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Heterosexual Transmission of Human Immunodeficiency Virus

Variability of Infectivity throughout the Course of Infection

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Although individuals infected with human immunodeficiency virus (HIV) seem to be more infectious in the late stages of HIV infection and possibly also during the seroconversion period, most estimates of per-sexual-contact infectivity have been obtained without allowing for variability over the course of infection. In this analysis, a probabilistic model was fitted to data from a European study carried out between 1987 and 1992 that involved 499 (359 males and 140 females) HIV-infected subjects (index cases) and their regular heterosexual partners. The model used allowed infectivity (the per-sexual-contact HIV transmission probability, μ) to vary through three stages: the first 3 months following infection, the subsequent asymptomatic period, and the advanced stage (HIV-related clinical symptoms or a CD4-positive T lymphocyte count less than 200/mm^3). Male-to-female infectivity through penile-anal sex was found to be higher in both the early and advanced stages of infection (μ = 0.183) than in the longer intermediate period (μ = 0.014) ($p < 0.03$). Failure to demonstrate significant differences between stages for other types of contact (male-to-female penile-vaginal contacts: μ = 0.0007; female-to-male transmission: μ = 0.0005) may reflect insufficient power rather than a true lack of variability. Indeed, the results for penile-anal sex suggest that persons who are in the process of seroconverting may be much more infectious than asymptomatic infected persons, whatever the type of contact. Prevention education should stress the risk of HIV transmission from subjects who may be unaware of their infection. *Am J Epidemiol* 1998;148:88–96.

acquired immunodeficiency syndrome; disease transmission; HIV; infectivity; sexual partners

Estimation of the per-contact probability of human immunodeficiency virus (HIV) transmission (infectivity) and assessment of how it could vary is important in understanding the course of the acquired immunodeficiency syndrome (AIDS) epidemic. Because of the general uncertainty regarding numbers of contacts at risk of transmission between partners, few such estimates have been made. Moreover, most published estimates were obtained assuming constant infectivity between couples and, within couples, over the time since the infection of the initially infected partner. However, it has been shown that, although the number of unprotected sexual contacts with an infected partner is indeed associated with the probability of infection (1, 2), the association is not well described by a model assuming a constant per-sex-act infectivity (1–6).

Both epidemiologic studies (7) and virologic studies of plasma (8, 9) and genital secretions (10–14) have found strong indications that infectiousness is higher in the advanced stages of HIV infection. Suggestions that infectivity may also be increased during the brief primary phase following infection are supported by the high female-to-male per-sex-act probability of HIV transmission estimated for female prostitutes early in the epidemic in Thailand (15). High levels of viremia have been found in plasma (16) and HIV has been detected in semen (17) of subjects with symptomatic primary HIV infection. However, increased shedding of HIV in semen prior to seroconversion has not yet been demonstrated (18).

We developed a probabilistic model, based on an approach proposed by Longini et al. (19), that allows infectivity to vary within couples, throughout the course of HIV infection, and between couples, according to the sex of the initially infected individual (index case) and to the type of sexual contact with the susceptible partner. The model, which handles left-censoring and can therefore be used when the date of

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Abbreviations: AIDS, acquired immunodeficiency syndrome; CD4+, CD4-positive; HIV, human immunodeficiency virus; STD(s), sexually transmitted disease(s).

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infection of the index case is unknown, was fitted to data from the European Study on Heterosexual Transmission of HIV (20–22). This approach is of particular interest in assessing whether infectivity is increased in the early infection period, since direct epidemiologic evidence concerning this stage is not easily obtainable.

MATERIALS AND METHODS

Population

From March 1987 to June 1992, 13 research centers in nine European countries participated in a study of heterosexual transmission of HIV. Details on the study design have been provided elsewhere (1, 20–22). Briefly, couples composed of HIV-infected men or women (index cases) and their regular heterosexual partners (contact partners) were included in the study, unless the contact partner had risk factors for HIV infection other than sexual contacts with the index case. The two partners were interviewed separately regarding their history of risk factors for HIV infection, frequency of sexual contacts, condom use, and sexual practices. If the partners gave differing descriptions of their sexual behavior, the couple was excluded from the study. Information on the clinical status and lymphocyte count of the index case was obtained upon inclusion. The HIV serologic status of the contact partner was determined by enzyme-linked immunosorbent assay and was confirmed by Western blot or radioimmunoprecipitation. The present analysis was based on couples included in the European study who did not report systematic use of condoms and for whom the information necessary for our model was complete.

Analytical methods

Three successive stages of HIV infection were defined: the primary phase of infection (the "seroconversion period"), the subsequent asymptomatic stage, and the advanced stage (clinical symptoms related to HIV infection or a CD4-positive (CD4+) T lymphocyte count less than 200/mm^3). The direction of transmission (male-to-female or female-to-male) was taken into account. Because anal intercourse has been shown to increase the risk of male-to-female transmission (7, 21, 23) and sexual intercourse during menses has been reported to increase the risk of female-to-male transmission (21), such contacts were designated "type 2" contacts (as opposed to "type 1" contacts) and the proportions of type 1 and type 2 contacts reported by the couple were taken into account.

For a given type of unprotected contact and for a given direction of transmission, the per-sexual-contact probability of HIV transmission (infectivity) was assumed to be constant within each of the three stages; it was denoted, respectively, by μ_1, μ_2, and μ_3 for type 1 contacts and by μ_1', μ_2', and μ_3' for type 2 contacts. For each couple, the numbers n_j of sexual contacts in stage j (j = 1, 2, 3) could be estimated for given (or assumed) dates of infection (t_1), seroconversion (t_2), and entry of the index case into stage 3 (t_3), according to the dates of first and last sexual contact between the couple prior to the contact partner's serologic analysis and to the reported frequencies of unprotected sexual contact before and after the index case's diagnosis of HIV infection (figure 1).

For index cases who had not reached stage 3 at the time of data collection, n_3 was set at zero. Otherwise,

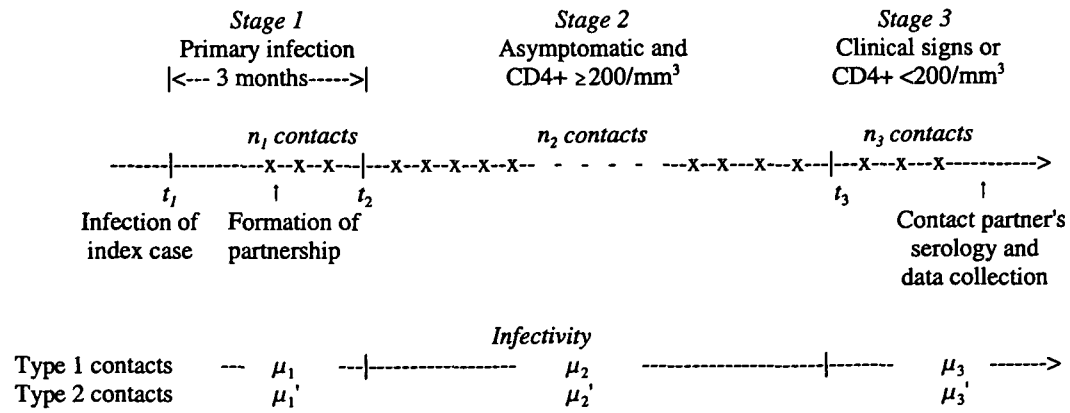

FIGURE 1. Model of human immunodeficiency virus (HIV) infectivity, European Study on Heterosexual Transmission of HIV, 1987–1992. For each couple, the infectivity of the index case (μ_j) was assumed to be constant within each of three successive stages. The number (n_j) of sexual contacts in each stage was estimated according to the (assumed) dates of the index case's infection (t_1), seroconversion (t_2 = t_1 + 3 months), and entry into the advanced disease stage (t_3), and according to the dates of first and last sexual contact between the couple. All possible dates of infection were considered and included in a probabilistic model (see text). Type 2 contacts were defined as penile-anal contacts (male index case) and sex during menses (female index case); other contacts are of type 1. (CD4+, CD4-positive T lymphocyte count).

t_3 was calculated as the earlier of two alternative dates: 1) the estimated time at which the CD4+ cell count fell below 200/mm^3 (determined by linear interpolation from available data on CD4+ cell count, assuming a constant rate of decline of 10.8 CD4+ cells/mm^3 per month in subjects with CD4+ cell counts below 200/mm^3 (24, 25)) and 2) the estimated time at which clinical symptoms appeared (obtained using estimates of median survival time after AIDS diagnosis (17 months (26)) and of median waiting time during the symptomatic period before development of AIDS (25 months (27))). (Note that, since index cases were recruited before June 1992, few are likely to have received antiretroviral treatments before being diagnosed with AIDS.)

The time t_2 at which the index case reached stage 2 was assumed to be 3 months after the time of infection (t_1). The choice of 3 months was motivated by a suggested typical course of early HIV infection (16), and is compatible with an estimated median duration of 2.4 months between HIV infection and first detection of HIV antibody (28). However, for assessment of the sensitivity of the results to the assumed duration of stage 1, the model was also fitted with durations of 2 months and 6 months.

The date of infection (t_1) was unknown for most index cases (91 percent). Because of the great variability in the duration of the asymptomatic period, it was not reasonable to estimate a single date of infection for each index case. Therefore, a series of possible dates t_1 was defined for each index case. Assuming that very few infections occurred in Europe before 1981, and using a time scale of months, possible dates were taken as each month from January 1981 (corresponding to $t_1 = 1$) to the month (τ) of inclusion in the study. This range was restricted if the index case was known to have been infected within a shorter period.

For each possible date t_1, the probability that the index case was indeed infected at t_1 given his/her CD4+ cell count at time τ was determined using estimates of the probability $p_{1k}(t_2,\tau)$ that an individual who seroconverted at time t_2 would have a CD4+ cell count in a given range (stage k) at time τ, obtained from published estimates (25) of rates of progression of infective persons through stages of a Markov model for the decline in CD4+ cell count (figure 2). Using Bayes' theorem, and assuming that the unconditional probability of infection at time t_1 is proportional to the prevalence $h(t_1)$ of HIV infection in the population, the (inverse) probability that a subject who is in stage k at time τ was infected at time t_1 (seroconverted at time t_2) is given by

$$\Pr(\text{index infected at time } t_1/\text{CD4}) = p_{1k}(t_2,\tau) \times h(t_1)/\sum_{1\le u\le \tau} p_{1k}(u+3,\tau) \times h(u). \quad (1)$$

For each year, country, and transmission group, estimates of HIV prevalence obtained by back-calculation (29) were used. Since only relative prevalences are effective in equation 1, only the shapes—and not the estimated absolute levels—of the HIV prevalence curves $h(u)$ are relevant.

The probability that the contact partner i would be seropositive at the time of data collection (τ) was formulated by associating with each possible date t_1 the probability that the index case i was indeed infected at t_1 given his/her CD4+ cell count at time τ, and the conditional probability that the contact partner would be seropositive given the numbers $n_{ji} = n_{ji}(t_1,t_2,t_{3i})$ of sexual contacts that the couple would have had in each stage j since t_1:

$$\Pr(Y_i = 1) = \Pr(\text{contact } i \text{ seropositive at time } \tau) = \sum_{1\le t_1\le \tau} [\Pr(\text{index}_i \text{ infected at time } t_1/\text{CD4}_i) \times \Pr(Y_i = 1/n_{ji})], \quad (2)$$

where $Y_i = 1$ if the contact partner is seropositive at the time of data collection and 0 otherwise. $\Pr(Y_i = 1/n_{ji})$, the probability that the partner would be

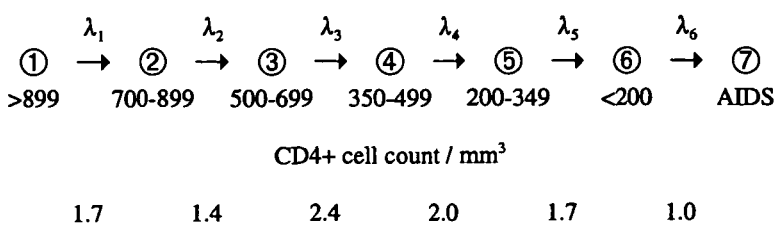

FIGURE 2. Model of human immunodeficiency virus (HIV) disease progression, European Study on Heterosexual Transmission of HIV, 1987–1992. Index cases were modeled to progress through seven stages of HIV infection defined by CD4-positive (CD4+) T lymphocyte count (25). λ_k is the monthly rate of progression from stage k to stage $k + 1$, and $1/\lambda_k$ is the estimated mean waiting time (years) spent in stage k. Estimates of λ_k based on data from the San Francisco Men's Health Study (25) were used. (AIDS, acquired immunodeficiency syndrome).

infected if the couple had n_{1i}, n_{2i}, and n_{3i} sexual contacts in stages 1, 2, and 3, respectively, with a proportion α_i of type 2 contacts, is given by

$$\Pr(Y_i = 1/n_{ji}) = 1 - (1 - \mu_1)^{(1-\alpha i)\,n1i} \times (1 - \mu_1')^{\alpha i\, n1i} \times (1 - \mu_2)^{(1-\alpha i)\,n2i} \times (1 - \mu_2')^{\alpha i\, n2i} \times (1 - \mu_3)^{(1-\alpha i)\,n3i} \times (1 - \mu_3')^{\alpha i\, n3i}. \quad (3)$$

Maximum likelihood estimates of infectivity in each stage (μ_1, μ_2, μ_3 and μ_1', μ_2', μ_3') were obtained using the BMDP program AR (BMDP Statistical Software, Inc., Los Angeles, California; 1990 version). For couple i, the likelihood contribution is given by

$$L_i = \{\Pr(Y_i = 1)\}^{Yi} \times \{1 - \Pr(Y_i = 1)\}^{1-Yi}, \quad (4)$$

where $\Pr(Y_i = 1)$ is obtained from equation 2 together with equations 1 and 3.

Estimates were constrained to be positive and less than 1. Because confidence intervals estimated by means of the likelihood ratio statistic were similar to those obtained by simply adding and subtracting two standard deviations, only standard deviations are given in the results shown here. The significance of the difference between estimates of infectivity by direction of transmission, by type of contact, or by stage was assessed via the likelihood ratio test. Various alternative models in which certain parameters were constrained to be equal were investigated in an attempt to determine the simplest model (with the fewest parameters) that fitted the data as well as the full model (i.e., with no significant decrease of likelihood).

RESULTS

Among a total of 645 couples enrolled in the European study, 120 were excluded from the present analysis because of incomplete data and 26 because of systematic condom use. Comparison of included and excluded couples revealed no significant differences with regard to mode of infection of the index case, history of sexually transmitted disease (STD), age of the index case or the contact partner, duration of relationship, or frequency of sexual contacts. Condom use was not associated with frequency of intercourse. Since, for index cases with AIDS, CD4+ cell count was not necessary to define the disease stage in the Markov model, the proportion of index cases in stage 3 was higher among couples included in the analysis than in couples excluded due to missing information. The proportion of HIV-infected partners was higher (19 percent) in couples that were included than in those excluded (11 percent) ($p < 0.05$). However, among couples with an index case in stage 3, this proportion did not differ between included and excluded couples (32 percent vs. 26 percent; $p > 0.10$).

Characteristics of the 499 couples included in the analysis are shown in table 1. A majority of index cases (66 percent) had been infected through intravenous drug use. Overall, 71 percent presented no clinical symptoms and had a CD4+ cell count above 200/mm^3 (stage 2). Anal sex was reported by 20 percent of the 359 couples with a male index case, and the proportion α of anal contacts, determined by the questionnaire responses, ranged between 0 and 0.8. Sex during menses was reported by 36 percent of the 140 couples with a female index case, and the proportion of such contacts ranged between 0 and 0.25. A history of STD was reported by 46 percent of the couples.

Table 2 presents estimates of infectivity by stage of infection of the index case, direction of transmission, and type of contact.

For male-to-female transmission, the full six-parameter model fitted better than the model that did not take into account the type of contact (likelihood ratio statistic (3 df) = 33.6 ($2 \times [228.38 - 211.58]$); $p < 0.01$). For vaginal contact, stage-specific estimates of infectivity ranged between 0.0005 and 0.0008. For anal sex, infectivity estimates were much higher and were almost eight and 20 times higher in stages 1 and 3, respectively, than in stage 2. The full six-parameter model did not fit the data significantly better than a simpler three-parameter model which assumed 1) constant infectivity throughout the infection period for vaginal contacts (i.e., $\mu_1 = \mu_2 = \mu_3$) and 2) no difference between infectivity in stages 1 and 3 for anal contacts (i.e., $\mu_1' = \mu_3'$). These results (table 3) suggest that male-to-female infectivity via vaginal sex is relatively low and varies little throughout the course of infection, whereas infectivity via anal sex is significantly higher at any stage, particularly when the index partner has been infected for less than 3 months or is in the advanced stage of infection. Assuming alternative durations of 2 and 6 months for stage 1, the same three-parameter model again fitted the data as well as the full model, and infectivity was again estimated to be significantly lower in stage 2 (table 3).

For female-to-male transmission (table 2), infectivity in stage 1 could not be satisfactorily estimated (the lower boundary limit was attained). Infectivity was estimated to be about 10 times higher in stage 3 than in stage 2. However, the hypothesis of constant infectivity (H_0: $\mu_1 = \mu_2 = \mu_3$) could not be rejected (disregarding type of contact, likelihood ratio statistic

TABLE 1. Characteristics of study couples according to the sex of the index case: European Study on Heterosexual Transmission of HIV, 1987–1992

	Female index case (n = 140)			Male index case (n = 359)		
	%	No.	Mean	%	No.	Mean
Mode of infection of index case						
Intravenous drug use	65.0	91		66.0	237	
Heterosexual contact	23.6	33		10.0	36	
Homosexual contact	0.0	0		15.9	57	
Transfusion recipient	6.4	9		3.3	12	
Hemophilia patient	0.0	0		2.2	8	
Unknown	5.0	7		2.5	9	
Index case in infectivity stage 3*	26.4	37		30.1	108	
Index case with AIDS†	15.0	21		15.3	54	
Age of index case (years)			28.5 (6.0)‡			30.1 (8.0)
Age of partner (years)			32.9 (8.8)			28.0 (7.8)
Duration of relationship (months)			29.5§			36.0§
Frequency of sexual contacts (no./week)			3.3 (2.2)			2.9 (2.2)
Couples with "type 2" sexual practices¶	36.4	51		20.1	72	
Couples with a history of STD† in the index case or partner (since 1980)	50.7	71		44.8	161	
Partner positive for human immunodeficiency virus	11.4	16		21.7	78	

* Stage 3: clinical symptoms related to human immunodeficiency virus infection or CD4-positive T lymphocyte count less than 200 cells/mm³.
† AIDS, acquired immunodeficiency syndrome; STD, sexually transmitted disease.
‡ Numbers in parentheses, standard deviation.
§ Median.
¶ Couples who reported engaging in anal sex (male index case) or sex during menses (female index case).

TABLE 2. Estimated human immunodeficiency virus infectivity (μ_j), by stage of infection in the index case, direction of transmission, and type of contact: European Study on Heterosexual Transmission of HIV, 1987–1992

Direction of transmission and type of contact	$\mu_j \times 1{,}000$				$\mu_j \times 1{,}000$	
	Stage 1	Stage 2	Stage 3	−log likelihood	Any stage	−log likelihood
Male-to-female						
Vaginal intercourse	0.8 (1.3)*	0.7 (0.1)	0.6 (0.5)	211.58	0.7 (0.1)	214.65
Anal intercourse	126.1 (91.7)	16.7 (10.9)	321.3 (225.3)		33.8 (7.8)	
Any type	2.9 (1.6)	0.9 (0.2)	1.3 (0.7)	228.38	1.0 (0.1)	229.19
Female-to-male						
Outside of menstrual period	—†	0.3 (0.2)	3.1 (2.2)	50.96	0.4 (0.1)	52.39
During menstrual period	—	0.9 (2.5)	6.3 (38.4)		1.9 (2.6)	
Any type	—	0.4 (0.1)	3.5 (2.4)	50.81	0.5 (0.1)	52.55
Any direction						
Any type	2.2 (1.3)	0.7 (0.1)	1.5 (0.7)	285.10	0.9 (0.1)	286.13

* Numbers in parentheses, standard error × 1,000.
† Lower boundary limit attained.

TABLE 3. Stage-specific estimates* of infectivity (μ_j) for male-to-female transmission of human immunodeficiency virus using three alternative durations of infectivity stage 1: European Study on Heterosexual Transmission of HIV, 1987–1992

Duration of stage 1† and type of contact	$\mu_j \times 1{,}000$			
	Stage 1	Stage 2	Stage 3	−log likelihood
3 months				
Vaginal intercourse	0.7 (0.1)‡	0.7 (0.1)	0.7 (0.1)	212.14
Anal intercourse	183.5 (83.0)	13.8 (10.2)	183.5 (83.0)	
2 months				
Vaginal intercourse	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	211.55
Anal intercourse	246.0 (115.9)	14.6 (10.2)	246.0 (115.9)	
6 months				
Vaginal intercourse	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	213.59
Anal intercourse	106.8 (47.1)	14.3 (10.3)	106.8 (47.1)	

* The simplest model that fitted the data was used.
† The seroconversion period (see text).
‡ Numbers in parentheses, standard error × 1,000.

(2 df) = 3.48 (2 × [52.55 − 50.81]); $0.10 < p < 0.20$).

Because μ_1 could not be estimated for female-to-male transmission, comparison between male-to-female and female-to-male transmission was based on estimates from the constant infectivity model (i.e., taking into account neither the type of contact nor the stage of the index case) (table 2). Under these simplifying assumptions, male-to-female infectivity was found to be significantly higher than female-to-male infectivity (0.001 vs. 0.0005; likelihood ratio statistic (1 df) = 8.78 (2 × [286.13 − (52.55 + 229.19)]); $p < 0.01$). However, the estimate of infectivity in stage 3 (all types of contacts combined) was in fact higher for female-to-male transmission than for male-to-female transmission (0.0035 vs. 0.0013), although the difference was not statistically significant.

DISCUSSION

To investigate the variability of per-sexual-contact infectivity according to disease stage and type of sexual contact, we developed a probabilistic model which copes with the problem of unknown dates of infection in partner studies.

In its simplest form (with infectivity assumed to be constant), the model yielded estimates of infectivity that were slightly higher than those obtained in a previous analysis of the same data (1). In that analysis, infectivity was almost certainly underestimated, because all unprotected sexual contacts occurring since 1981 carried the same risk of HIV transmission, regardless of the probability that the index case was actually infected (0.001 vs. 0.0005 for male-to-female transmission and 0.0005 vs. 0.0003 for female-to-male transmission). Our estimates of male-to-female infectivity lie in the range of those found in North American partner studies under the constant infectivity hypothesis (5, 23). In contrast, much higher estimates of female-to-male infectivity (>0.01) have been reported from studies of female prostitutes and their clients in Thailand (15) and in Kenya (30). However, high prevalences of STD(s) among prostitutes and, in Thailand, the recent nature of the epidemic (with many prostitutes being in the primary infection phase) (15) are believed to have contributed to the high infectivity in these populations. Moreover, as was pointed out elsewhere (1, 15), estimates from prostitute studies are not directly comparable with those obtained in studies of regular partnerships. Our results are in agreement with the increased risk of transmission from infected men as compared with women reported in several studies (7, 21, 23) and with many findings of increased risk of male-to-female transmission in couples reporting anal sex (7, 21, 23).

Since most published estimates have been obtained while assuming a constant infectivity, our results concerning variability throughout the course of infection are more difficult to assess. When neither direction of transmission nor type of contact was taken into account, infectivity was estimated to be higher in early- and late-stage infection than in the intervening asymptomatic period. Applying a four-stage model to data on 45 male and female heterosexual partners of persons with AIDS, Longini et al. (19) estimated infectivity to be very low in asymptomatic patients (approximately equivalent to our stage 2) and high in patients with AIDS, but they could not estimate infectivity in the primary phase of infection; our estimate of 0.0015 for

stage 3 lies between their estimates for subjects with "pre-AIDS" symptoms (0.0007) and subjects with AIDS (0.057). Other models proposed for assessment of the variability of infectivity (31) are based on time since infection of the index case and do not explicitly take into account disease progression.

For male-to-female transmission, infectivity through penile-anal sex was found to be higher in both early- and late-stage infection than in the intermediate asymptomatic stage, as has also been suggested (32) by combining results from heterosexual studies with estimates of per-anal-contact infectivity in the primary infection phase (0.05–0.30) obtained from epidemic modeling among homo-/bisexual men. No significant differences were found, however, between stage-specific infectivities for penile-vaginal sex. While this result may reflect a true lack of variability, alternative explanations should be considered. Cofactors not taken into account, such as the susceptibility of the contact partner or the presence of STD in one or both of the partners, may have interacted to produce an apparently constant infectivity. An alternative hypothesis is that the risk of male-to-female transmission associated with anal intercourse was so high (46 percent of female partners who reported anal intercourse were infected vs. 16 percent of others) that infectivity through a single non-anal contact was estimated to be very small and we had insufficient power to detect variability related to a much lower risk. Two small studies which had indirect information on contacts occurring during the primary phase of infection were also unable to demonstrate a significantly increased risk of HIV infection among women exposed during the seroconversion period (33, 34), although in one study (34) the rate of transmission was higher among couples who resumed sexual activity within 60 days of an infecting transfusion than in others. For female-to-male transmission, infectivity in the early infection period could not be satisfactorily estimated, probably because of the scant information on contacts occurring during this very short period (19).

Potential sources of error and uncertainty concern the nature of the data and the assumptions of the model. The continuous-time Markov process used to model index cases' progression through six stages of CD4+ cell count (in order to assign probabilities to possible infection dates) is believed to provide a good description of HIV disease progression (24) and yielded a mean duration of 10.2 years from seroconversion to AIDS, a result that is in good agreement with those from numerous cohort studies (25).

Although the reliability of retrospectively collected data on sexual behavior may be questionable, the exclusion of couples that gave discordant replies should have reduced the measurement error associated with reported frequencies of sexual intercourse, anal sex, and condom use. Unfortunately, no data were available for these couples or for those excluded from the study because the contact partner had other risk factors for HIV transmission. As compared with couples excluded from the present analysis because of missing information, both the proportion of index cases in stage 3 and the proportion of HIV-infected partners were higher among the included couples. However, among couples with an index case in stage 3, the proportion of HIV-infected partners did not differ significantly between included and excluded couples, and the results are therefore unlikely to be biased toward an overestimation of infectivity in stage 3.

Details on sexual behavior both before and after diagnosis of HIV infection were obtained. However, if the frequency of sexual intercourse decreased further when the index partner became more seriously ill, the numbers of contacts in stage 3 could have been overestimated. This would have resulted in an underestimation of stage 3 infectivity and could be an additional reason for the lack of significant difference between stage 2 and stage 3 infectivities for penile-vaginal contacts. In comparison with the long asymptomatic period, our data provided less information on contacts occurring in stage 1 (a much shorter period) or stage 3 (a shorter period and one which most index cases had not yet reached). Infectivity was therefore estimated with higher confidence in stage 2. Estimates of stage 1 infectivity are sensitive to the assumed duration of this stage (estimates decreased as assumed duration increased). Nevertheless, even with a first stage of 6 months, the estimate of male-to-female infectivity for anal sex was as much as four times higher in the early stage than in the following asymptomatic stage.

Potential heterogeneity of infectivity between couples was partly allowed for by distinguishing both the direction of transmission and the type of contact. Although, in the European study, an older age of the female contact partner and a history of STD were associated with higher rates of HIV transmission (21), we were unable to assess the influence of either of these factors, since only 5 percent of the female contact partners were over age 45 years and the timing of the STD episode(s) was unknown. Since neither the proportion of index cases in stage 3 nor reported anal sex was associated with a history of STD, the differences found between stages and between types of contact are unlikely to be due to confounding effects of STD. Infectivity could not be satisfactorily estimated when the analysis was restricted to couples without a history of STD (boundary limits were attained) or to couples with a history of STD (conver-

gence criteria were not satisfied).

Other factors which may influence the risk of transmission include genotypic HIV subtype (35), male circumcision (36), antiretroviral treatment (9, 12, 37), and heterogeneity in the susceptibility of contact partners to HIV (38, 39). No data on viral subtype, circumcision, or treatment were available in our study. However, among these Europeans, the virus was probably mostly subtype B and male circumcision was probably infrequent; in addition, since the data were collected before mid-1992, few index cases are likely to have been treated before they developed AIDS, and none are likely to have received bimodal or trimodal therapy. Nevertheless, if some index cases were actually less infectious because of treatment (mainly in the late phase of disease progression), our estimates could be biased toward an underestimation of infectivity in untreated advanced-stage disease. The implementation of a more complex model designed to assess the effects of variable susceptibility among the contact partners would require a much larger data set. Finally, we emphasize that our estimates were obtained from monogamous stable partnerships and are not appropriate for modeling the risk of HIV transmission to a susceptible individual from a randomly chosen infected partner.

In agreement with the findings of virologic studies (8–14, 16, 17), HIV infectivity was estimated to be higher in the months following infection and in the advanced stage of disease than in the longer intermediate period, at least for penile-anal contacts. Although we failed to show significant differences in stage-specific infectivity for vaginal intercourse, infectiousness may nevertheless vary over the infection period, whatever the type of contact. Furthermore, although a single penile-vaginal contact seems to carry a much lower risk of infection than a single penile-anal contact, the cumulative risk of infection through repeated acts of non-anal intercourse remains considerable, since such contacts predominate even among couples who indulge in anal intercourse.

Because most individuals are unaware of their HIV status during the seroconversion period, prevention efforts targeted toward recently infected individuals are difficult to implement. Thus far, the issue has received very little attention. However, because of the clinical importance of early detection of HIV infection (the poor prognosis associated with symptomatic primary infection and the possibility of eradicating the virus by treating patients during the primary phase), more and more patients are now being diagnosed during this phase. Besides offering medical care, health professionals should strongly recommend safer sex to individuals who may be in the process of seroconverting (subjects who have symptoms possibly related to primary infection or are reporting potential exposure to HIV infection).

Since treatment may reduce infectivity, treating subjects in the primary stage of infection may have important public health implications. At a population level, an epidemic will develop only if the basic reproduction number (i.e., the average number of secondary cases an infective person gives rise to) is greater than 1, and it has been shown that the subsequent size and scope of an epidemic is largely determined by the initial spread (32). Higher infectivity during the primary phase of infection therefore underlines the great importance of reacting early in emerging epidemics, when most infected individuals have been infected recently.

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