PAPERS

Risk factors for male to female transmission of HIV

European Study Group

Abstract

Objective—To identify risk factors for sexual transmission of HIV from infected men to their female sexual partners.

Design—Cross sectional analysis as part of a continuing study. Data were obtained by interviewing heterosexual couples in which the man was infected with HIV. Risks were assessed by comparing couples in which transmission had occurred (woman infected with HIV) with those in which it had not (woman not infected) and estimated by independent odds ratios and their 95% confidence intervals.

Setting—Infectious disease and public health departments from nine centres in six European countries.

Participants—153 Male index patients (mean age 30·4 years) and their 155 female partners (mean age 27·8 years).

Interventions—Women were tested to determine their HIV antibody state. Women with a risk of infection with HIV other than sexual contact with their infected partner were excluded.

End point—Three risk factors for male to female transmission of HIV.

Measurements and main results—Three risk factors were identified: a history of sexually transmitted disease in the previous five years for the female partner (odds ratio 3·1, 95% confidence interval 1·1 to 8·6); index patient with full blown AIDS (5·4, 1·2 to 25·2); and practice of anal intercourse (5·8, 2·3 to 14·8). The proportion of women positive for HIV antibody was 27% (42/155), ranging from 7% (1 to 13%) (4/60) for couples with none of the three risk factors to 67% (45 to 89%) (12/18) for those with two or three of the risk factors. Duration of the relationship (median three years), frequency of sexual contacts, sexual practices other than anal intercourse, and contraceptive behaviour were not associated with infection of the partner.

Conclusions—The risk of sexual transmission of HIV from an infected man to his female partner varies considerably according to the characteristics of the couple. The differences in rates of transmission in high risk groups may be considerably reduced if the risk factors are taken into account during individual and public health counselling.

Introduction

A full list of participating centres and investigators is given at the end of this paper

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In Africa the main route of transmission of HIV is by heterosexual contact.[1] In Europe most cases of AIDS still occur among homosexual men.[2] Nevertheless, the sharp increase in the number of cases of AIDS among European heterosexual intravenous drug users is a key link for the spread of HIV to the heterosexual population and to children through transmission from their mothers.[3]

Since 1983 both male to female and female to male transmission of HIV has been well described.[4] Several important questions about transmission, however, remain unsolved. The aims of the present, continuing study are to identify risk factors for heterosexual transmission (factors associated with infectivity of people positive for HIV, susceptibility of the host, and sexual behaviour); to compare the relative efficacy of male to female and female to male transmission; and to assess the effectiveness of counselling offered to each partner in a couple.

We present here the first results of a European study undertaken in several centres because of the small numbers of cases of heterosexually acquired HIV infection in each country. This report analyses the risks of male to female transmission. Because of the considerable differences between the behavioural and clinical characteristics of couples in which the index patient was male and those in which the index patient was female and because of the small number of female index patients results on female to male transmission will be presented when more data are available.

Patients and methods

Since March 1987 nine centres from six countries (see table I) of the European Community have been participating in this study. After their informed consent has been obtained patients infected with HIV and their heterosexual partners are recruited from hospital wards, outpatient clinics, and local public health departments (HIV screening centres, drug treatment centres). The index patient (the first infected) is defined as a patient positive for HIV antibody with a known risk of HIV infection (intravenous drug user, bisexual, resident in an endemic country, transfusion recipient, haemophiliac, heterosexual partner of a patient known to be infected with HIV). The contact partner is defined as a person of the opposite sex who has had at least one sexual contact with the index patient within the past year. In four couples who had lived in endemic countries (Africa and Haiti) both partners were positive for HIV antibody; the men were considered to be the index patients because they reported extraconjugal sexual relationships whereas their regular partners did not.

Participants are interviewed individually on entry to the study, and contact partners negative for HIV antibody are followed up every six months. In most cases described here (130/155) both partners were interviewed on the same day. To ensure consistency the number of interviewers is limited to one or two in each centre. Subjects are questioned about risk factors for HIV infection; history of sexually transmitted diseases in the previous five years; and number of sexual partners for various periods (lifetime, previous five years, previous six months). Contraceptive behaviour (including use of condoms) and sexual practices both before and after diagnosis of HIV infection in the index patient are also investigated. Current HIV antibody state is determined by enzyme

TABLE I—*Characteristics of 155 couples (153 male index patients and their 155 female partners) and prevalence of HIV-1 antibody among female partners*

	No of couples	No (%) of partners infected		No of couples	No (%) of partners infected
Centre of enrolment:			**Clinical status of index patient:**		
Bologna	33	5 (15)	No symptoms	68	12 (18)*
Athens	32	12 (38)	Lymphadenopathy syndrome or		
Paris	28	12 (43)	AIDS related complex, or both	59	16 (27)
Milan	17	4 (24)	AIDS	19	10 (53)
Creteil	15	5 (33)	Unknown	7	
Amsterdam	13	0 (0)	Total lymphocyte count for index patient ($\times 10^9$/l):		
Madrid	11	3 (27)	≤0·8	9	5 (56)†
Berlin	3	0 (0)	−1·5	21	7 (33)
Barcelona	3	1 (33)	−2·5	62	15 (24)
Risk group of index patient:			>2·5	19	3 (16)
Intravenous drug user	92	20 (22)*	Unknown	42	
Bisexuals	33	11 (33)	T4 lymphocyte count for index patient ($\times 10^9$/l):		
Transfusion recipients	7	1 (14)	≤0·15	15	8 (53)†
African or Caribbean	5	4 (80)	−0·3	17	5 (29)
Heterosexual	13	3 (23)	>0·3	74	16 (2)
Unknown	3		Unknown	47	
Age of male patient:			**History of sexually transmitted disease**		
≤25	41	5 (12)	**in past five years:**		
26-35	82	26 (31)	For index patient:		
>35	27	8 (30)	No	86	17 (20)‡
Unknown	3		Yes	59	19 (32)
Age of partner:			Unknown	8	
≤25	74	17 (23)	For partner:		
26-35	57	19 (33)	No	120	28 (23)*
>35	24	6 (25)	Yes	35	14 (40)
No of sexual partners during past five years:			**History of hepatitis B in past five years**		
For index patient:			**for the index patient:**		
0	21	6 (29)	No	75	20 (27)
1-3	34	5 (15)	Yes	70	16 (23)
≥4	82	21 (26)	Unknown	8	
Unknown	16		**Anal intercourse:**		
For the partner:			Never	107	17 (16)*
0	59	15 (25)	At least once	48	25 (52)
1-3	62	17 (27)	**Oral sex:**		
≥4	32	10 (31)	Fellatio:		
Unknown	2		Never	25	3 (12)
Duration of sexual relationship (years):			At least once	130	39 (30)
≤1	43	11 (26)	Cunnilingus:		
-3	44	11 (25)	Never	24	5 (21)
-7	37	11 (30)	At least once	131	37 (28)
>7	31	9 (29)	**Intercourse during menses:**		
No of sexual contacts/week:			Never	77	16 (21)
≤1	34	10 (29)	At least once	78	26 (33)
2-3	56	16 (27)	**Ejaculation during vaginal intercourse:**		
≥4	65	16 (5)	≤Half of the time	59	16 (27)
Contraceptive behaviour:			Most of the time or always	96	26 (27)
No contraceptive	20	5 (25)			
Oral contraceptive	47	15 (2)			
Intrauterine device	15	6 (40)			
Shield	4	1 (25)			
Condom	11				
Ejaculation during vaginal intercourse avoided	32	8 (25)			
Ligation of genital tubes	3	1 (33)			
Other	23	6 (26)			

*χ^2: $p \leqslant 0.05$. †χ^2 for trend, $p<0.05$. ‡χ^2, $p<0.10$.

linked immunosorbent assay (ELISA) and confirmed by western blotting or radioimmunoprecipitation in the laboratories of the participating centres. Total, T4, and T8 lymphocyte counts in the index patient are also recorded. Clinical state according to the Centers for Disease Control's classification[5] is obtained from medical records. To improve the consistency of the data all of the investigators from participating centres meet every six months. The completed questionnaires are checked and revised with information obtained from interviewers. Analysis is undertaken in the Paris centre.

By May 1988, 224 couples had been enrolled (161 male index patients with their 163 female partners). An index patient with two partners was considered to be two independent couples. Eight women who had a risk factor for HIV infection other than sexual contact with the index patient were excluded. Seven of these women had used intravenous drugs in the previous five years, and one reported a previous regular heterosexual partner originating from west Africa. Thus male to female transmission was analysed from the data from the first interview for 155 couples. Couples with the same antibody state (both positive for HIV) were compared with couples in which only the index patient was positive for HIV. For multivariate analysis of specific risk factors for transmission eight of the 155 couples, who knew that the man was positive for HIV

antibody and had always used condoms since the first sexual contact to prevent transmission of HIV, were also excluded. (All eight female partners were negative for HIV antibody.)

χ^2 Tests and the χ^2 test for trend were used for statistical analyses. Odds ratios with their 95% confidence intervals were calculated by the method of Cornfield.[6] Mean (SEM) values are given for quantitative variables. Multivariate analyses were computed by logistic regression.

Results

CHARACTERISTICS OF THE STUDY POPULATION

Most of the index patients were intravenous drug users (92) or bisexual (33) (table I). The mean (SEM) age was 30·4 (0·6) years for the index patients (range 18 to 56) and 27·8 (0·6) years for their partners (18 to 54). Both the women positive and those negative for HIV antibody had had a median of one sexual partner (other than the index patient) in the previous five years. The median duration of the couples' relationship was three years (range two months to >20 years).

RISK FACTORS AND RATE OF TRANSMISSION: UNIVARIATE ANALYSIS

The rate of male to female transmission was 27% (95% confidence interval 20 to 34) (42/155). Extreme

rates of transmission were observed in couples in which the index patient had received blood transfusions (14%) or was African or Caribbean (80%), but numbers were too small to be valid statistically.

The duration of the sexual relationship and the frequency of sexual contact were similar for couples in which both partners were HIV positive and those in which only the index patient was. No significant differences in contraceptive methods were found between women positive and negative for HIV antibody, although those with intrauterine devices had the highest rate of infection (40%). None of the 11 women who used condoms regularly for contraception or prevention of HIV infection was infected (Fisher test, users of condoms v others, p=0·03).

Couples were followed up to assess the efficacy of individual counselling in preventing transmission, particularly with respect to use of condoms. After at least six months' follow up none of the 26 partners who always used condoms during sexual contacts became positive for HIV antibody, but two of the 11 partners who did not use condoms regularly did become positive for the antibody.

The rate of transmission of HIV was greater for men with full blown AIDS (53%) than for those without symptoms (18%). Lymphocyte counts were available for 111 men. Total and T4 lymphocyte counts tended to be lower when transmission had occurred (χ^2 test for trend; p=0·03 and p=0·02 respectively). The risk of transmission was significantly increased when T4 lymphocyte counts were below $0·15\times10^9/l$ (odds ratio=4·1, 95% confidence interval 1·1 to 15·3). The same tendency was found for ratios of T4 to T8 cells, although the difference was not significant.

A recent history of a sexually transmitted disease was more common among men whose partners were infected with HIV (32% (19/59) v 20% (17/86), p=0·09). Women were more likely to be positive for HIV when they reported a history of sexually transmitted disease in the past five years (40% (14/35) v 23% (28/120), p=0·05). The sexually transmitted diseases reported were syphilis, gonorrhoea, chlamydiosis, candidiasis, genital ulcers, genital warts, trichomoniasis,and genital herpes. The part played by each sexually transmitted disease as a cofactor for transmission could not be assessed because of the small numbers of cases of each disease reported. To check that sexually transmitted diseases among the women were not related to extraconjugal sex we compared the history of such diseases in the women with that in their partners and the number of sexual partners (excluding the index patient) for women with and without a history of sexually transmitted disease. The median number of sexual partners in the previous five

	No (%) of couples in which both partners were positive for HIV (n=39*)	No of couples in which only index patient was positive for HIV (n=102*)
None of the three risk factors	4 (7)	56
History of sexually transmitted disease in partner	7 (26)	20
Male index patient with full blown AIDS	3 (43)	4
Anal intercourse	13 (45)	16
Two or three of the risk factors	12 (67)	6

*Clinical state was unknown for six index patients.

years was one in both groups of women. Except for candidiasis each sexually transmitted disease reported by a woman was also reported by her partner. Sexually transmitted diseases reported by the men, however, were not always reported by the women. A history of hepatitis B in the previous five years was reported by 70 men and was not correlated with higher rates of transmission. Only nine women reported a history of hepatitis B (four positive and five negative for HIV).

Anal intercourse was the only sexual practice clearly related to higher rates of transmission. Of the women who engaged in anal intercourse, 52% (25/48) were infected with HIV versus 16% (17/107) of those who had never practised anal intercourse.

After adjustment for anal intercourse, none of the other sexual practices (oral sex, sex during menses, number of ejaculations during vaginal intercourse) was linked to transmission of HIV.

MULTIVARIATE ANALYSIS OF FACTORS MOST HIGHLY CORRELATED WITH TRANSMISSION

The centre of enrolment was associated with the prevalence of HIV infection in the women and also with the sexual behaviour of the couple, the category of transmission of HIV, and the clinical state of the index patient. A high proportion (47%; 9/19) of index patients with full blown AIDS were recruited from French centres, anal intercourse was common in Greek couples (47%; 15/32), and most German and Dutch index patients did not have symptoms (63%; 10/16).

To estimate independent risks and to take into account the centre of enrolment multivariate analysis was performed by logistic regression. Table II gives the results. The clinical state of the index patient, anal intercourse, and a history of sexually transmitted disease in the woman were found to be associated independently with the risk of transmission. The risk associated with a history of sexually transmitted disease in the man was not significant (odds ratio=1·9; 95% confidence interval 0·8 to 4·8). None of the following variables improved the fit of the model: length of the relationship; frequency of sexual contacts; risk group of the index patient; and sexual practices other than anal intercourse.

Couples were classified according to the three risk factors identified during the analysis (table III). Couples either had none, one, or two or three of the risk factors (history of sexually transmitted disease in the woman, index patient with full blown AIDS, practice of anal intercourse). Table III shows the rates of transmission in these groups. The rates ranged from 7% (95% confidence interval 1 to 13%) (4/60) for couples with none of the risk factors to 67% (45 to 89%) (12/18) for couples with two or three of them.

Discussion

Men with full blown AIDS seem to be more infective than carriers without symptoms. A long relationship (and therefore a long exposure to the risk of trans-

	No of couples in which both partners were positive for HIV (n=42)	No of couples in which only index patient was positive for HIV (n=105)	Odds ratio (95% confidence interval)	Odds ratio adjusted by logistic regression* (95% confidence interval)
Clinical state of the patient:				
No symptoms	13	52	1·0	1·0
Lymphadenopathy syndrome or AIDS related complex, or both	16	42	1·5 (0·6 to 3·8)	1·3 (0·4 to 3·8)
Full blown AIDS	10	8	5·0 (1·4 to 17·7)	5·4 (1·2 to 25·2)
Unknown	3	3		
History of sexually transmitted disease in partner (past 5 years):				
No	28	85	1·0	1·0
Yes	14	20	2·1 (0·9 to 5·1)	3·1 (1·1 to 8·6)
Anal intercourse:				
Never	17	84	1·0	1·0
At least once	25	21	5·9 (2·5 to 13·9)	5·8 (2·3 to 14·8)

*Variables were centre of enrolment, clinical state of index patient, anal intercourse, history of sexually transmitted disease in the past five years for partner.

mission) may be a confounding factor. The clinical state of the carrier, however, remains a risk factor regardless of the duration of the relationship and the frequency of sexual contacts. Lymphocyte counts, although strongly linked to clinical state, are less predictive of transmission. These results are supported by the facts that viral cultures (mononuclear blood cells) are more often positive and T4 cell counts decrease when patients develop full blown AIDS (J K Nicholson et al and R W Coombs et al, fourth international conference on AIDS, Stockholm, 1988), but to our knowledge there are no reports that correlate the presence of HIV in cultures of sperm and the clinical state of infected men.

We found that a recent history of sexually transmitted disease, independently of extraconjugal sex, increased the susceptibility of women to infection. These results are supported by African studies, in which syphilis, genital ulcers, and gonorrhoea were implicated.[7-9] Although sexually transmitted diseases may simply be markers for sexual promiscuity, the associations persisted after adjustment for other factors of sexual behaviour, such as number of sexual partners. These findings are complemented by prospective studies of high risk subjects; seroconversion was found to occur more commonly in prostitutes from Nairobi who had had genital ulcers or chlamydiosis (F Plummer et al, fourth international conference on AIDS, Stockholm, 1988) and in American homosexuals who had been infected with herpes simplex virus type 2.[10] Several hypotheses have been put forward to account for the causal part that sexually transmitted diseases may play in the susceptibility of the host.[4] The most probable is that the mucosal epithelium is impaired. Other suggestions are that immunological modifications occur because of infection or that the number of target cells for HIV at the site of infection increase.

The only sexual practice that clearly increased the risk of male to female transmission was anal intercourse. To avoid a possible bias at interview (better reporting of sexual behaviour by women infected with HIV) we compared the answers of women who knew their HIV state at inclusion and those who did not. The results showed that anal intercourse was not reported more commonly by women who knew their HIV state (23%; 14/61) than by women who did not (30%; 11/37).

Receptive anal intercourse is a well known risk factor for transmission of HIV among homosexual men[11-13] and has been described as a risk factor in heterosexual couples by Padian et al.[14] In their study, as in the present one, anal intercourse was reported commonly by couples (30%), particularly when the index man was bisexual. Bisexuality of the index patient, however, was not a risk factor for transmission to the contact partner and therefore not a confounding factor. In two studies that did not find an increase in risk with anal intercourse the number of couples who engaged in anal intercourse was too small (2/55, 5/45) for statistically significant differences to be determined.[15 16]

No other sexual practices have been associated with the risk of transmission. Other epidemiological studies in homosexual[11-13] and heterosexual[14 15] populations failed to find any association between oral sex and transmission of HIV. Negative epidemiological results, however, must be interpreted carefully because oral sex is strongly associated with other sexual practices and therefore should be analysed only in couples who do not engage in anal intercourse. In our study, given the small number of these couples, the risk related to oral sex would have to be increased by at least a factor of three in order to be detected (power of the tests). This factor is obviously much higher than any possible true risk.

Neither the length of the sexual relationship nor the reported frequency of sexual contact was associated with efficacy of transmission. Adjustments for possible confounding factors, such as the clinical state of the index patient, anal intercourse, or risk group for the index patient, did not change the results. We were not able, however, to assess the date of infection for both the index patients (except for the seven who had had transfusions) and the women who were positive for HIV. Thus the duration of the relationship was an inexact estimate of the period of exposure. Among studies of heterosexual couples only one, carried out on partners of patients with HIV infection acquired by transfusion, had data on the date of infection with HIV in the index case.[15] Therefore estimates of the total number of potentially infectious sexual exposures were possible. Nevertheless, no association was found. These negative results could be due to the pooled analysis of couples with index patients of different infectivity. Indeed, the risk of transmission related to the number of high risk sexual exposures in some couples may have been masked by multiple low risk exposures in others.

In the present study the characteristics of couples in each participating centre differed, in particular with respect to the clinical state of the index patients and the practice of anal intercourse. Furthermore, hospital wards may have been more likely than health services to recruit couples in which both partners were HIV positive because doctors enrol couples by either the index patient or the infected partner whereas health services (Amsterdam, Berlin) enrol couples only by the index patient (intravenous drug users and prostitutes). When the three risk factors identified in this study were taken into account by multivariate analysis the differences in rates of transmission among the centres were sharply reduced.

The important part played by cofactors or mechanisms of transmission might account for the wide range of rates of transmission observed in studies on populations with different distributions of risk factors, including unidentified risk factors. Low rates of transmission among haemophiliacs, ranging from 7% to 14%, (J J Goedert et al, fourth international conference on AIDS, Stockholm, 1988)[17-19] and among men who have had transfusions (18%)[15] could be linked to low risk sexual behaviour (low prevalence of anal intercourse and coinfections of spouses).

These risk factors could also (at least in part) account for differences observed in rates of transmission from men to women and women to men. Further results of this continuing study may lead to a better understanding of the differences in levels of risk. In particular, changes in transmissibility, differences in the susceptibility of the host, and risks linked to other sexual practices, such as oral sex, may be determined more precisely.

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HIV infection in patients attending clinics for sexually transmitted diseases in England and Wales

Collaborative study by consultants in genitourinary medicine and the Public Health Laboratory Service

Abstract

A national study of the prevalence of HIV antibody designed to monitor sexual spread of HIV infection in England and Wales was made of homosexual and heterosexual patients attending sexually transmitted disease clinics in four districts in 1985, seven in 1986, and 14 in 1987. Patients were invited to participate and were counselled. Among homosexual men in two clinics in south east England, HIV antibody was found in 92 (12·9%) of 711 in 1985, 65 (15·2%) of 428 in 1986, and 81 (14·6%) of 556 in 1987: corresponding findings in the other regions were 16 (5·0%) of 321, 41 (6·3%) of 654, and 21 (3·1%) of 678. The prevalence of HIV antibody was higher in homosexual than bisexual men, in patients aged 25 years or more, or with one or more specified minor complaints. Among heterosexual patients in the south east in 1986, HIV antibody was found in seven (3·0%) of 230 men and three (1·3%) of 233 women and in 1987 in 10 (1·0%) of 962 men and seven (0·7%) of 949 women. In other areas corresponding findings in 1986 were two (0·2%) of 950 men and three (0·4%) of 752 women and in 1987 were three (0·06%) of 5312 men and one (0·02%) of 4778 women. All but one of the heterosexual patients with the antibody were intravenous drug abusers or had had sexual contacts in or were from an area abroad with a high prevalence of AIDS.

Failure to identify a heterosexual patient with HIV antibody not in a risk group (other than that of being an attender at the clinic) or who did not have a sexual partner in a risk group suggests that their prevalence in the patient population of the clinics in the south east is less than one in 700 and in the other regions less than one in 3000. Refusals to participate increased during the study but comparisons of patients who agreed and refused in terms of age, the presence of symptoms suggesting AIDS, travel abroad, and number of sexual partners a month showed little evidence of selective bias.

Introduction

All available means of assessing the extent of HIV infection in the general population have limitations.

Routine laboratory reports of the presence of HIV antibody reflect results of a self selected population. Ethical and legal restraints on HIV antibody testing without consent dictate that for special surveys testing is anonymous or voluntary, after counselling.[1] In anonymous studies subjects found to be positive cannot be informed nor can risk factors be investigated.[2] Voluntary studies that include a means of assessing non-compliance are an acceptable option.

The choice of group is clear, as the prevalence of HIV antibody in patients attending sexually transmitted disease clinics, who have had on average more sexual partners than the general population, should indicate the upper limit of prevalence in the general population and serve as an early warning system of the spread of infection.

This study was designed to estimate the prevalence of HIV antibody in these patients throughout England and Wales and is continuing.

Methods

Genitourinary physicians and consultants at local public health laboratories collaborated with the hepatitis epidemiology unit, Central Public Health Laboratory, during the study. In 1985 homosexual patients in four districts were included; this increased in 1986 to seven districts and included a 10% sample of heterosexuals and in 1987 to 14 districts and a 20% sample.

Patients are invited to complete a study record and, after counselling, to consent to an HIV antibody test. Heterosexuals attending only for HIV tests are excluded. The study record, designed for completion by the patient, includes inquiries on: age and sex; weight loss, malaise, diarrhoea, night sweats, and skin lumps; sexual preference and number of sexual partners each month; and travel abroad in the previous two years.

In 1987 patients who refused to complete the study record were matched with participants for age, sex, and sexual preference. Diagnoses coded as in the yearly returns of the Department of Health and Social Security[3] were noted from the hospital records.

Collaborative Study Group
A list of collaborators is given at the end of this paper

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