

Factors affecting seropositivity to human T cell lymphotropic virus type III (HTLV-III) or lymphadenopathy associated virus (LAV) and progression of disease in sexual partners of patients with AIDS

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SUMMARY Fifty four sexual partners of homosexual men with the acquired immune deficiency syndrome (AIDS) were studied, of whom 32 were seropositive and 22 seronegative for human T cell lymphotropic virus type III or lymphadenopathy virus (HTLV-III/LAV) antibody, which showed that repeated exposure by anal intercourse does not necessarily lead to seroconversion. Seropositivity to HTLV-III/LAV was not associated with the absolute number of sexual partners, receptive anal intercourse, or the use of recreational drugs, but was associated with a history of other sexually transmitted diseases (STDs), particularly in the year preceding the patient's initial examination. Acquisition of an STD after the date of last sexual contact with a person with AIDS was strongly associated ($p < 0.001$) with the development of persistent generalised lymphadenopathy (PGL). Concurrent or recent STDs would seem to be an important cofactor in developing antibody to HTLV-III/LAV and in the progression of infection from a person being asymptomatic to having PGL.

Introduction

Human T lymphotropic virus type III or lymphadenopathy virus (HTLV-III/LAV) has now been established as the causative agent of the acquired immune deficiency syndrome (AIDS) and related disorders.¹⁻³ Serological studies in many centres have shown that the presence of antibody to HTLV-III/LAV is strongly associated with AIDS and persistent generalised lymphadenopathy (PGL).^{4,5} Cheingsong-Popov *et al* in a study of 2000 serum samples in Britain showed that only 42% (15/36) of the male sexual partners of homosexual men with AIDS were seropositive for HTLV-III/LAV.⁶ Geodert *et al* showed in a cohort study that risk factors for acquiring antibody to HTLV-III/LAV included a large number of sexual partners and receptive anal intercourse.⁷ Melbye in a study of 250 Danish homosexual men showed that the incidence of receptive anal intercourse was a highly significant factor in seropositivity, but the number of

sexual partners was not an independent risk factor.⁸ Gazzard *et al* also noted that 3/19 sexual partners of patients with AIDS were seronegative, but did not analyse further the factors associated with seropositivity.⁹ This prospective study of sexual partners of patients with AIDS was designed specifically to investigate the risk factors for sexual acquisition of HTLV-III/LAV, as assessed by serology, in an exposed population.

Patients and methods

We selected 54 homosexual men, all of whom had had sexual intercourse with a patient subsequently diagnosed as having AIDS (by the criteria of the Centers for Disease Control). Intercourse had been either anal insertive or receptive (or both), and had occurred on at least four occasions in the two years preceding the diagnosis of AIDS. None of the contacts was a user of intravenous drugs or a haemophiliac, and none had received any blood products, including gamma globulin or hepatitis B vaccine.

Of the sexual contacts, 34 were the current sexual partners of patients with AIDS seen at this hospital and 20 were past regular partners traced by the stan-

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ard techniques as used by the sexually transmitted diseases (STD) clinic. Casual sexual partners were not included in this study. The two groups of sexual contacts were matched for age, age at first sexual intercourse, duration of sexual activity, lifetime number of sexual partners, and seropositivity to HTLV-III/LAV.

Each man had a structured interview with a single physician (JNW), who completed an extensive questionnaire. Details of sexual lifestyle, sexual history, numbers of sexual partners, and types of sexual activity were obtained. Details of the type of anal intercourse were taken and recorded as ranging from entirely anal receptive (passive) (0%) to entirely anal insertive (active) (100%). This enabled a coarse measure of active as opposed to passive intercourse to be made on a linear scale.

A full history of STD was recorded; whenever possible, this information was checked against clinical data previously recorded in the STD clinic. For the purposes of this study, recorded STDs were restricted to acute episodes and were defined as a proved episode of primary or secondary syphilis, gonorrhoea at any site, non-specific urethritis, or primary herpes simplex infection. Infections such as hepatitis B virus infection, human papillomavirus infection, or tertiary syphilis were excluded, as the date of acquisition of these infections is often unknown. The temporal relation between the episodes of STD and contact with the index cases was noted.

HTLV-III/LAV serology was measured by indirect immunofluorescence, and by enzyme linked immunosorbent assay (ELISA) (Organon Laboratories, Cambridge, England); there was good correlation between these methods on random assessment. If the initial results were negative patients followed up for six months or more underwent repeat serology tests at every six monthly visit.

At each visit blood samples were taken for a full blood count, liver function tests, and syphilis serology tests. Serum was stored at -70°C , and lymphocytes were separated from heparinised blood for T lymphocyte subsets to be counted.

Results

Of the 54 men in this study, 34 presented because of illness in their current or recent sexual partner, and 20 were actively traced (A McC). Despite the different origin of these two groups, they did not differ appreciably in the proportions who were seropositive to HTLV-III/LAV or had PGL.

Men who were seropositive (32) and those who were seronegative (22) at the first visit were well matched. No significant difference was found between positive and negative groups for age, age at first intercourse (either with men or women), number of casual sexual partners in the preceding six months, or type of sexual intercourse (measured as passive anal intercourse only (0%) ranging through both active and passive intercourse to active anal intercourse only (100%). The proportions of regular, stable, long term (for more than six months) partnerships were 81.5% in the seropositive group and 85.4% in the seronegative group (not a significant difference).

Table I shows the results of studies of sexual behaviour and history of STDs in the two groups. The difference between the two groups in the type of sexual intercourse was not significant. The seropositive groups, however, had had significantly ($p < 0.01$) more STDs during their lives and in the year preceding examination, which in effect represented the time of exposure to the patient with AIDS.

The association between passive anal intercourse and seropositivity was not significant in this study. Three seropositive men had a lifelong history of active

TABLE I Risk factors for acquiring antibodies to HTLV-III/LAV in 54 sexual contacts of patients with AIDS

Variable	HTLV-III/LAV positive (n=32)	HTLV-III/LAV negative (n=22)	Difference
Mean (range) No of casual partners in previous six months	9.5 (0-99)	7 (0-100)	NS
No (%) passive anal intercourse only	2/27 (7.4)	1/20 (5)	NS
No (%) active anal intercourse only	3/27 (11.1)	3/20 (15)	NS
Mean (SD) passive v active anal intercourse (scale of 0-100%)	44.8 (5.5)	53.9 (6.6)	NS
No (%) using amyl nitrite	26 (81)	15 (68)	NS
Mean (range) episodes of STD in lifetime	6.5 (0-21)	2 (0-45)	$p < 0.01^*$
Mean (range) episodes of gonorrhoea	2.5 (0-10)	0.5 (0-30)	$p < 0.05^*$
No (%) who had episodes of STD in previous year	15/29 (51.7)	1/18 (5.6)	$p < 0.01^*$
No (%) who had episodes of STD after last contact with AIDS	24/30 (80)	14/21 (66.7)	NS

HTLV-III/LAV = human T lymphotropic virus type III or lymphadenopathy virus.
AIDS = acquired immune deficiency syndrome.

* By Fisher's exact test.

(penile insertive) intercourse only. This history was confirmed at a second interview, and examination of past STD clinic records showed no history of rectal infection at any time.

Table II shows the relation between episodes of STD after the last date of sexual intercourse with a patient with AIDS and the number of contacts developing PGL. The association between an episode of any acute STD and the finding of PGL in the seropositive group was significant ($p < 0.001$). There was no such association in the seronegative group. It will be noted, however, that two of the seronegative contacts presented with PGL, and both had had an episode of STD after their last sexual contact with a known patient with AIDS. These two patients subsequently seroconverted to HTLV-III/LAV positivity after having had PGL for 10 and 18 months, respectively.

The interrelationships of our patients were not straightforward. The figure shows the sexual interrelationships of 26 seropositive and four seronegative contacts who were sexually linked — generally unknown to the contacts themselves. This figure is incomplete, but represents nine months intensive interview and contact tracing. One seronegative contact had had intercourse with more than one patient with AIDS, whereas 7/26 seropositive contacts had been

TABLE II Incidence of contacts presenting with PGL related to episodes of STD after last sexual intercourse with patient with AIDS

	No (%) presenting with PGL	
	HTLV-III/LAV positive	HTLV-III/LAV negative
Episode of STD since last intercourse	15/18 (83.3)*	2/6 (33.3)
No STD since last intercourse	2/14 (14.3)*	0/15 (0.0)

PGL = persistent generalised lymphadenopathy.
 STD = sexually transmitted disease.
 AIDS = acquired immune deficiency syndrome.
 HTLV-III/LAV = human T lymphotropic virus type III or lymphadenopathy virus.
 * $p < 0.001$ by the χ^2 test.

sexually exposed to two or more patients with AIDS ($p < 0.05$). Seropositive contacts were also more likely to have had sexual intercourse with a patient with PGL (data not shown).

Discussion

This is the first prospective study to report the relevance of a specific cofactor — acute infection — to seroconversion and the development of disease.

Studies of the risk of infection with HTLV-III/LAV in homosexual men may be difficult to interpret unless the control groups are equally at risk of infection. By studying the known regular sexual partners of patients with AIDS, people who have been sexually exposed in an identical or similar manner may be compared. Previous studies have shown that not all exposed homosexual men are seropositive for HTLV-III/LAV,⁶ and similarly not all infected haemophiliacs are antibody positive, despite unequivocal exposure.¹⁰

The seropositive and seronegative contacts in this study were well matched for age, sexual behaviour, and sexual exposure to index cases. No significant differences were found between the contacts who presented themselves and those traced by us. This elimination of selection bias permitted direct comparison between the seropositive and seronegative contacts.

It would be naive to believe that the infection with HTLV-III/LAV necessarily came to the sexual contact from the patient with AIDS. We can, however, define the contact cohort as being definitely exposed, and analyse the factors present in the one year since the last sexual exposure to the index case.

These results show that there was no significant association between seropositivity and the number of

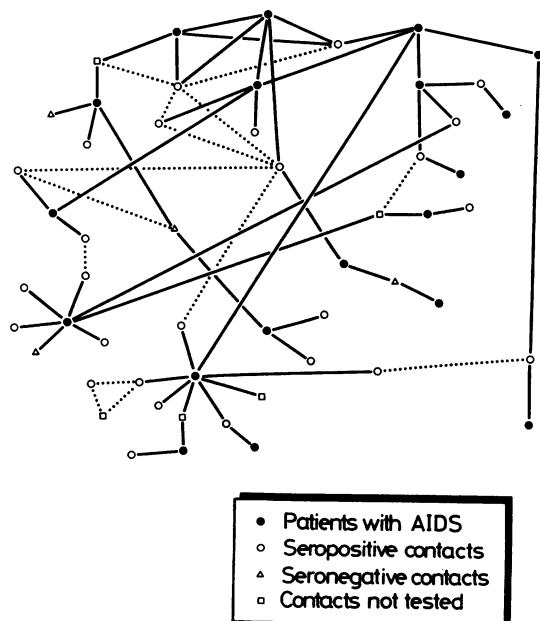


FIGURE Sexual interrelationships of 19 patients with AIDS (index cases), 26 seropositive and four seronegative contacts, and five contacts who had not been tested for antibodies to HTLV-III/LAV.

casual sexual partners or the type of anal intercourse. Sexual promiscuity itself was not a risk factor for developing antibody to HTLV-III/LAV; similarly, both active (insertive) and passive (receptive) anal intercourse were equally associated with the risk of infection. The association between the detection of antibody to HTLV-III/LAV and numbers of lifetime episodes of STD was significant, particularly for episodes of STD in the year preceding entry into this study, which was the period since sexual exposure to the index cases.

In the seropositive group, the development of an episode of STD in the period after the last sexual intercourse with an index case was strongly associated with the finding of PGL on presentation. This highly significant relation was not associated with absolute numbers of sexual partners. The two seronegative contacts with PGL both subsequently seroconverted (asymptomatically), one 10 and the other 18 months after the onset of PGL. In these two cases, there was objective evidence of HTLV-III/LAV related disease in the absence of positive serology test results; seroconversion followed a documented episode of STD. The design of the study made it impossible to define accurately the temporal relation between STD and seroconversion more accurately than to within four months.

This study, in common with all those of HTLV-III/LAV epidemiology, has used serology tests to assess infection. It has shown that detection of HTLV-III/LAV antibody in an exposed population is related principally to recent STD. HTLV-III/LAV related disease in the seronegative population has been reported previously.¹¹ This study has shown, however, that seroconversion may occur after an acute episode of STD. These findings could be explained by the existence of an HTLV-III/LAV infected but seronegative state. This could be caused by completely integrated proviral DNA without sufficient viral replication to generate an antibody response, by sequestration of infected cells, or by a failure in antigen presentation. In each case, acute infection may lead to T cell activation, viral replication, and hence a humoral response. False negative serology test results secondary to the formation of an immune complex is also a possible explanation, with acute intercurrent infection leading to an altered proportion of antigen and antibody.

The study published here has shown that STD may be an important cofactor in infection with HTLV-III/

LAV. Clearly, any intercurrent infection may lead to T cell activation. STDs were chosen for this study because their documentation was readily available. The possible role of other infections must now be assessed. Meanwhile, the implications for counselling patients are clear. HTLV-III/LAV infected people should avoid intercurrent infection; this strengthens the need for a reduction in sexual partners by infected patients. Varying rates or types of intercurrent infection, for example in central Africa, may be responsible for the differing rates of progression to AIDS in infected patients.

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