts by geography, class, race, risk behavior, sex act preferences, or any other factor.” Any reader can check their article to see that the italicized words and phrases do not appear in either of their papers. They simply do not address these topics. We do not know how to interpret their severe attack on their own articles. They do not even reference their article\textsuperscript{16} in their letter. They do refer to another of their articles\textsuperscript{21} that describes various hypotheses to conclude that the primary stage is important. There is no doubt that the primary stage can be important, and in a population of gay men, 10% of whom had more than 200 contacts per year, primary-stage men were capable of driving the initial phase of the epidemic. We find that the third-stage men were important in driving the later phase of the epidemic, however.

Koopman and Simon\textsuperscript{20} say specifically that they believe our infectivity estimates “are not robust to realistic violation” of our assumption that “the SFCCC is representative of the actual transmission system.” Their article used the same data, in part, for obtaining first-stage infectivity, however, without mentioning that they thought the data were unreliable.

They say we should consider what happens when the behavior of people fluctuates (their third point). Of course, the SFCCC data are from men whose sexual activity level fluctuated throughout the year before being interviewed. We assumed the behavior of men persists for some years, and we reported that the Bell and Weinberg study of 1969\textsuperscript{22} published in 1979, supports this view. They found that 28% of the men interviewed had had more than 1000 lifetime partners and that another 27% had had 49 or fewer.

Their 1997 article\textsuperscript{21} references no behavioral data whatsoever and says that their hypotheses may not fit actual populations. We next see why the authors felt that way.

It is instructive to see how they treat “fluctuating behavior” in an unrealistic manner that guarantees the primary stage is the predominant transmitter of infection. They create 2 levels of sexual activity; men in the core (<5% of the population) average approximately 6 times the number of contacts of the rest of the population. In contrast to the data by Bell and Weinberg,\textsuperscript{22} they assume that men remain in the core for only 1 year on the average. The men who are most likely to get infected are those in the core. Their hypothesis implies that core individuals who get infected can infect many partners while still in the primary stage. By the time they reach stage 3, however, they almost certainly have left the core. Thus, the 1-year assumption means that stage 3 individuals have few contacts. There is no need to run a computer model to see how unimportant stage 3 is in their hypothesis.

Their 1997 article\textsuperscript{21} employs a second implausible hypothesis. They break the population into 2-year age groups and stipulate that 80% of the contacts are with individuals in the same age group. If people simply tried to choose partners whose age they guessed was as close as possible to their own, to achieve the 80% goal, they would have to choose sex partners whose age differs from their own by a median of two fifths of a year. In particular, individuals aged 26.1 or 27.9 years would often choose people outside the 26.0–28.0-year-old age group; thus, to average 80%, those approximately 27 years old would have to choose almost all their partners in the 26.0–28.0-year-old age group. It seems impossible to achieve such accuracy in guessing people’s ages. Even if they could, why would this be a determinant in choice of sex partners? As a result of their implausible hypothesis, they create an artificial situation in which approximately 80% of the people they infect are in their own age group. A person infected at 20 years of age who reaches the third stage at the age of 27 years largely infects people in the 26.0–28.0-year-old age group, and those, in turn, would infect still older people when they reach their third stage. Hence, the third stage cannot sustain the epidemic. They create highly artificial constraints that force the predominance of the primary stage. These 2 hypotheses invalidate all the conclusions of their article.

**ROBUSTNESS OF OUR INFECTIVITY RESULTS**

To come to our infectivity conclusions, we tried to determine what the SFCCC data imply, without forcing any preconceptions on our conclusions. We created a model in which the only unknowns were the infectivities. Our model separates the population into 6 groups by partnering rates according to SFCCC data. We determine what choice of infectivities best fits the reported outbreak data and show how our best-fit epidemic compared with the reported SFCCC outbreak. Do we guarantee that our results are the actual infectivity results? Of course not. To determine the robustness of the conclusions about the infectivity of the 3 stages, we tried many variants, such as allowing variations from the observed number of new cases of HIV in the SFCCC. We also discussed how the results would have changed if men selected men who had partnering rates similar to their own and described why it would have increased our stage 3 infectivity estimate. Recently, we have extended our model to include transient populations, accounting for a portion of the population entering and leaving San Francisco. In all variations, we still
conclude that the symptomatic stage is at least 5 times more infectious than the primary stage.

AFRICA

Koopman and Simon\(^\text{[9]}\) correctly say that our assumptions for San Francisco are not realistic for (sub-Saharan) Africa. Conversely, we did not use the assumptions for San Francisco to model Africa. We use only the pattern of infectivity obtained from the San Francisco study (medium, low, and high) and not the actual values of the infectivities. For example, if women are only 10% as infectious as gay men, each of their 3 infectivities would be 10% of the gay male infectivities. Using the pattern of Wawer et al\(^\text{[7]}\) obtained from monogamous partners to model the situation in Africa is not realistic either. The African epidemic is driven by sex workers. Monogamous couples are an insignificant factor in the exponential growth of HIV.

Our discussion of Africa is based on an observation that the epidemic in Africa grew by a factor of 1000,000 between 1950 and 1990 (eg, doubling every 2 years). For such an epidemic, it is a simple calculation to determine that of all the individuals infected at that moment, what fractions are in the primary, second, and third stages, given some mild assumptions on how fast people progress from stage to stage. A pattern of infectivities implies what fraction of people is infected by people from each stage. A more detailed study yields an average time from infection to transmission. We wrote: “We estimate the mean transmission time about \(T = 7.44\) years based on our values of infectivities when an epidemic grows by a factor of 1,000,000 in 40 years.”\(^\text{[1]}\) There are no assumptions about contact rates, group behaviors, or other social interactions. We make no assumptions that men and women have the same transmission rates or even that all the contacts are heterosexual. We do assume that people have the same pattern of infectivities.

DISCUSSION

Belief in the conclusions of 1994\(^\text{[6]}\) may be a major factor in the current levels of HIV in the United States. Would population screening have a significant impact on the transmission of HIV? This is an important question. Cuba is an example where health officials believe the answer is “yes,” and that country seems to have low levels of HIV.\(^\text{[23]}\) As we write this, Washington, DC has the highest rate of new cases in the United States, and health officials are discussing widespread testing of HIV to try to slow the epidemic. Is this a marginal effort, or could it have real impact? We argue that the infectivity estimates of 1994\(^\text{[6]}\) suggest it is marginal and that 70% of the infections in the United States are now being caused by primary individuals who have not yet developed antibodies, and therefore could not be detected by screening for antibodies. In contrast, the infectivity results of Rapatski et al\(^\text{[11]}\) suggest that it could have real impact. One section of our article was entitled “Testing Whether...Symptomatic [stage 3] Infectivity Is Greater Than Primary Infectivity.” We view that as the critical question. Stage 3 before AIDS is 12 times as long as the primary stage. If stage 3 infectivity even equals primary infectivity, for an epidemic near an endemic equilibrium, a person would infect at least 12 times as many people when he is in the third stage as when he is in the primary stage.

RELATIVE RISK OF THE 3 STAGES

Jacquez et al\(^\text{[10]}\) give a range of values for the HIV infectivities for each stage. The median values are 0.175 for stage 1, 0.00055 for stage 2, and 0.0055 for stage 3. To see how dangerous these stages are, one weights them by how long the stages are, yielding the following:

\[
0.175 \times \left( \frac{1}{6} \right) \text{ year} \sim 0.03 \text{ for stage 1}
\]

\[
0.00055 \times (7 \text{ years}) \sim 0.004 \text{ for stage 2}
\]

\[
0.0055 \times (2 \text{ years}) \sim 0.01 \text{ for stage 3}
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(To estimate how many people would be infected by someone who has 50 susceptible partners per year, multiply the above numbers by 50). These 3 figures suggest that in a steady state or slowly changing epidemic, approximately 70% of the people who are infected sexually are infected by a primary-stage person.

In contrast, the infectivity estimates of Rapatski et al\(^\text{[11]}\) imply that 97% of the infections occur in third-stage HIV. The operational importance is not the exact value of this fraction. Instead, it suggests that population screening would be effective if identified people could be brought under treatment and could be convinced to abstain from unsafe sex.

REFERENCES