HIV-1 Transmission, by Stage of Infection

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Background. The epidemiological impact of public health interventions targeted at reducing transmission of human immunodeficiency virus type 1 (HIV-1) during early or late-stage infection depends on the contribution of these disease stages to transmission within a particular epidemic.

Methods. Transmission hazards and durations of periods of high infectivity during primary, asymptomatic, and late-stage infection were estimated for HIV-1–serodiscordant heterosexual couples in Rakai, Uganda, by use of a robust probabilistic framework.

Results. Primary infection and late-stage infection were estimated to be 26 and 7 times, respectively, more infectious than asymptomatic infection. High infectiousness during primary infection was estimated to last for $\frac{3}{10}$ months after seroconversion, whereas high infectiousness during late-stage infection was estimated to be concentrated between 19 months and 10 months before death.

Conclusions. Primary and late-stage HIV-1 infection are more infectious than previously estimated, but for shorter periods. In a homogeneous population, the asymptomatic stage of infection will typically contribute more to the net transmission of HIV-1 over the lifetime of an infected individual, because of its longer duration. The dependence of the relative contribution of infectious stages on patterns of sexual behavior and the phase of epidemics is discussed.

The early (primary) and late stages of HIV-1 infection have long been known to be associated with high rates of transmission, because of the high viral loads observed for these periods [1–4]. The relative infectiousness during each stage of HIV-1 infection has previously been estimated by examining viral load changes [5], fitting epidemic models to incidence data [6–11], estimating relative risks from limited studies [12, 13], and extrapolating from transmission estimates based on transmission as a function of viral load [14–16]. The relative contribution of early infection to transmission has been estimated using epidemic models [8, 10, 17–19] and by phylogenetic clustering of samples from early and chronic infection [20–23]. The phylogenetic studies suggest that chains or groups of transmission associated with primary infection play an important role in transmission within these cohorts, which are predominately made up of men who have sex with men (MSM). However, inevitably partial sampling of the population means that these methods cannot directly quantify the relative proportion of transmissions during each stage, particularly because the proportions will change during the course of an epidemic [7, 8, 10, 19, 24].

In 2005, Wawer et al. [25] published extensive empirical data from a cohort in Rakai, Uganda, that quantified how transmission within stable partnerships between heterosexuals varies by stage of infection. This landmark study presents the best available data from which to directly estimate both the relative transmissibility of HIV-1 during each stage of infection and the duration of periods of high infectiousness. Wawer and colleagues estimated that, during the first 5 months of infection, the probability of transmission per coital act was 8–10 times higher than during asymptomatic infection and that the probability of transmission also increased by 4–8-fold during the 2 years before death. For a person newly infected outside of the partnership, the probability of infecting their long-term partner within $\frac{2.5}{10}$ months was 43%. However, only 10–13 (15%–20%) of 66 transmis-
sions observed in this study can be said to have occurred during primary infection. These data have led some authors to propose that a large proportion of HIV-1 transmissions occur during primary infection [26, 27], whereas others have emphasized that because of its short duration, particularly compared with the duration of asymptomatic infection, primary infection may be responsible for ~23% of transmissions [28].

Although the data presented by Wawer et al. [25] are groundbreaking, the methods they used to interpret their observations included a number of unnecessary simplifications. First, because the probability of transmission per coital act was estimated as the number of transmissions divided by the number of reported coital acts in a given observation interval, coital acts that occurred after transmission were not discounted. Second, these estimates relied on accurate reporting of numbers of coital acts, but previous analysis has shown the difficulty of interpreting data on the reported number of coital acts [29, 30] and converting the probability of transmission per coital act into the rate of transmission per partnership per unit of time [31, 32]. Here, within a clearly defined probabilistic framework, we estimate the hazard (i.e., rate) of transmission as a function of time since the partnership was first observed. Third, Wawer et al. [25] assumed that incident infection and death of the seropositive partner occurred halfway through the 10-month observation interval in which they took place. We instead consider these as unknown hidden events, such that infection and death have an equal probability of occurring at each possible time under study. Finally, the duration of periods of high infectivity were not estimated by Wawer and colleagues but instead were assumed to be multiples (or quarter/half multiples) of the observation interval. In our inference framework, we use the Rakai data to estimate both transmission rates and the duration of the periods of high infectiousness. The opportunities for transmission in each stage of infection are determined not only by the infectiousness of each stage but also by their length.

It is not possible to directly translate the relative infectiousness during each stage of infection throughout an infected individual’s lifetime into the contribution of that individual to an epidemic at any particular point in an epidemic, because of variation in risk behavior and population epidemic dynamics. The number of new infections caused by an infected individual during an average life span in a fully susceptible population, also known as the basic reproduction number $R_0$, is a useful policy tool in designing HIV-1–control programs. $R_0$ predicts the magnitude of effort required to control transmission during an epidemic, as well as the likely impact of preventing transmission during the different stages of infection. The estimation of $R_0$ is complicated by its dependence on the sexual mixing network, and thus $R_0$ may vary by population, subpopulation, and setting. To provide a measure of a range of possible outcomes, we estimate $R_0$ for populations characterized by 2 extremes of sexual behavior, namely random mixing and serial monogamy.

The main goals of this analysis were to estimate the hazard of transmission and the duration of high HIV-1 transmissibility for each stage of HIV-1 infection, both of which contribute to the infectiousness during each stage. We consider our estimates to be more reliable and informative than those previously published and note that the estimates of the relative infectiousness during different disease stages are very different from findings of previous analyses of these data. We discuss the impact of variable infectiousness on the epidemiology and transmission dynamics of HIV-1 by estimating $R_0$, and we outline the public health implications of our estimates.

**SUBJECTS AND METHODS**

HIV-1-serodiscordant couples in the Rakai study were observed at 10-month observation intervals and their serostatus recorded [25]. The incident infection group consisted of HIV-1–serodiscordant couples in which both partners were seronegative at the beginning of an observation period and at least 1 of the persons in the couple seroconverted by the end of the observation period. The late-stage infection group consisted of HIV-1–serodiscordant couples in which the seropositive partner died during the study. The prevalent infection group consisted of HIV-1–serodiscordant couples in which the seropositive partner had infection throughout the observation period.

Seroconversion was detected using immunoassays, with discordant samples and new HIV-1 seroconversions confirmed by Western blot analysis [25]. Fiebig et al. [33] have shown that these assays can detect infection within 2–4 weeks after HIV-1 acquisition and that this interval is fairly consistent across individuals. We therefore assume that observing the time between seroconversion of the index partner and seroconversion of the initially seronegative partner is equivalent to observing the time between onset of their respective infections.

Of the 23 couples who were serodiscordant immediately before the death of the index partner, 13 were followed up, and none contained a partner who seroconverted. A decrease in the frequency of sexual activity before death of the index partner [25], probably because of AIDS-associated symptoms, is the most likely explanation for the lack of seroconversions. Data obtained after the death of the index partner were not used by Wawer et al. [25] because many of the surviving partners were lost to follow-up. Because more than half of the at-risk partners were followed up in our study and because all of them were seronegative, we considered this to be an important observation and included follow-up data from these subjects in our analysis.

We assume that the hazard profile $\beta(s)$ for transmission during primary infection, asymptomatic infection, and the period immediately before death is a function of the time since infection $s$ and is of the form illustrated in figure 1. The probability of transmission during each observation period is then calculated and fitted to the observed data by maximizing the likelihood function

$$
\log L = \sum_{i=1}^{n} \left[ \log f_i(t_i) + \log I_i(t_i) \right]
$$

where $f_i(t_i)$ and $I_i(t_i)$ are the observed and estimated numbers of transmissions at time $t_i$. The likelihood function is

$$
L = \prod_{i=1}^{n} \left[ \frac{f_i(t_i)}{N(t_i)} \right]^{r_i(t_i)} \left[ 1 - \frac{f_i(t_i)}{N(t_i)} \right]^{1-r_i(t_i)}
$$

where $N(t_i)$ is the number of study participants at risk at time $t_i$, and $r_i(t_i)$ is the number of observed transmissions at time $t_i$. The estimated $R_0$ is

$$
R_0 = \frac{\int_{t_0}^{t_f} \beta(s) \, ds}{\int_{t_0}^{t_f} \int_{t_0}^{s} \beta(s') \, ds' \, ds}
$$

where $t_0$ and $t_f$ are the beginning and end of the observation period, respectively.

Finally, we estimate the duration of periods of high infectivity, $\Lambda$, by simulating transmission per partnership per unit of time $\beta(s)$ and $\Lambda$ for each stage of infection. The simulation is based on the assumption that the hazard profile $\beta(s)$ is constant during each stage of infection. The simulation is repeated 100 times, and the mean duration of periods of high infectivity is estimated for each stage of infection.

**REFERENCES**


To illustrate the contribution of each stage of infection to transmission under the 2 extremes of sexual behavior, we formulated expressions for $R_0$ for moderate rates of partner change (i.e., serial monogamy) and for very high rates of partner change, resulting in random contacts between individuals (appendix).

RESULTS

The estimated transmission parameters are given in table 1. The transmission rate during different disease stages are shown in figure 2A. From this best-fit model, the predicted proportion of individuals being infected is shown in figure 2B and compared with the data. The inferred transmission parameters indicate that (1) the period of high transmissibility during primary infection lasts 3 months, (2) HIV-1 is 26 times more infectious during primary infection than during the asymptomatic period, (3) the hazard during asymptomatic infection is 10.6 transmissions per 100 person-years, (4) the transmission rate 19–10 months before death is 7 times higher than that during asymptomatic infection, and (5) the transmission rate during the final 10 months before death is zero.

The $R_0$ calculations show that HIV-1 transmission can barely be sustained in populations in which the risk of transmission is relatively low ($R_0 = 1.09$ for the serial monogamy scenario) (table 2). The reproduction number and resulting epidemic growth rate are higher for a population in which people make random contacts ($R_0 = 2.15$). The relative contribution of the asymptomatic stage to the transmission of HIV-1 is higher in the serial monogamy scenario than in the random mixing scenario (71% vs. 42%), although this stage represents the largest proportion of infections in both scenarios.

DISCUSSION

We have robustly estimated both the hazard of transmission and the duration of periods of high transmissibility of HIV-1 by stage of infection, using a statistical model that fits the observed data well (figure 2A). The estimated relative transmission hazard during primary infection is significantly higher than the relative transmission rate previously estimated from these data [25]. Comparison with transmission rates as a function of viral load estimated elsewhere [34] indicates that the transmission rate during primary infection is significantly higher than would be expected on the basis of the plasma viral loads observed during these periods, with no overlap of confidence intervals (figure 3).

Table 1. Hazards of HIV-1 transmission and durations of high infectiousness, by infection stage.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_p$</td>
<td>Transmission hazard per 100 person-years</td>
<td>276 (131–509)</td>
</tr>
<tr>
<td>$d_p$</td>
<td>Duration of stage, months</td>
<td>2.90 (1.23–6.00)</td>
</tr>
<tr>
<td>$P_p$</td>
<td>Probability of transmission if in a monogamous partnership, %</td>
<td>49 (27–70)</td>
</tr>
<tr>
<td>Asymptomatic infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission hazard, cases per 100 person-years</td>
<td>10.6 (7.61–13.3)</td>
</tr>
<tr>
<td>$P_{year}$</td>
<td>Probability of transmission per 12-month duration of monogamy, %</td>
<td>10</td>
</tr>
<tr>
<td>Before death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_A$</td>
<td>Transmission hazard, cases per 100 person-years</td>
<td>76.0 (41.3–128)</td>
</tr>
<tr>
<td>$d_A$</td>
<td>Duration of high transmission risk before death, months</td>
<td>9.00 (4.81–14.0)</td>
</tr>
<tr>
<td>$d_0$</td>
<td>Duration of no transmission risk before death, months</td>
<td>10.0 (6.97–12.7)</td>
</tr>
<tr>
<td>$P_A$</td>
<td>Probability of transmission if in a monogamous partnership, %</td>
<td>43 (27–62)</td>
</tr>
</tbody>
</table>

NOTE. Transmission hazards and durations were estimated from data reported by Wawer et al. [25]. Parameters are illustrated in figure 1. The probability of transmission, if in a single partnership throughout the stage, is also given as $P_1 = 1 - e^{-\beta d}$, where $\beta$ is the transmission hazard per year, and $d$ is the duration of the stage in years. CI, univariate confidence interval.
Transmission rates before death are also higher than those that would be expected as a result of high plasma viral loads during this period (figure 3). The reasons for these higher than expected transmission rates should be further investigated; coinfection with other sexually transmitted pathogens is a likely cause of enhanced infectiousness during primary infection, but this has not been conclusively demonstrated.

Our estimate of 2.9 months of high infectivity during primary infection suggests coincidence with the 2–3-month period of high viral loads observed in patients [37]. The duration of AIDS is more variable and is highly dependent on the characteristics of population studied, the AIDS-defining event, and the population’s geographic location, ranging from 3 months to >2 years in South Africa [38], Europe [39], and Thailand [40] and averaging 9.2 months in Uganda [41]. Our estimate of 19 months (95% confidence interval, 12–27 months) falls between these clinical estimates. The relationship between the timing of both high transmission rates 10–19 months before death and limited sexual behavior before death (during the final 10 months of life) and known virological, immunological, or clinical markers during late-stage infection is not identified here and merits further investigation.

Estimates of the role of each stage of infection in transmission are sensitive not only to the relative infectiousness during each stage, but also to sexual behavior and the phases of an epidemic [7, 8, 10, 19, 24]. Mathematical models of HIV-1 transmission have long included variable infectiousness at the different stages of disease [1, 4–7, 9, 19], usually within frameworks similar to that illustrated in figure 1. The relative importance of different disease stages to the overall incidence of infection is intimately tied up with epidemic dynamics. Early in a novel outbreak, a large proportion, perhaps even the majority, of new infections are transmitted from persons with primary infection, irrespective of how infectious the primary stage of infection is. As the epidemic progresses, relatively more individuals enter later stages of infection, and thus the proportion of new infections acquired from persons with later-stage disease increase, again irrespective of their actual infectiousness.

To estimate the lifetime contribution of each stage to transmission, we calculated \( R_0 \) for serially monogamous and random mixing scenarios (table 2). The long duration of the asymptomatic stage allows many opportunities for transmission in both sexual behavior scenarios despite the low relative hazard of transmission. Increased levels of testing, resulting in earlier diagnosis, counseling, and treatment, have the potential to dramatically reduce transmission during this long period of decreased infectivity [17, 27, 44].

HIV-1 in persons with primary infection is highly infectious and may result in clusters of transmission in high-risk populations in which individuals have many sexual contacts per unit time, as illustrated here, or if there are high levels of concurrency [42, 43]. In serially monogamous populations, transmission during primary infection only occurs if HIV-1 is acquired in a partnership, the partnership breaks up, and a new partnership is formed within the 3-month window of high infectivity, which reduces the contribution of onward transmission (table 2).

The period of high infectivity before death plays a larger role in lifelong transmission in high-risk populations than in less sexually active populations (0.57 vs. 0.21 new infections) because of the increased number of contacts during this relatively short period of high infectiousness (table 2). A diagnosis made years or even a few months before late-stage infection has the potential to limit transmission during the period of increased infectivity in the final months before death.

Our relatively simple estimates of \( R_0 \) do not consider complex sexual networks, age-dependent increases, or decreases in sexual activity, stratified risk behavior, concurrent partnerships, or polygamous relationships, which have been shown to affect trans-
mission dynamics [8, 10, 43, 45, 46]. Even under more-complex sexual mixing scenarios, transmission during primary infection and late-stage infection is constrained by the short duration of these periods.

Couples in the Rakai cohort were counseled and provided with condoms [25], which may have reduced the frequency of unprotected sex, leading to underestimates of transmission rates in the wider population. Higher frequencies of unprotected sex within partnerships may be straightforwardly included in our framework by scaling the transmission rates by a constant factor, thus increasing the basic reproduction number while keeping the relative roles of each stage of infection in HIV-1 transmission similar. Thus, we conclude that our analysis provides a robust assessment of the relative contribution of different stages of infection to transmission yet remains cautious about extrapolating these findings to total transmission levels.

The transmission rates estimated here are also almost certainly an underestimate of transmission rates for partnerships between MSM or for injection drug users, because transmission probabilities per contact for these modes of transmission have been shown to be higher than that for vaginal sex.

The inferences drawn in our study from the data presented by Wawer and colleagues have some limitations: there may have been a selection bias in the middle and late-stage partnerships in this cohort for discordant couples who had not yet seroconverted; male-to-female and female-to-male transmission rates may be different, although previous analysis of this cohort has found no significant difference [25, 36]; and variability in risk behavior could not be studied because of the small sample size. It has also been suggested that transmission events could have occurred outside the studied sexual partnership or by another method [47]. However, Wawer et al. [25] selected sexual partners and performed analyses to confirm the epidemiological link between transmitting and newly infected partners.

A major conclusion of our study is that there is substantial potential for transmission to occur during the asymptomatic and late stages of infection and that interventions targeted at reducing transmission during these periods have the potential to have a large impact on an epidemic. For populations in which there is a moderately high rate of testing or high awareness of

### Table 2. Calculation of the basic reproduction number ($R_0$), according to the contribution from each stage of HIV-1 infection, under 2 extremes of sexual behavior.

<table>
<thead>
<tr>
<th>Infection stage</th>
<th>Hazard of transmission ($\beta$) per person-year</th>
<th>Duration of high infectiousness (d/interval between seroconversion and death) (%)</th>
<th>No. (%) of new transmissions, by sexual behavior$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>2.76</td>
<td>0.24/10.2 (2)</td>
<td>0.10 (9)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.106</td>
<td>8.38/10.2 (82)</td>
<td>0.77 (71)</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.760</td>
<td>0.75/10.2 (16)</td>
<td>0.21 (20)</td>
</tr>
<tr>
<td>$R_0$</td>
<td></td>
<td></td>
<td>Total: 1.09 (100)</td>
</tr>
</tbody>
</table>

$^a$ The mean interval between seroconversion and death (10.2 years) was adopted from the report by Morgan et al. [48].

$^b$ The formula for calculating the number of new transmissions in a scenario of serial monogamy is $\beta \cdot d \cdot (\beta + c + 1/d)$, where $c$ is 1.25 partner changes/year. The formula in a scenario of random mixing is $\beta d$ (appendix).

$^c$ d was calculated by subtracting the mean durations of the periods of high transmissibility during primary infection (0.24 years) and AIDS (0.75 years) and the mean duration of zero transmission risk before death (0.83 years) from the mean interval between seroconversion and death (10.2 years).

$^d$ d corresponds to the period 10–19 months before death during which $\beta$ was greatest for this infection stage. $\beta$ was zero during the 10-month period immediately before death.

**Figure 3.** Comparison between transmission rates as a function of viral load and during each stage of infection. Comparison between the transmission rates expected from the blood plasma HIV-1 RNA viral loads observed in each stage of infection and the actual transmission rates in each stage. The transmission rate as a function of viral load as derived by Fraser et al. [34] from data from the study published by Fideli et al. [35] is shown as a solid line with confidence intervals as a dotted line. The mean transmission rate for this cohort is 10.6 per 100 person-years. The transmission rates by stage estimated here are shown as points with their confidence intervals as vertical lines. These transmission rates are placed on the graph according to published mean viral loads during this period: primary infection, ~100 million HIV-1 RNA copies per mL of blood plasma [33]; asymptomatic infection, ~12,500 HIV-1 RNA copies per mL of blood plasma [mean viral load in study of the Rakai cohort by Quinn et al. [36]]; and AIDS, ~162,000 copies per mL of blood plasma [37]. In the cohort analyzed by Wawer et al. [25], the average viral load observed before the index partner’s death was 112,600 copies per mL of blood (5.05 log copies per mL of blood).
risk, together with high levels of access to successful antiretroviral therapy, transmission during these later stages may already be partially contained. Under these conditions, the proportion of transmissions from persons with primary infection will increase, and initiatives aimed at identifying and possibly treating early infection may be an important addition to rather than a replacement for existing public health programs. For high-prevalence populations in which diagnosis currently occurs late during infection, increased rates of testing by means of relatively rapid tests (which do not identify primary infection), combined with reductions in transmission through changes in behavior and adherence to treatment, have the potential to have a significant impact on the epidemic.

References


Note added in proof. A recent article addressed this same topic by fitting mathematical models to prevalence data on generalized heterosexual epidemics in Africa and came to very similar conclusions, specifically that all stages of infection are contributing to the transmission of HIV-1 in these settings and that no stage is dominant: Abu-Raddad LJ, Longini IM. No HIV stage is dominant in driving the HIV epidemic in sub-Saharan Africa. AIDS 2008; 22:1055–61.