PAPERS AND SHORT REPORTS

Heterosexual spread of human immunodeficiency virus in Edinburgh

A J FRANCE, C A SKIDMORE, J R ROBERTSON, R P BRETTLE, J J K ROBERTS, S M BURNS, C A FOSTER, J M INGLIS, W B F GALLOWAY, S J DAVIDSON

Abstract

Heterosexual transmission of human immunodeficiency virus (HIV) was investigated in 123 subjects with no apparent risk factor for infection other than having had heterosexual intercourse with a person who was either infected with HIV or at high risk of being infected with it. Seven subjects were found to be infected with the virus. Risk factors for transmission included being the regular sexual partner of an abuser of intravenous drugs and having a sexual relationship of more than 18 months' duration. Anal intercourse was not a risk factor in the three subjects who admitted to it. There were 41 regular partnerships with abusers of intravenous drugs in which the antibody state and history were fully known for both partners. In these partnerships male to female transmission of the virus occurred in five out of 34 (15%) and female to male in one out of seven. In 30 couples in whom one partner was known to be positive for HIV and an abuser of intravenous drugs four female partners were found to be seropositive at first testing, but there were no new positive results on subsequent serial testing. In six of these 30 couples both partners abused intravenous drugs but the partner who was negative for HIV remained so. Few of the partnerships always practised safe sexual techniques, even after a partner was known to be positive for HIV.

Heterosexual transmission of HIV occurred but was incomplete and may be related to the timing of the relationship with the infection.

City Screening Clinic and Infectious Diseases Unit, City Hospital, Edinburgh
A J FRANCE, MA, MRCP, senior registrar
R P BRETTLE, MB, FRCPED, consultant
S J DAVIDSON, SRN, SCM, researcher

Edinburgh Drug Addiction Study, West Granton Medical Group, Edinburgh EH4 4PL
C A SKIDMORE, MA, research associate
J R ROBERTSON, MB, MRCGP, general practitioner
J J K ROBERTS, MB, MRCGP, general practitioner
C A FOSTER, MRCGP, DRCOG, general practitioner
W B F GALLOWAY, MB, CHB, general practitioner

Regional Virus Laboratory, City Hospital, Edinburgh
S M BURNS, MB, CHB, senior registrar
J M INGLIS, PHD, MRCPATH, director

Correspondence to: Dr Robertson.

Introduction

The most important determinant of the future spread of AIDS may well be the transmission of virus from an infected to a non-infected person during heterosexual vaginal intercourse. In several African countries evidence exists that transmission by this route may be rapid.[1-4] In Europe and America, however, transmission of the virus heterosexually seems not to happen in every case, even when expected, as shown by the comparatively few people who have become infected by heterosexual intercourse[5] (D Des Jarlais, World Health Organisation meeting, West Berlin, 1986). Although much evidence exists for heterosexual transmission from drug users and the sexual contacts of bisexuals and haemophiliacs,[6-9] studies were generally unable to determine when in the relationship the first partner became infected or transmission to the other partner occurred. Indeed, most studies have been carried out in couples with an infected partner (index case) already in the advanced stages of infection with human immunodeficiency virus (HIV), AIDS, or AIDS related complex. A recent study on haemophiliacs suggested that transmission may occur from an infected man to his partner when he is progressing towards clinical AIDS, as measured by severe loss of T cells (J J Goedert *et al*, third international AIDS conference, Washington, 1987), but more information on this is needed urgently.[10 11]

Our study was made possible because since 1983 many abusers of intravenous drugs in Edinburgh have been infected with HIV as a result of sharing needles.[12 13] All the infected drug abusers whom we have seen have been heterosexual, and many have had partners who have not abused drugs. Some women who abused drugs paid for their habit through prostitution. Thus we had a natural cohort of heterosexual people at risk of infection with HIV.

Our study includes separate analysis of heterosexuals with varying degrees of risk of infection with HIV by virtue of the length

and type of exposure to an infected partner. Unlike in previous studies of heterosexual transmission, the index partners in our study were seropositive but clinically well.

Subjects and methods

Subjects selected themselves and were recruited from two sources. Some came from the City Hospital's screening clinic, which was opened in October 1985 to provide counselling and HIV antibody testing. Many male and female drug users and people in other risk groups have been seen at this clinic.[14] The remainder came from the Edinburgh drug addiction study, which is based in a large general practice (West Granton medical group) with a long established interest in people who inject heroin and a high percentage of patients infected with HIV on its list.[12]

Blood samples from many of these subjects or their consorts had been obtained (for hepatitis B testing) and stored before the introduction of screening for HIV antibodies, and the results of tests for HIV on these samples formed part of our study.

We studied 123 subjects (79 women, 44 men) with no known risk factor for infection with HIV other than heterosexual intercourse with a partner who was either infected with HIV or at high risk of being infected with it. The subjects were carefully questioned by a nurse or a doctor, or both, and were excluded if there was any suspicion of another risk factor. Their partner's risk factor was classified as abuser of intravenous drugs, prostitute, or other. No new subjects were recruited after October 1986, which allowed us to assess the rate of attendance for repeat testing of subjects after recent heterosexual contact. Subjects were classified as having regular or casual heterosexual contact. A stable relationship with more than three sexual encounters was classified as regular. Intermittent sexual encounters with no stable partnership or fewer than three encounters were classified as casual.

We studied in more detail a subgroup of 30 couples in whom one or both partners were known abusers of intravenous drugs and one partner was known to be positive for HIV (see table II).

For all subjects information on drug abuse and sexual behaviour was collected systematically with a confidential standardised questionnaire and was combined with laboratory data (serostate for HIV and markers of hepatitis, with dates of tests). From these sources we recorded the length of time that subjects had been seropositive; the length of unprotected sexual exposure (deducting when possible periods of enforced abstinence from sexual relations); and, in the case of stable relationships, the antibody state of both partners for hepatitis virus and HIV.

HIV antibodies were detected by competitive enzyme linked immunosorbent assay (ELISA). Positive results were confirmed by an antiglobulin ELISA and Western blotting.

Results

SUBJECTS AT RISK FROM A HETEROSEXUAL PARTNER

Altogether 123 subjects were at risk of infection with HIV from a heterosexual partner; 114 were recruited from the City Hospital's screening clinic and nine from the general practice's outpatient clinic. All were tested for HIV antibodies; seven (6%) were positive (one man, six women).

Partner's risk group—Eighty five partners were abusers of intravenous drugs, seven were prostitutes, and 31 were classified as other (extramarital partner (five); partner who supplied sexual intercourse in massage parlour (three); west African (one); bisexual man (one); and unspecified or unknown (21)). All seven subjects positive for HIV had partners who abused intravenous drugs.

Regular or casual partner—The seven subjects positive for HIV had been having regular heterosexual intercourse with their partners. Thirty nine subjects were tested after a casual heterosexual encounter and none became positive for HIV, although for many of them the encounter had occurred less than three months before the antibody test. Repeat testing was offered to 21 of them after an appropriate time, but only seven kept this appointment. All remained seronegative.

The duration of heterosexual relationships ranged from one day to eight years (mean 22 months). For 33 subjects their partnerships had lasted for 18 months or longer and for 90 subjects fewer than 18 months. For all seven subjects positive for HIV their partnerships had lasted for 18 months or more ($\chi^2=16{\cdot}5$, $p<0{\cdot}0001$).

Partner's antibody state—Table I shows the HIV antibody state of the infected partners of the 123 subjects. Altogether 63 subjects claimed that they knew that their partner was positive for HIV. This was confirmed for 42 partners who had been tested at the City Hospital's screening clinic or the West Granton Medical Group, but the remaining 21 partners had been tested elsewhere, usually in prison, and written confirmation of the result was not available. The group of 63 subjects included the seven who were positive for HIV: male to female transmission had occurred in six partnerships and female to male in one. Male to female transmission occurred in a total of 48 relationships (13%), or 44 (14%) when casual episodes were excluded. When the analysis was confined to regular partnerships in which we had ourselves confirmed the antibody state male to female transmission occurred in five out of 34 (15%). Female to male transmission occurred in one out of 15 relationships, or eight when casual episodes were excluded. When only regular partnerships with known antibody state were considered the rate of transmission was one out of seven.

TABLE I—*HIV antibody state of infected partners of 123 subjects studied*

	Partner				
	Regular		Casual		
	Male	Female	Male	Female	Total
Known positive	34*	7†	0	1	42
Claimed positive	10†	1	4	6	21
Unknown	24	8	7	21	60
Total	68	16	11	28	123

*Five subjects acquired HIV from their partner.
†One subject acquired HIV from his or her partner.

Sexual practices—All subjects were interviewed alone. Details of the sexual practices of each partner—for example, vaginal, oral, or anal intercourse—were obtained for 31 partnerships. In 11 partnerships the descriptions did not agree. Three subjects admitted to anal intercourse, and in none of these liaisons was HIV transmitted. No couple had used barrier contraception throughout the period of risk. The data were gathered before the government's campaign to change sexual practices.[15]

ABUSERS OF INTRAVENOUS DRUGS

Thirty couples were studied in more detail, 24 in whom only one partner abused intravenous drugs (21 men, three women) and six in whom both partners did. In all couples one partner was known to be positive for HIV. The women were aged 15-39 (mean 23) and the men 20-50 (mean 26). Table II gives details of these 30 couples.

Antibody state—Four women with no risk factor other than heterosexual intercourse with their partner, who was positive for HIV, were found to be positive for HIV on first testing. Antigen (p24) tests were performed on these women and their partners, but results were negative in all. The remaining 26 partners (three men, 23 women) were negative on first and subsequent testing for HIV antibody, including five women and one man who abused intravenous drugs and were therefore subject to two risk factors (sexual exposure and sharing syringes). The mean exposure time was 16·6 months (range 1-37) (table II). In 19 of the 30 couples the index partner was positive for hepatitis B markers and in nine couples both partners were (in four of these nine couples the partner negative for HIV antibody had used intravenous drugs).

Results of questionnaire—In eight couples both partners were interviewed and in 17 only one was interviewed, giving a total of 33 completed interviews. In five couples no interview data were available. The average rate of intercourse a month was 16·3 (range 4-56). No one admitted to anal intercourse, but six had practised oral intercourse and swallowed semen. None of the couples had used condoms before they knew about their HIV state, and only nine had used them after discovering that one of the partnership was positive for HIV. Only five of the nine used condoms at every sexual contact. Four women had an intrauterine device and 10 used oral contraceptives throughout. Three women started taking medroxyprogesterone acetate (Depo-Provera) after they knew about their consort's HIV state. Twelve couples never used contraceptives. Ten couples had finished their relationship at the time of most recent contact with the clinics, and only 11 couples continued to live together after they knew that one partner was positive for HIV. None of those interviewed had had a blood transfusion or travelled abroad in the past seven years.

Eighteen pregnancies occurred in these couples while the data were being collected, but no significant difference existed between the number of pregnancies in women who were seropositive and the number in those remaining negative for HIV ($\chi^2=0{\cdot}14$).

TABLE II—*Details of 30 couples in whom at least one partner abused intravenous drugs and was positive for HIV. Index partner was male except in couples 18-20*

Couple No	Age (years)	Sex	Intravenous drug abuser	Date of HIV test: HIV negative	Date of HIV test: HIV positive	Hepatitis B markers	Length of exposure (months)	No of pregnancies during exposure (year)
1	21	F	–	6 Jan 1986, 9 June 1986		–	23	
		M			1 June 1984	+		
2	21	F	–	27 Mar 1986, 19 Jan 1987		+	37	1 (1984)
	20	M	+		14 Dec 1983	+		
3	25	F	–	18 Mar 1986, 3 Apr 1986		–	26	1 (1980*)
	27	M	+		31 Jan 1984	Not tested		
4	21	F	–	21 Aug 1985, 23 May 1986		–	24	1 (1985†)
	21	M	+		1 May 1984	Not tested		
5	23	F	–	23 Jan 1985		+	12	
	21	M	+		1 Dec 1984	+		
6	24	F	–	1 Apr 1985, 18 Nov 1986		+	23	
	30	M	+		20 Nov 1983	+		
7	19	F	–	29 Jan 1987, 26 Feb 1987		–	2	
	23	M	+		24 Nov 1986	+		
8	23	F	+	23 Dec 1986, 14 Aug 1987		+	23	2 (1985, 1987*)
	27	M	+		4 Jan 1985	+		
9	20	F	–	2 May 1986		–	25	1 (1985)
	24	M	+		19 Apr 1984	+		
10	30	F	–	4 Oct 1985, 11 Feb 1987, 20 Feb 1987		–	33	
	31	M	+		5 June 1984	+		
11	19	F	+	11 Feb 1987, 4 May 1987, 21 Aug 1987		+	1	
	22	M	+		12 Jan 1987	+		
12	15	F	–	16 Feb 1987, 1 June 1987		+	3	2 (1987, currently pregnant)
	21	M	+		1 Oct 1984			
13	22	F	+	5 Dec 1986, 16 Feb 1987, 6 July 1987		+	10	
	28	M	+		1 Feb 1984	+		
14	21	F	–	16 Dec 1986, 16 Feb 1987		–	13	1 (1986)
	21	M	+		13 Jan 1986	–		
15	29	F	–	1 Mar 1986		+	8	
	27	M§	+		22 Jan 1985			
16	17	F	–	1 Oct 1985, 21 Jan 1987		–	20	1 (1986)
	21	M	+		24 Feb 1984	+		
17	22	F	–	7 Feb 1986, 29 Jan 1987, 4 May 1987		–	2	
	23	M	+		9 Feb 1987	–		
18	21	F	+		8 Feb 1984	+	24	2 (1985*, 1986‡)
	26	M	+	26 Aug 1986, 3 Oct 1986, 29 Jan 1987, 7 May 1987		–		
19	35	F	+		20 Mar 1984	+	25	
	31	M	–	29 Apr 1986		–		
20	39	F	+		1 Sep 1985	Not tested	15	Not known
	50	M	–	5 Dec 1986, 14 Aug 1987		–		
21	24	F	–	10 Mar 1987		–	33	1 (1984)
	29	M	+		6 June 1984	Not tested		
22	17	F	+	13 Feb 1987		–	9	
	25	M	+		27 May 1986	+		
23	23	F	–	16 Aug 1987		–	4	
	27	M	+		1 Feb 1984	–		
24	22	F	–	8 Aug 1987		–	3	
	27	M	+		1 Feb 1984	–		
25	24	F	+	24 Apr 1987		+	1	1
	23	M	+		1 July 1987	Not tested		
26	19	F	+	4 May 1987		+	18	
	24	M	+		3 Sep 1984	+		
27	23	F	–		1 May 1986	+	11	3 (1984†, 1986*, 1987*)
	22	M	+		25 June 1985	+		
28	19	F	–		28 May 1986	Not tested	11	1
	26	M	+		26 Feb 1986	+		
29	28	F	–		1 Sep 1986	Not tested	16	
	30	M	+		10 May 1985	+		
30	23	F	–		23 Apr 1986	–	27	
	25	M	+		13 Jan 1984	+		

*Termination of pregnancy. †Baby positive for HIV antibody. ‡Spontaneous abortion. §Died October 1985.

Discussion

In Edinburgh the first serum sample positive for HIV antibody was collected in August 1983. During the second half of 1983 and the first half of 1984 an epidemic of infection with HIV occurred among abusers of intravenous drugs, over half of whom became infected during this time.[12] This created a natural cohort of infected subjects, and our study shows that nearly 15% of their sexual partners also became infected at a rate of about 5% a year. The low proportion of partnerships between a seropositive woman and seronegative man is probably behavioural: female drug users seem to choose male drug users for sexual partners, whereas male drug users often choose women who do not take drugs.

Our findings suggest that heterosexual relationships lasting for more than 18 months with an infected partner are particularly hazardous, as reflected by a prevalence of HIV antibody of 21% in this group. The index partners might, however, have been more infectious in 1983-4, when they themselves became infected, than in later years. The data from the 30 infected drug abusers and their partners tend to support this as the index partners were all seropositive at first testing and none of their consorts became positive for HIV thereafter, even those who shared needles. Those

who failed to transmit infection had long relationships in many cases, and their contraceptive or other "safe" practices were no different from those of the couples in whom both partners were infected.

This apparent non-infectivity may be an illusion as further testing of seronegative partners may show that they have become infected. It suggests, however, that many subjects who are positive for HIV antibody are, at least for a while, unable or unlikely to transmit their infection sexually. The transient nature of HIV antigenaemia in the early stages after an initial infection from contaminated blood products supports this hypothesis,[16] but evidence suggests that infectivity recurs during the development of frank AIDS related complex or AIDS (J J Goedert *et al*, third international AIDS conference, Washington, 1987). Other factors must also play a part because transmission did not occur in 79% of the partnerships of more than 18 months' duration, and these relationships must have started shortly after the index partner became infected. The effect of enforced sexual abstinence during imprisonment for crimes related to drugs may be a factor.

The accuracy of the information given by the subjects may be questionable. Thus, although knowledge of a partner's HIV state seemed to be correct and accurately reported, 40% of couples disagreed about their sexual practices. This shows that they either did not understand the question or were too shy to admit such intimate details. In this group drug abuse carries no stigma and is freely discussed, but sexual practices are not. Notably, none of these couples attended a genitourinary medicine clinic for advice on HIV.

The evidence of heterosexual transmission of HIV in this country is strengthened by our findings, showing an infection rate of about 15% in the partners of seropositive drug addicts compared with 6·8%[7] and 9·5%[17] in the wives of infected haemophiliacs. Abusers of intravenous drugs in Edinburgh have travelled widely in Britain and shared needles with other drug abusers around the country.[14] Thus the drug abusing community, both addicts and occasional users, presents a serious risk of infection to the heterosexual population. The lack of use of contraceptives was alarming, and emphasised by the large number of pregnancies in one of our study groups. Pregnancy did not, however, seem to increase the mother's risk of infection with HIV.

Although infection with HIV was transmitted heterosexually in only a small proportion of our subjects, the next phase of the local (Edinburgh) epidemic may result from transmission by this route as inadequate precautions are being taken and infected partners will probably become ill with AIDS in the near future. An epidemic of sexually transmitted HIV infection may be expected to follow this development, and the problems of heterosexual and paediatric AIDS, more familiar to New York, may become commonplace.[18]

Many difficulties arise in studying heterosexual behaviour in young people, and the collection of data can never be complete. The circumstances of this study, particularly the availability of stored blood samples, allowed us to make retrospective observations on relationships and the duration of unprotected exposure to infection that may be less easy to obtain in future.

We thank the doctors and staff of the West Granton medical group and the City Hospital's screening clinic for helping to collect the data; Dr Martin Bland of St George's Hospital Medical School for providing the computer program for statistical analysis; Dr J R Peutherer of Edinburgh University's department of clinical bacteriology for the Western blot analyses; and the Scottish Home and Health Department, which funds the Edinburgh drug addiction study.

References

1 Biggar RJ. The AIDS problem in Africa. *Lancet* 1986;i:79-83.
2 Mann JM, Bila K, Colebunders RL, *et al*. Natural history of human immunodeficiency virus infection in Zaire. *Lancet* 1986;ii:707-9.
3 Mann JM, Francis H, Quinn T, *et al*. Surveillance for acquired immunodeficiency syndrome in a central African city: Kinshasa, Zaire. *JAMA* 1986;225:3255-9.
4 Anonymous. *AIDS in the Third World*. London: Panos Institute, 1986.
5 Centers for Disease Control. Heterosexual transmission of human T-lymphocytic virus type III/lymphadenopathy-associated virus. *MMWR* 1985;34:561-3.
6 Redfield RR, Markham PD, Salahuddin SZ, *et al*. Frequent transmission of HTLV-III among spouses of patients with AIDS-related complex and AIDS. *JAMA* 1985;253:1571-3.
7 Allain JP. Prevalence of HTLV-III/LAV antibodies in patients with haemophilia and their sexual partners in France. *N Engl J Med* 1986;315:517-8.
8 Jones P, Hamilton PJ, Bird G, *et al*. AIDS and haemophilia: morbidity and mortality in a well defined population. *Br Med J* 1985;291:695-9.
9 Fischl MA, Dickson DM, Scott GB, *et al*. Evaluation of heterosexual partners, children and household contacts of adults with AIDS. *JAMA* 1987;257:640-4.
10 May RF, Anderson RM. Transmission dynamics of HIV infection. *Nature* 1987;326:137-42.
11 Piot P, Kreiss JK, Ndinya-Achola JO, *et al*. Transmission of HIV. *AIDS* 1987;1:199-206.
12 Robertson JR, Bucknall ABV, Welsby PD, *et al*. Epidemic of AIDS related virus (HTLV-3/LAV) infection among intravenous drug abusers. *Br Med J* 1986;292:527-9.
13 Brettle RP, Davidson J, Davidson SJ, *et al*. HTLV-3 antibodies in an Edinburgh clinic. *Lancet* 1986;i:1099.
14 Brettle RP, Bisset B, Burns S, *et al*. Human immunodeficiency virus and drug misuse: the Edinburgh experience. *Br Med J* 1987;295:421-4.
15 Department of Health and Social Security. *Don't die of ignorance*. London: HMSO, 1987.
16 Allain J-P, Laurian Y, Paul DA, Senn D. Serological markers in early stages of human immunodeficiency virus infection in haemophiliacs. *Lancet* 1986;ii:1233-6.
17 Kreiss JUK, Kitchen LW, Prince HE, Kaspar CK, Essex M. Antibody to human T-lymphotropic virus type 3 in wives of haemophiliacs. *Ann Intern Med* 1985;102:623-6.
18 Weinberg DS, Murray HW. Coping with AIDS. The special problems of New York City. *N Engl J Med* 1987;317:1469-73.

(Accepted 12 January 1988)

SHORT REPORTS

Benign multinodular goitre and reversible Horner's syndrome

Horner's syndrome due to thyroid disease has been reported before, and the possibility that benign conditions might be responsible has been suggested but not proved conclusively.[1 2 3] We present a case of Horner's syndrome in which histological proof of a benign thyroid cause was obtained and in which the symptoms resolved after surgery.

Case report

A 63 year old man presented with a six week history of right sided ptosis and a gritty feeling in the right eye. He had a smooth non-tender goitre that had been present but untreated for many years. On examination his trachea was found to deviate to the left. The percussion note was dull over the right apex anteriorly, and breath sounds were diminished in this region. He had a complete right Horner's syndrome. There was a partial ptosis, with half of the pupil covered on forward gaze. The diameter of the right pupil was about half that of the left when viewed in normal room lighting. There was anhydrosis of the right side of his face. The results of neurological examination were otherwise normal. A chest *x* ray film showed an opacity in the right upper zone, and Pancoast's tumour was provisionally diagnosed. A computed tomograph of the neck and upper thorax showed that the mass extended from the hyoid bone almost to the carina and that it arose from the thyroid. The contrast enhanced films showed the right carotid sheath being compressed by the mass (figure), thus causing Horner's syndrome. Tests of thyroid function all gave normal results.

A right thyroid lobectomy was performed through a standard collar incision. The thyroid gland was very tense within its capsule, compressing the surrounding structures at the level of the thoracic inlet. Histological examination confirmed that it was a benign multinodular goitre. The acini were distended with colloid, and the epithelium was flattened. There was evidence of haemorrhage in places. Six weeks after surgery there was a considerable improvement in his ptosis, the pupils were of equal size, and the discomfort in the eye had gone.

Comment

Horner's syndrome caused by thyroid masses has been reported before, but there is a tendency to assume that an invasive malignant process is responsible.[1 2] In a review of 216 cases of Horner's syndrome 12 were reportedly due to thyroid adenoma.[2] No clinical details were given, so the diagnostic criteria are unknown. The subsequent management and outcome were also unreported. Recently a patient who had bilateral Horner's syndrome due to multinodular goitre has been described.[3] In this case there