Decline in HIV infectivity following the introduction of highly active antiretroviral therapy

Travis C. Porcoa, Jeffrey N. Martinb,c, Kimberly A. Page-Shaferd, Amber Chengb, Edwin Charleboisd,e, Robert M. Grantd,f and Dennis H. Osmondb

Objective: Little is known about the degree to which widespread use of antiretroviral therapy in a community reduces uninfected individuals’ risk of acquiring HIV. We estimated the degree to which the probability of HIV infection from an infected partner (the infectivity) declined following the introduction of highly active antiretroviral therapy (HAART) in San Francisco.

Design: Homosexual men from the San Francisco Young Men’s Health Study, who were initially uninfected with HIV, were asked about sexual practices, and tested for HIV antibodies at each of four follow-up visits during a 6-year period spanning the advent of widespread use of HAART (1994 to 1999).

Methods: We estimated the infectivity of HIV (per-partnership probability of transmission from an infected partner) using a probabilistic risk model based on observed incident infections and self-reported sexual risk behavior, and tested the hypothesis that infectivity was the same before and after HAART was introduced.

Results: A total of 534 homosexual men were evaluated. Decreasing trends in HIV seroincidence were observed despite increases in reported number of unprotected receptive anal intercourse partners. Conservatively assuming a constant prevalence of HIV infection between 1994 and 1999, HIV infectivity decreased from 0.120 prior to widespread use of HAART, to 0.048 after the widespread use of HAART – a decline of 60% (P = 0.028).

Conclusions: Use of HAART by infected persons in a community appears to reduce their infectiousness and therefore may provide an important HIV prevention tool.

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Introduction

Combination highly active antiretroviral therapy (HAART) using three or more drugs in HIV-infected patients leads to a substantial reduction in plasma HIV RNA levels, decreased incidence of opportunistic infections, and a decrease in the risk of transmission to uninfected sexual partners.
infections, and lower mortality rates [1,2]. Besides these clinical benefits, HAART is believed to decrease the probability of transmitting HIV to others, as (1) viral load in untreated HIV-infected persons is correlated with the transmission risk to sexual partners [3]; (2) antiretroviral therapy decreases the rate of transmission to infants [4,5]; and (3) HAART reduces viral shedding in semen [6]. Although these findings indirectly support the hypothesis that HAART reduces the infectiousness of treated persons [7], few data are available to confirm it [8]. We estimated the per-partnership probability of transmission from an infected partner (i.e., infectivity) for homosexual men in San Francisco using seroconversion and behavioral data collected during the San Francisco Young Men’s Health Study [9], a longitudinal cohort study of young homosexual men which began before HAART was introduced and continued subsequently. Using two study visits before widespread use of HAART began in San Francisco and two study visits after, we examined trends in incidence and self-reported unsafe sex, and estimated the infectivity from a probabilistic risk model [10–14] using the method of maximum likelihood [15].

Methods

The San Francisco Young Men’s Health Study is a multistage probability sample (which began in 1992) of single men aged 18–29 years who resided in 21 census tracts with the highest cumulative AIDS incidence [9]. It included 428 homosexual men at baseline and then enrolled an additional 622 referral subjects at the next follow-up time. At each approximately yearly study visit, subjects were tested for HIV antibodies and were asked, with respect to the previous 12 months, for their (1) number of sex partners; (2) number of sex partners under 30 years of age; (3) number of receptive anal intercourse partners; and (4) number of receptive anal intercourse partners with whom condoms were always used. The last four study visits used consistent questions about behavior and provided two periods at risk both before (April 1994 to September 1995; and September 1995 to November 1996) and after (November 1996 to September 1997; and September 1997 to March 1999) the introduction of HAART in San Francisco and were used in this analysis.

Crude incidence rates were calculated by dividing the number of seroconverters in each period by the person-time between HIV tests for each person for the period, assigning each seroconverter one-half of his person-time for the period [16].

To estimate the transmission probability and infectivity of HIV per partnership for each of the four periods, we used a probabilistic risk model [10–14] (see Appendix). The transmission probability per partnership is the product of two components: the infectivity (by which we mean the per-partnership probability that an uninfected person acquires the infection from an infected partner), and the probability that the partner is infected (the prevalence among the partners). In this paper, we first show evidence that the transmission probability has declined over time, and then we use prevalence estimates to attribute this to a decline in infectivity.

Results

Incidence rates and risk behavior

At the beginning of the first study period we analyzed, 534 study participants were uninfected (Table 1). Over the four study visits, we observed little change in the number of overall receptive anal intercourse partnerships reported during the study period, but a significant increase in the number of unprotected partnerships reported for the previous 12 months, for their (1) number of sex partners; (2) number of sex partners under 30 years of age; (3) number of receptive anal intercourse partners; and (4) number of receptive anal intercourse partners with whom condoms were always used. The last four study visits used consistent questions about behavior and provided two periods at risk both before (April 1994 to September 1995; and September 1995 to November 1996) and after (November 1996 to September 1997; and September 1997 to March 1999) the introduction of HAART in San Francisco and were used in this analysis.

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Table 1. Summary statistics for the four study periods.

<table>
<thead>
<tr>
<th>Study period</th>
<th>Time period at risk for infection</th>
<th>No. of Subjects</th>
<th>Mean no. of RAI partners</th>
<th>Mean no. of unprotected RAI partners</th>
<th>HIV Seroconversions</th>
<th>Crude incidence rate/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/94 – 9/95</td>
<td>534</td>
<td>2.65</td>
<td>0.6</td>
<td>10</td>
<td>1.36%</td>
</tr>
<tr>
<td>2</td>
<td>9/95 – 11/96</td>
<td>481</td>
<td>1.97</td>
<td>0.75</td>
<td>7</td>
<td>1.29%</td>
</tr>
<tr>
<td>3</td>
<td>11/96 – 9/97</td>
<td>445</td>
<td>2.15</td>
<td>0.8</td>
<td>3</td>
<td>0.78%</td>
</tr>
<tr>
<td>4</td>
<td>9/97 – 3/99</td>
<td>320</td>
<td>2.44</td>
<td>1.3</td>
<td>5</td>
<td>1.02%</td>
</tr>
</tbody>
</table>

Trimmed means are reported with the most extreme outlier trimmed. The dates reported in the text correspond to the intervals between the median of the dates of the study visit beginning the period, and the median of the dates of the study visit ending the period. RAI, receptive anal intercourse.
To assess this possibility, we first used the risk model given in the Appendix [10–14] to test the hypothesis that the transmission probability per partnership was the same in the post-HAART study periods as it was in the pre-HAART study periods. We estimated the transmission probability per-partnership to be 0.0276 pre-HAART, and 0.011 post-HAART, and rejected the hypothesis that the transmission probability was constant \( P = 0.028 \). Having found this evidence of a decline in the per-partnership transmission probability, we next determined which of its two components (infectivity or prevalence) was responsible for the decline. Although precise prevalence estimates are not available, we showed that unrealistic declines in prevalence would be required to explain the observed decline in the transmission probability. We assumed plausible prevalence scenarios, and for each scenario, we estimated the infectivity and tested the hypothesis that the infectivity was the same before and after HAART was introduced. First, assuming a constant prevalence of 23% among the partners of the men (the cohort prevalence of HIV among men reporting receptive anal intercourse at the 1992 baseline of the study [9]), we found that the per-partnership infectivities (with asymptotic standard errors in parentheses) at each study visit were 0.118 \( (0.042) \) and 0.124 \( (0.049) \) for the pre-HAART study periods, and 0.055 \( (0.032) \) and 0.044 \( (0.020) \) for the two post-HAART study periods. Combining the two pre- and two post-HAART time periods into two estimates to increase statistical power, we obtained an estimate of 0.120 \( (0.034) \) per partnership in the first two periods, and 0.048 \( (0.017) \) per partnership in the last two periods, for an overall 60.4% decline in HIV infectivity \( P = 0.028 \). Finally, a goodness-of-fit test yielded no evidence of insufficient fit \( P = 0.63 \); see Appendix.

Although the above analyses assumed a constant prevalence, in fact HIV prevalence is believed to have been declining among homosexual men prior to HAART (because HIV deaths were continuing to outweigh recent infections [18]), but to have been increasing after the introduction of HAART due to substantial declines in AIDS mortality [19]. Assuming increased prevalence after the introduction of HAART yields stronger evidence in favor of an infectivity decline; if, for example, we assume that after the introduction of HAART, the prevalence increased 17.2% (relative to the pre-HAART value), then the infectivity decline would be significant at the 0.01 level. If, however, we assume a decrease in prevalence, then the reduced incidence shown earlier (Table 1) would be partially explained by the assumption of reduced prevalence among partners; assuming that the prevalence decreased more than 9.3% relative to baseline yields \( P \)-values greater than 0.05 for the test of constant infectivity.

To systematically examine infectivity estimates over a wide range of possible prevalence patterns, we chose a Latin Hypercube Sample \( [20–22] \) of 10,000 random prevalence patterns, with the prevalence at each study visit uniformly distributed over the plausible (though arbitrary) range 0.1 to 0.3 (other plausible choices yield similar results). For each random prevalence scenario, we performed the hypothesis test of constant infectivity. The \( P \)-value was less than 0.1 in all of the 4986 scenarios in which the average prevalence was greater post-HAART than pre-HAART; the \( P \)-value exceeded 0.05 only in 17 unrealistic scenarios for which the prevalence was very high at visits one and three and very low for visits two and four. Finally, infectivity estimates for representative prevalence patterns are shown in Table 2. Thus, for plausible assumed patterns of the prevalence over the 6 years of follow-up, infectivity decline is a robust finding.

In addition to probable variations in time, HIV prevalence varies with age among homosexual men in San Francisco \([23–25]\). As in the first three study periods, our study subjects were asked how many of their total partners were under 30 years of age, we adjusted for the fraction of partners under 30 years of age as described in the Appendix. The Urban Men’s Health Study, a random-digit-dialing survey of homosexual men in San Francisco conducted between 1996 and 1998 \([25]\), yielded 6.0% of men under 30 years of age reported being HIV-infected, and 22.4% of men 30 and older reported being HIV-infected \((L.\) Pollack, pers. comm.; random-digit-dialing samples should include sexually inactive men at lower risk for HIV infection than the partners of the men in our study.) As before, we chose a Latin Hypercube Sample of 10,000 prevalence scenarios, and for each, performed the hypothesis test of constant infectivity; for each study period, the prevalences among men under 30 and among men 30 years old and over were chosen from a uniform distribution between 0.1 and 0.3. Only 14 unrealistic scenarios (with high prevalence at periods 1 and 3 and low prevalence at periods 2 and 4 among men 30 years old and over) yielded a \( P \)-value greater than 0.05 with an increasing prevalence. Finally, selected estimates for various age- and period-specific scenarios are also included in Table 2. Thus, after adjusting for self-reported age of the partners, we continue to conclude that the infectivity declined after the introduction of HAART.

We compared the characteristics of those individuals who remained in the study with those who were never known to seroconvert, but who were lost to follow-up. We found no significant differences between dropouts and those remaining for age, education, number of male sexual partners, number of partners with whom anal or oral sex was reported, recreational drug use, and self-reported sexually transmitted diseases. Drop-outs
Table 2. Estimated infectivity of HIV under different assumptions regarding age-class specific prevalence and prevalence over time.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>β₁</th>
<th>β₂</th>
<th>β₃</th>
<th>β₄</th>
<th>Percentage decline</th>
<th>X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant prevalence (other choices give same P-value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.23</td>
<td>0.23</td>
<td>0.117</td>
<td>0.124</td>
<td>0.055</td>
<td>0.044</td>
<td>60.4%</td>
<td>4.81</td>
<td>0.028</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.20</td>
<td>0.20</td>
<td>0.117</td>
<td>0.124</td>
<td>0.058</td>
<td>0.046</td>
<td>58.6%</td>
<td>4.35</td>
<td>0.037</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.21</td>
<td>0.21</td>
<td>0.117</td>
<td>0.124</td>
<td>0.061</td>
<td>0.048</td>
<td>56.5%</td>
<td>3.90</td>
<td>0.048</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.20</td>
<td>0.20</td>
<td>0.117</td>
<td>0.124</td>
<td>0.064</td>
<td>0.050</td>
<td>54.4%</td>
<td>3.44</td>
<td>0.063</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.21</td>
<td>0.20</td>
<td>0.117</td>
<td>0.130</td>
<td>0.070</td>
<td>0.057</td>
<td>56.0%</td>
<td>3.77</td>
<td>0.052</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.25</td>
<td>0.26</td>
<td>0.117</td>
<td>0.130</td>
<td>0.049</td>
<td>0.035</td>
<td>57.4%</td>
<td>7.11</td>
<td>0.008</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.23</td>
<td>0.21</td>
<td>0.23</td>
<td>0.117</td>
<td>0.136</td>
<td>0.055</td>
<td>0.036</td>
<td>66.7%</td>
<td>6.78</td>
<td>0.009</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.17</td>
<td>0.17</td>
<td>0.23</td>
<td>0.117</td>
<td>0.168</td>
<td>0.075</td>
<td>0.044</td>
<td>61.2%</td>
<td>5.03</td>
<td>0.025</td>
</tr>
<tr>
<td>All ages</td>
<td>0.25</td>
<td>0.22</td>
<td>0.22</td>
<td>0.25</td>
<td>0.108</td>
<td>0.130</td>
<td>0.058</td>
<td>0.040</td>
<td>60.8%</td>
<td>4.91</td>
<td>0.027</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.20</td>
<td>0.20</td>
<td>0.23</td>
<td>0.117</td>
<td>0.143</td>
<td>0.064</td>
<td>0.044</td>
<td>60.8%</td>
<td>4.92</td>
<td>0.027</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.17</td>
<td>0.20</td>
<td>0.20</td>
<td>0.117</td>
<td>0.168</td>
<td>0.064</td>
<td>0.050</td>
<td>59.3%</td>
<td>4.54</td>
<td>0.033</td>
</tr>
<tr>
<td>All ages</td>
<td>0.23</td>
<td>0.17</td>
<td>0.20</td>
<td>0.23</td>
<td>0.117</td>
<td>0.168</td>
<td>0.064</td>
<td>0.044</td>
<td>63.0%</td>
<td>5.56</td>
<td>0.018</td>
</tr>
</tbody>
</table>

All models in which the prevalence was declining prior to highly active antiretroviral therapy (HAART) and rising after the introduction of HAART produce a larger decline in infectivity than assuming constant prevalence. The prevalences of 6% for men under age 30 and of 22% for men over age 30 were derived from Urban Men’s Health Study (see text for details). Column 10 (Percentage decline) is the percentage decline in the aggregated estimate for the last two waves compared with the aggregated estimate for the first two waves (aggregated estimates omitted).

were more likely to report being bisexual, a difference captured by including the number of receptive anal intercourse partners in our models.

To quantify the potential importance of bias due to frailty selection (the differential removal of individuals with a higher per-partnership infectivity), we conducted a Monte Carlo sensitivity analysis [26]. We assumed that the infectivity was constant for each individual, but differed between individuals, with some individuals having a per-partnership risk of zero and others having a higher per-partnership risk. We kept the overall average per-partnership infectivity (the fraction of individuals in the high per-partnership risk group times their per-partnership risk) equal to 0.1. We repeatedly simulated HIV infection given reported risk behaviors and different sizes of the high per-partnership risk group, and determined the probability of rejecting the null hypothesis of constant decline. From a logistic model fit to these simulation results, we estimated that to have a 20% chance of finding an apparent infectivity decline, we would have needed approximately 15% of the population to be in the high per-partnership risk group (and their per-partnership infectivity would be approximately 0.69 ≈ 0.1/0.15); to have a 10% chance of finding an apparent infectivity decline, we would have needed approximately 36% of the population in the high per-partnership risk group (and their per-partnership infectivity would be approximately 0.28 ≈ 0.1/0.36). Less extreme distributions of heterogeneity of risk yield small probabilities of finding an apparent infectivity decline; for instance, assuming a risk of 0.05 per partnership in half of the individuals and a risk of 0.25 per partnership in the other half yielded 6.3% out of 1000 simulations in which a false infectivity decline was observed – scarcely different from the 5% we would expect given the assumed 5% type I error rate of the test.

As partners of high-risk men may themselves be at high risk, we repeated the estimation of the infectivity decline assuming that individuals with five or more unprotected partnerships have 50% higher prevalence of infection among their partners than individuals with
fewer than five partners. Under this assumption, the infectivity decline remains statistically significant ($P = 0.019$); the estimated per-partnership infectivity was 0.107 for the first two study periods and 0.040 for the last two periods.

Finally, we also obtained an estimate of the degree of protection afforded by (reported) consistent condom usage (see Appendix). Under the assumption of 23% prevalence, HIV infectivity in partnerships for which condoms were always reportedly used was 5.4% of the infectivity for those partnerships not protected by condoms (95% bootstrap confidence interval [0.0, 0.019]); the estimated per-partnership infectivity was 0.040 for the first two study periods and 0.019 for the second two study periods. 

Several design limitations, however, apply to our findings. First, the absolute magnitude of our infectivity estimates depends on the prevalence of HIV among the partners of the study participants. However, the magnitude of our pre-HAART estimates is similar to the value of 0.1 found from the San Francisco Men’s Health Study in the 1980s [10], and whereas we assumed a constant prevalence to obtain the infectivity decline of 60%, qualitatively similar findings hold for other patterns of HIV prevalence. Only if we assume that the prevalence of HIV declined by at least 9.3% does the estimated infectivity decline fail to be statistically significant at the 0.05 level (such a pattern is believed to be highly unlikely, owing to declines in HIV-related mortality in the HAART era). Under what we believe is the most plausible pattern of HIV prevalence, a decline prior to HAART followed by an increase following HAART introduction, we observed a 67% decline in infectivity. Second, the experience of our cohort may not represent all infected persons; for example, differences in medication adherence across infected persons may influence the effect of HAART on infectiousness. Third, it is not possible to conclusively rule out frailty selection bias (or effects of aging); however, any such effects would need to be implausibly large to provide an alternative explanation of the decline in the infectivity estimates. Fourth, indinavir and ritonavir were approved in March of 1996 [34,35] – during the second study period of our analysis (although the majority of this second period was in early 1996 when few people were using HAART); however, this biases our statistical analysis away from finding a significant difference. Fifth, while no quantitative evidence regarding changes in serosorting patterns is available, there is no reason to suppose decreasing preference of HIV-negative individuals for HIV-positive partners during this time of decreasing perceived HIV threat, nor is there any evidence that HIV-negative individuals increased their risk behavior disproportionately when compared to HIV-positive individuals (which would have produced a declining effective prevalence.)

The 60% decline in HIV infectivity we observed following the introduction of HAART suggests that use of HAART in infected persons not only confers clinical benefit, but is also an attractive tool for prevention. Unfortunately, during the same time that we observed a decline in infectivity, an increase in unprotected sexual behavior both in San Francisco [36,37] and in other cities [38,39] was observed. Furthermore, although we had observed a falling HIV seroincidence through the end of our study period in early 1999, community-level data among homosexual men in San Francisco revealed a rising incidence soon thereafter [19]. Thus, the benefit in reduced HIV transmission in the community due to widespread use of HAART may be offset by increases in unsafe sexual

Discussion

We observed a 60% decline in the per-partnership infectivity of HIV that coincided with the introduction of HAART under the conservative assumption of constant HIV prevalence. For the more realistic assumption of increased prevalence after HAART, declines of over 67% were estimated. These represent an average decline experienced by the men in the study, and is thus likely to underestimate the true individual level effect of HAART; the HIV-infected partners of the study participants in all likelihood included individuals not using HAART at all as well as individuals using HAART. Many treated individuals would be expected to have a very low plasma viral load because of successful treatment; while in many others, reduction of plasma HIV RNA while on HAART may continue even if drug resistance emerges [28]. In San Francisco, use of protease inhibitor-based combination antiretroviral therapy began in December 1995 with the hard-gel formulation of saquinavir [29], but did not become widespread until mid to late 1996 [19]; by 1997 it was being used by 53% (L. Pollack, pers. commun.) of homosexual men known to be HIV-infected [30]. Although it is biologically plausible that HAART reduces the infectiousness of treated patients [7,8] and mathematical transmission models [31–33] based on the assumption that treatment reduces infectivity have shown that such high levels of treatment could reduce the incidence of HIV infection (whether by directly reducing the viral load in treated patients, or by selecting for potentially less transmissible drug-resistant strains), our results provide an empirical estimate of the declines in infectivity that may have been due to HAART. Computing the infectivity on a per-partnership basis allowed us to separate the infectivity decline itself from the increases in unsafe sex which have offset many of the epidemiologic benefits of treatment [19].
encounters. Use of HAART is a potentially important HIV prevention tool, one that is likely to succeed, however, only if accompanied by a continued emphasis on avoidance of exposure.

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References


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Appendix

We statistically modeled infection for each of the four time periods $i$ ($i = 1, 2, 3, 4$) using a simple risk model [10–14]. We denote the infectivity for study period $i$ by $\beta_i$, and the prevalence among the partners during study period $i$ by $p_i$. We assumed that when condoms are always reported used, the infectivity per partnership is reduced by $\beta_i$, with $0 \leq 0 \leq 1$. For subject $j$ at study visit $i$ ($i = 1, \ldots, N_j$), we denote the number of partnerships reported in 12 months for which condoms were not always used by $n_{ij}$ ('unprotected partnerships') and the number of partnerships reported in the last 12 months for which condoms were always used by $m_{ij}$ ('protected partnerships'). For each individual, let $f_{ij}$ be the time in years since the latest negative HIV antibody test. We then let the fraction of the one year reporting period that has elapsed since the last HIV antibody test be denoted $\phi_{ij}$ for each subject $j$ at each study visit $i$, i.e. $\phi_{ij} = \min(f_{ij}/1$ year, 1) (where we divided $f_{ij}$ by 1 year since $\phi_{ij}$ is a dimensionless fraction). Finally, we let $\tau_{ij}$ be the time (in years) over and above 1 year that has elapsed since the last HIV antibody test, i.e. $\tau_{ij} = \max(0, f_{ij} - 1$ year, 0). We assumed that each reported partner has a probability $\phi_{ij}$ of having been a partner during the reporting period.

The risk model was constructed as follows. For subjects with less than one year since the last antibody test, the probability of infection for each reported unprotected partnership is the product of the probability that the partnership occurred since the last test ($\phi_{ij}$), the probability the partner was infected ($p_i$), and the infectivity ($\beta_i$). The probability of escaping infection from all the reported unprotected partnerships, assuming independence, is then $(1 - \phi_{ij} p_i \beta_i)^{n_{ij}}$. Similarly, the probability of escaping infection from the reported protected partnerships is $(1 - \phi_{ij} p_i \beta_i m_{ij})^{m_{ij}}$.

For subjects with greater than 12 months since the last antibody test, $\phi_{ij} = 1$ and $\tau_{ij} > 0$; for such individuals, the probability of escaping infection is the probability of not being infected by the partners reported in the first 12 months times the probability of not being infected by any further, unreported, partnerships (which is given by $\exp(-\beta_i p_i n_{ij} \tau_{ij})$ for unprotected partnerships, and $\exp(-\beta_i p_i m_{ij} \tau_{ij})$ for protected partnerships [14]). The derivation assumes that individual partnerships occurred according to a Poisson process with rate $n_{ij}$ per year for unprotected partnerships and with rate $m_{ij}$ per year for protected partnerships.

Therefore, the probability that individual $j$ at study period $i$ has escaped infection is

$$
(1 - \phi_{ij} p_i \beta_i)^{n_{ij}} \exp(-\beta_i p_i n_{ij} \tau_{ij}) \times
(1 - \phi_{ij} p_i \beta_i m_{ij})^{m_{ij}} \exp(-\beta_i p_i m_{ij} \tau_{ij})
$$

so that the probability that individual $j$ at study period $i$ is infected is given by

$$
q_{ij} = 1 - (1 - \phi_{ij} p_i \beta_i)^{n_{ij}} \exp(-\beta_i p_i n_{ij} \tau_{ij}) \times
(1 - \phi_{ij} p_i \beta_i m_{ij})^{m_{ij}} \exp(-\beta_i p_i m_{ij} \tau_{ij})
$$

Denoting the HIV infection status of individual $j$ at the end of study period $i$ by $Y_{ij}$ (0 if uninfected, 1 if infected), the likelihood function is then

$$
L(\beta_1 p_1, \beta_2 p_2, \beta_3 p_3, \beta_4 p_4, \theta) =
\prod_{i=1}^{4} \prod_{j=1}^{N_i} (1 - q_{ij})^{(1 - Y_{ij})}(q_{ij})^{Y_{ij}}.
$$

To estimate the transmission probabilities $\beta_i, p_i$, this likelihood is maximized with respect to $\beta_i, p_i$, $i = 1, 2, 3, 4$ (and $\theta$); to estimate the infectivities given assumed values of the prevalences $p_i$, this likelihood is then maximized with respect to $\beta_1, \beta_2, \beta_3, \beta_4$, and $\theta$ given assumed values of the prevalences $p_i$, $i = 1, 2, 3, 4$. The statistical test of constant transmission probability is equivalent to a test of constant infectivity assuming constant prevalence.

To test the hypothesis that the infectivity is the same pre-HAART and post-HAART, we assumed that $\beta_1 = \beta_2 = \beta_1 = \beta_1$ and $\beta_3 = \beta_4 = \beta_3$ and estimated $\beta_{12}$.
\[ \beta_{34}, \text{ and } \theta; \text{ we then assumed that } \beta_{12} = \beta_{34} = \beta_{1234} \text{ and estimated } \beta_{1234} \text{ and } \theta. \] These nested models were compared using the likelihood-ratio chi-square test [15]. Asymptotic standard errors were computed using the observed information matrix [15]. Analyses were conducted using the \textit{R} statistics package (http://www.r-project.org) on a Linux workstation.

We adjusted for the age of the reported partners by assuming that the prevalence among the receptive anal intercourse partners of each individual was the weighted average of the assumed prevalences for men 30 years of age or older and for men under 30 years old, based on the fraction of partners the individual reported to be under 30 years of age. For the final study visit, which formed the baseline of a new study of human herpesvirus 8, we used the same proportion reported on the previous visit, since at that time the subjects were not asked how many partners they had had who were under 30 years of age.

We assessed the goodness-of-fit using model in which we allowed the infectivity to vary with the number of unprotected receptive anal intercourse partners [10] (but because we also include protected partnerships, this procedure does not yield a saturated model). Specifically, we divided the population into categories of 0–1, 2, 3, 4 and 5 or more partners, and allowed a different infectivity for each category; we then tested the hypothesis that the infectivity is the same at every number of unprotected receptive anal intercourse partners.