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How many sexually-acquired HIV infections in the USA are due to acute-phase HIV transmission?

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Abstract

Objective: To estimate the number of persons in the USA who acquire HIV as a consequence of risky sexual activities with an acutely-infected sex partner.

Methods: Estimates of the number of incident infections in the USA that are due to acute-phase HIV transmission were derived from a simple mathematical model that combined epidemiological data with information regarding the relative transmission rates for acutely-infected, nonacutely infected but serostatus-unaware, and serostatus-aware persons living with HIV.

Results—Approximately 2760 (8.6%) of the estimated 32 000 sexually-acquired HIV infections in the USA each year are due to acute-phase transmission of the virus. Multivariate sensitivity analyses with a liberal range of values for key parameters produced an upper bound of 5537 infections, representing 17.3% of the total number of sexually-acquired infections.

Conclusions—Acute-phase HIV transmission accounts for fewer sexually-acquired infections in the USA than is generally assumed.

Keywords

acute infection; HIV transmission; mathematical model; serostatus awareness

Introduction

The first few weeks to months following the acquisition of HIV are characterized by rapid viral replication and dissemination of the virus throughout the body [1]. During this period of acute infection, high titres of viral RNA are likely to be present in the genital tract as well as in plasma [2]. Notably, during this time most recently-infected persons will test negative or indeterminate on standard HIV antibody tests. Therefore, they are likely to continue to engage in high-risk behaviors such as unprotected intercourse.

Previous studies have demonstrated that persons living with HIV (PLWH) who are unaware of their HIV status are significantly more likely than HIV-status-aware PLWH to engage in practices that place their sexual partners at risk for HIV acquisition [3,4]. Marks *et al*. estimate that 54% of all sexually-acquired HIV infections in the USA are due to the transmission risk behaviors of PLWH who are unaware of their HIV status [5]. As viral load is elevated by several log units (factors of 10) during the acute phase of infection compared with the asymptomatic stage of infection [1,6], with corresponding increases in the probability of HIV transmission [7,8], acutely-infected persons may be much more likely to transmit HIV to sex partners than are other PLWH who are unaware of their HIV status [9].

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Mathematical modeling studies have suggested that transmission during the brief, high viral load period of acute infection could play a disproportionate role in fueling or sustaining HIV epidemics under certain circumstances [10-12]. The actual impact of acute-phase transmission on the current USA HIV epidemic is not however, known. The present study utilized a simple mathematical model to estimate the number and proportion of sexually-acquired HIV infections that are due to the transmission risk activities of persons with acute infection. These estimates are needed to assist HIV prevention resource allocation decision makers who must determine whether to implement potentially costly strategies to prevent acute-phase transmission (such as HIV RNA testing coupled with enhanced counseling and partner notification programs [13-15]), and to help prioritize research into acute-phase HIV transmission within the context of the larger HIV prevention scientific agenda.

Methods

Approximately 25% of the 1 million persons living with HIV in the USA are unaware of their HIV status [16]. Each year an estimated 40 000 people in the USA acquire HIV and pass through the relatively brief period of acute infection [17]. Let T denote the duration of the acute phase of infection, in days. On average, on any given day there are $N_1 = 40\,000 * (T/365)$ acutely-infected PLWH, $N_2 = 250\,000 - 40\,000 * (T/365)$ persons with non-acute infection who are unaware of their HIV status, and $N_3 = 750\,000$ serostatus-aware PLWH.

Let γ_k ($k = 1, 2, 3$) denote the average number of secondary infections expected, per day, among the sex partners of PLWH in group N_k (γ_k is the daily 'HIV transmission rate' [18]). The total number of sex partners in the USA who acquire HIV on any given day is then

$$I = \gamma_1 N_1 + \gamma_2 N_2 + \gamma_3 N_3 \quad (1)$$

The proportion of these incident infections that are due to acute-phase HIV transmission is

$$I_A = \frac{\gamma_1 N_1}{\gamma_1 N_1 + \gamma_2 N_2 + \gamma_3 N_3} \quad (2)$$

which also can be written

$$I_A = \frac{\mu_{12}\mu_{23} N_1}{\mu_{12}\mu_{23} N_1 + \mu_{23} N_2 + \gamma_3 N_3} \quad (3)$$

where $\mu_{12} = \gamma_1/\gamma_2$ and $\mu_{23} = \gamma_2/\gamma_3$ are the transmission rate ratios for acutely-infected versus nonacutely infected serostatus-unaware PLWH, and for nonacutely infected, serostatus-unaware versus serostatus-aware PLWH, respectively. Approximately 32 000 persons acquire HIV each year in the USA as a consequence of sexual risk behaviors [16]; 32 000 * I_A of these incident infections are due to acute-phase HIV transmission.

Parameter values

The duration of the acute phase of infection is uncertain and likely varies from one person to the next. On average, detectable plasma viremia first appears about 7 days postinfection, reaches peak concentration 7 to 10 days later, and then decreases to a steady-state, 'set point' level within 8 weeks of viral acquisition [9,19,20]. The base-case analysis therefore assumed a 7-week ($T = 49$ day) period of acute infectiousness, with lower and upper bounds of 6 and 8 weeks ($T = 42$ and 56, respectively).

Marks *et al.* estimated that the transmission rate for PLWH who are unaware of their HIV status is 3.47 times larger than the transmission rate for serostatus-unaware PLWH [5]. Their model assumed that serostatus-aware PLWH engage in 57% fewer acts of unprotected intercourse with at-risk (HIV-negative or serostatus-unknown) partners than do serostatus-unaware PLWH; that 60% of serostatus-aware PLWH receive highly-active antiretroviral therapy

(HAART); and that 55% of persons on HAART are incapable of transmitting the virus due to plasma viral load levels below 500 copies/ml. As this model did not account for the transmission facilitating effects of acute infection, the 3.47 estimate is best interpreted as the ratio of the transmission rates for nonacutely infected, serostatus-unaware versus serostatus-aware PLWH. Consequently, μ_{23} was set to 3.47 in the base-case analysis. The sensitivity analyses considered two extreme cases in which μ_{23} was set to 1.49 (43% of the base-case value), which corresponds to the pessimistic assumption of no behavioral change of any kind after PLWH learn their serostatus, or to 6.94 (twice the base-case value), which corresponds to the possibility that PLWH who are aware of their serostatus might have half as many sex partners as HIV-status-unaware PLWH. Alternatively, this range is sufficient to account for any of a number of deviations from the assumptions of Marks *et al.* regarding the sexual activity levels of serostatus-aware versus unaware PLWH, the proportion of PLWH on HAART, or the proportion of PLWH for whom HAART has effectively eliminated the potential for transmission.

Little is known regarding the acute-phase transmission rate ratio, $\mu_{12} = \gamma_1/\gamma_2$. As shown in the explanatory mathematical section that precedes the reference list, however, if the number of sex acts during the acute phase of infection and during a comparable period of nonacute, serostatus-unaware infection (n_A and n_S, respectively) are not too large, then the ratio $n_A\alpha_A/n_S\alpha_S$ provides an approximate upper bound for μ_{12}, where α_A and α_S, respectively, denote the *average* per-act transmission probability during the acute phase of infection and the (constant) per-act transmission probability during the nonacute, asymptomatic period of infection. A lower bound of $\alpha_A/\alpha_S = 4.2$ was derived from a modeling study of male-to-female HIV transmission perfomed by Pilcher *et al.* [9] and an upper bound of 12.0 was obtained from the model of male-to-male sexual transmission developed by Rapatski *et al.* [21] (see explanatory mathematical section below). The parameter μ_{12} was set to the average of these values, 8.1, in the base-case analysis and was varied from 4.2 to 12.0 in the sensitivity analyses. Notably, in comparison with the base-case value, the sensitivity analyses allow for the possibility that acutely-infected persons might engage in 48.1% more or 48.1% fewer unprotected sex acts than do nonacutely infected, serostatus-unaware PLWH in the same period of time.

Results

In the base-case scenario, acute-phase HIV transmission accounted for 2760 (8.6%) of the 32 000 infections that are acquired each year through risky sexual activities. Of the remaining sexually-acquired infections, approximately half (48.5%) were due to transmission from nonacutely infected serostatus-unaware persons and 42.9% were due to serostatus-aware persons (see Table 1).

As indicated in Table 2, the proportion of incident infections due to acute-phase transmission was moderately sensitive to each of three of the main model parameters (μ_{12}, μ_{23}, and T), ranging from 4.7 to 12.3% in univariate sensitivity analyses that varied one of the three parameters while holding the other two at their base-case values. Notably, when μ_{23} and T were set to their base-case values, the percentage of infections due to acute-phase transmission was approximately equal to the acute-phase transmission rate ratio, μ_{12}. The minimum percentage of infections due to acute-phase transmission, which was obtained when all three parameters were set to their minimum values, was 2.5% and the maximum was 17.3%.

Discussion

The results of the preceding analysis suggest that approximately 2760 (8.6%) of sexually-acquired HIV infections in the USA are due to acute-phase transmission. Despite the relatively small predicted impact of acute infection on the USA epidemic, this analysis nevertheless

highlights the significant risk of HIV transmission during acute infection. The HIV transmission rate for acutely-infected persons was 16 times larger than the overall transmission rate for PLWH in the USA. Although acutely-infected persons may be much more likely than other PLWH to transmit the virus to their sex partners, their relatively small census (approximately 0.5% of all PLWH) and the very brief duration of the acute phase of infection minimizes the impact of acute-phase transmission on the overall HIV epidemic in the USA.

The results of this analysis are consistent with the estimate of Xiradou *et al.* that 11% of HIV infections among gay men in Amsterdam can be attributed to acute-phase HIV transmission [22]. In the study of HIV transmission in heterosexual Ugandan couples performed by Wawer *et al.*, 43.4% (10/23) of recently-infected persons transmitted the virus to their primary sex partner within an estimated 5 months of seroconverting [23]. This finding is the basis for some commentators' assertion that acute-phase transmission could account for ‘nearly one-half’ of all incident infections [14]. An unpublished modeling study based on these data suggests, however, that despite the elevated risk of HIV transmission during acute infection, acute-phase transmission would account for ‘only’ 11% of new infections in the Ugandan population at epidemic equilibrium [24].

The findings of the present study are also consistent with previous analyses of the impact of serostatus awareness, which indicate that the annual HIV transmission rate for PLWH who are unaware of their positive serostatus is approximately 3.5 to 3.7 times larger than the transmission rate for HIV-status-aware PLWH [5,25].

Acute-phase HIV transmission accounts for a very small portion of this difference: if acutely-infected persons were no more likely to transmit the virus than other HIV-status-unaware PLWH (i.e., if $\mu_{12} = 1$), the percentage of infections due to the transmission risk activities of HIV status-unaware persons would decrease only slightly, from 54.8 to 53.6%. Increasing the proportion of PLWH who are aware of their HIV status should remain a high-priority objective of HIV prevention efforts in the USA [26].

The present analysis is limited by uncertainty in several key parameters, particularly the acute-phase transmission rate ratio. This analysis utilized parameter values drawn from several previous studies, including Marks *et al.* [5], Pilcher *et al.* [9], and Rapatski *et al.* [21], and is subject to the limitations of these previous studies. The results of the multivariate sensitivity analyses—in which the values of key parameters were independently varied over relatively broad ranges—suggest that the impact of acute-phase transmission on the USA epidemic could be much smaller or larger than indicated by the base-case value.

In summary, the results of this study indicate that the proportion of sexually-acquired infections in the US due to acute-phase transmission is not nearly as large as has been suggested by some commentators. Uncertainties notwithstanding, this study provides little support for the assertion that, in the USA, “as many as half of all new infections may be acquired from an index case in the acute phase [of infection]” [27]. Additional research is needed to more precisely determine the overall epidemiological impact of acute-phase HIV transmission in the USA.

Explanation of mathematical techniques

Herein a justification is provided for approximating the transmission rate ratio, $\mu_{12} = \gamma_1/\gamma_2$, by the ratio $n_A\alpha_A/n_S\alpha_S$, and the derivation of the α_A/α_S estimates used in the analyses is described. Here, γ_1, n_A, and α_A denote the HIV transmission rate (i.e., the expected number of transmission events per PLWH), the number of unprotected sex acts, and the *average* per-act transmission probability during the acute phase of infection, whereas γ_2, n_S, and α_S denote the corresponding values for a comparable period of nonacute, serostatus-unaware infection.

An HIV-infected person with m uninfected sex partners would be expected to transmit the virus to $\gamma = \beta_1 + \beta_2 + \ldots + \beta_m$ of these partners, where $\beta_k = 1 - (1 - \alpha_1)(1 - \alpha_2) \ldots (1 - \alpha n_k)$ is the probability of transmission to partner k, n_k is the number of unprotected sex acts with partner k, and α_i is the transmission probability associated with the i-th sex act (for simplicity we assume that the risk of transmission for condom-protected acts is zero) [28].

During the asymptomatic phase of infection, the per-act transmission probability is assumed to be constant: $\alpha_i = \alpha_S$ for $i = 1,2, \ldots, n_k$, and therefore, $\beta_k = 1 - (1 - \alpha_s)^{nk}$. As α_S is relatively small (e.g., $\alpha_S = 0.00055$ [9] or $\alpha_S = 0.002$ [21]), $1 - (1 - \alpha_S)^{nk} \approx \alpha_S n_k$,[29] and consequently, $\gamma_2 = \beta_1 + \beta_2 + \ldots + \beta_m \approx \alpha_S n_S$, where $n_S = n_1 + n_2 + \ldots + n_m$ is the total number of unprotected sex acts, summed across partners.

More generally, $\beta_k = 1 - (1 - \alpha_1)(1 - \alpha_2) \ldots (1 - \alpha n_k) \leq \alpha_1 + \alpha_2 + \ldots + \alpha n_k$, and therefore $\gamma \leq \sum \alpha_i$, where the sum is taken over all sex acts with all partners. If the n_A acts during the acute phase of infection are evenly or randomly distributed throughout this period, then $\sum \alpha_i \approx n_A \alpha_A$, where α_A is the *average* per-act transmission probability during the acute phase of infection. Thus, on average, $\gamma_1 \leq n_A \alpha_A$ and $\mu_{12} = \gamma_1/\gamma_2 \leq n_A \alpha_A / n_S \alpha_S$.

Estimates of α_A/α_S were obtained from Rapatski *et al.* [21], who estimated the per-act transmission probability during male-to-male receptive anal intercourse at $\alpha_A = 0.024$ for the acute phase of infection and $\alpha_S = 0.002$ for asymptomatic infection (hence, $\alpha_A/\alpha_S = 12.0$), and from Pilcher *et al.* [9] The latter study estimated the set point per-act transmission probability for male–female intercourse at $\alpha_S = 0.00055$ and the *overall* probability of transmission from an acutely-infected male to his female sex partner during the acute phase of infection at $p_A = 0.032$, assuming eight unprotected sex acts per month over a 55-day period; this is approximately $n = 14$ total acts of intercourse over a 7-week period of acute infectiousness (i.e., excluding the approximately 7-day noninfectious latency period before detectable viremia appears). The average per-act transmission probability during the acute phase of infection was derived from this estimate using the equation: $\alpha_A = 1 - (1 - p_A)^{1/n}$. The resultant estimate of α_A/α_S equaled 4.2 (0.00055/0.0023).

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Table 1

Sexual transmission of HIV by persons living with HIV (PLWH) status.

	Daily census	Daily trans. rate (%)[a]	Annual trans. rate (%)[a]	Annual HIV infections (%)
Acutely-infected (unaware)	5370	0.1408	51.40	2760 (8.6%)
Nonacute, unaware	244 630	0.0174	6.35	15 524 (48.5%)
Nonacute, aware	750 000	0.0050	1.83	13 716 (42.9%)
Unaware	250 000	0.0200	7.31	18 284 (57.1%)
Overall	1 000 000	0.0088	3.20	32 000 (100%)

[a]The transmission rate is the average number of transmission events, per PLWH, per unit time.

Table 2

Sensitivity analyses: Proportion of sexually-acquired HIV infections due to acute-phase transmission.

	μ_{23}=1.49[a]			μ_{23}=3.47			μ_{23}=6.94		
μ_{12}[b]	*T*=42[c]	*T*=49	*T*=56	*T*=42	*T*=49	*T*=56	*T*=42	*T*=49	*T*=56
4.2	2.5	2.9	3.3	4.0	4.7	5.3	5.2	6.0	6.8
8.1	4.7	5.5	6.2	7.5	8.6[d]	9.8	9.5	11.0	12.4
12.0	6.9	7.9	9.0	10.7	12.3	13.8	13.5	15.4	17.3

[a] Transmission rate ratio for (nonacutely infected) serostatus-unaware versus serostatus-aware persons living with HIV (PLWH).

[b] Transmission rate ratio for acutely-infected versus nonacutely infected serostatus-unaware PLWH.

[c] Duration of acute phase of infection (days).

[d] Base-case value.

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