

## The Vancouver Lymphadenopathy - AIDS Study: 2. Seroepidemiology of HTLV-III antibody

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Testing for antibody to human T-lymphotropic retrovirus (HTLV-III) was carried out in 448 participants in the Vancouver Lymphadenopathy-AIDS (acquired immune deficiency syndrome) Study. The overall prevalence rate of seropositivity was 34%. Of 130 seronegative subjects followed for an average of 8.5 months, 14 became seropositive; thus, the approximate annual seroconversion rate was 15%. More than 100 male sexual partners in one's lifetime, frequent receptive anal intercourse, fisting, a history of gonorrhoea or hepatitis, and frequent sexual contact in clubs were found to be independent risk factors for HTLV-III seropositivity.

On a recherché les anticorps contre le rétrovirus T-lymphotrope humain (HTLV-III) chez 448 sujets dans le cadre de l'Étude sur la lymphadénopathie et le syndrome immunodéficientaire acquis (SIDA) de Vancouver. Le taux global de séropositivité est 34%. Parmi 130 sujets séronégatifs, on assiste sur une moyenne de 8,5 mois au virage de 14 sujets, soit un taux annuel de séroconversion de quelque 15%. Chacun des facteurs suivants est en corrélation avec la séropositivité: un nombre de partenaires sexuels masculins dépassant 100 pour toute la vie, le coït anal passif fréquent, la stimulation manuelle du rectum, l'antécédent de gonorrhée ou d'hépatite, et le contact sexuel fréquent dans un club.

In part 1 of this series (*Can Med Assoc J* 1985; 132: 1273-1279) we presented data suggestive of an association in our study population of homosexual men between

persistent generalized lymphadenopathy and elevated lifetime number of male sexual partners, frequent receptive anal intercourse, a history of gonorrhoea, use of illicit drugs and sexual contact in Los Angeles. These are similar to risk factors reported for acquired immune deficiency syndrome (AIDS).<sup>1-3</sup>

The lymphadenopathy-associated virus (LAV), discovered in France,<sup>4</sup> and the human T-lymphotropic virus (HTLV-III)<sup>5</sup> and the AIDS-related virus (ARV),<sup>6</sup> discovered in the United States, have been identified as the putative etiologic agent(s) for AIDS. Serologic tests for detecting antibody to HTLV-III have recently become available. We report on the prevalence of HTLV-III antibody and behavioural risk factors for seropositivity in a group of homosexual men recruited from primary care practices.

### Methods

A total of 726 homosexual men were recruited from six general practices in central Vancouver between November 1982 and February 1984. The subjects completed a questionnaire and underwent a physical examination and laboratory testing on two occasions that were at least 3 months apart. This has been described in greater detail in part 1.

Serum was frozen and stored at  $-70^{\circ}\text{C}$ . Testing for HTLV-III antibody was done at the Laboratory Centre for Disease Control, Ottawa, by means of the enzyme-linked immunosorbent assay (ELISA); equivocal results were tested by the Western blot technique.<sup>7</sup>

For the case-control analysis the following definitions were used: the subjects were all participants who were HTLV-III positive at the time of either visit, and the controls were all participants who were HTLV-III negative at the time of the first visit and, if completed, the second visit.

Univariate analysis was based on Mantel-Haenszel methods<sup>8</sup> and the Mantel extension<sup>9</sup> as a test of linear trend. All p values are two-sided. Missing and unknown values were omitted from analysis. For multivariate analysis we used the stepwise logistic regression program of the BMDP Statistical Software Package.<sup>10</sup>

Stepwise logistic regressions were performed to account for the independent effects of the variables. For the purposes of analysis we grouped the variables of sexual contact in other cities together to form a single variable and did the same with the illicit-drug variables. The fisting variables (insertive and receptive) were also grouped because of collinearity into a single variable representing fisting behaviour (ever or never).

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## Results

### Prevalence of HTLV-III antibody

At the time of analysis, results were available for 448 men, 188 who had completed both visits and 260 who had completed one visit (Table I). Of the 448 men, 151 were HTLV-III positive on one or both occasions; thus, the overall period prevalence rate was 34%. Of the 352 men for whom results from the first visit were available, 101 (29%) were seropositive, and of the 284 for whom results from the second visit were available, 107 (38%) were seropositive. It is noteworthy that the prevalence rate was 26% (43 out of 164) among those for whom only first-visit results were available and 38% (36 out of 96) among those for whom only second-visit results were available.

Of the 130 men who were seronegative at the first visit and for whom second-visit results were available, 14 were seropositive at the second visit; thus, the seroconversion rate was 11%. Since the average duration of follow-up was 8.5 months, the crude annual seroconversion rate was approximately 15%. One man's serum converted from positive to negative.

Of the 151 eligible subjects, 57 were seropositive at both visits, 79 were seropositive at their single visit, and 14 were seropositive only at the second visit. The remaining subject was seropositive at the first visit but seronegative at the second; he was omitted from the case-control analysis. Of the 297 eligible controls, 116 were seronegative at both visits, and 181 were seronegative at their single visit; for 121, second-visit results

were not available. As the observed seroconversion rate was 10%, approximately 12 subjects whose serum converted may have been included as controls.

The age distributions of the subjects and controls were virtually identical, with means (and standard deviations) of 32.0 (6.5) and 32.0 (7.1) years respectively.

### Sexual partners

Data concerning the number of sexual partners are presented in Table II. Because of the established association between lifetime number of sexual partners and both AIDS<sup>1</sup> and persistent generalized lymphadenopathy (part 1), we adjusted for this potential confounder. More than 100 male sexual partners in one's lifetime was significantly associated with seropositivity, as was more than 20 sexual partners in the previous year ( $p < 0.001$ ). The association of the latter variable, however, was only marginally significant when adjusted for lifetime number of partners. No association with age at which regular sex with men was initiated was detected.

### Sexual practices

The practices associated with the greatest risk for HTLV-III seropositivity were receptive anal intercourse and insertive and receptive fisting ( $p < 0.001$ ) (Table III). These associations remained statistically significant even after adjustment for lifetime number of sexual partners, whereas oral-anal sexual contact (insertive and receptive) was only marginally significant after adjustment. Frequent sexual contact in clubs or bathhouses was significantly associated with HTLV-III seropositivity before and after adjustment.

### History of infectious disease

A history of gonorrhea, hepatitis or infestation with pubic lice was significantly associated with HTLV-III seropositivity ( $p < 0.001$ ), even after adjustment for lifetime number of sexual partners (Table IV). A history of syphilis, nonspecific urethritis or gay bowel syndrome had no significant association after adjustment.

Table I—Results of testing for antibody to human T-lymphotropic retrovirus (HTLV-III) in 448 homosexual men

First visit	Results; no. of men			Total
	Second visit			
	Positive	Negative	Not available	
Positive	57	1	43	101
Negative	14	116	121	251
Not available	36	60	—	96
Total	107	177	164	448

Table II—Relative risk for HTLV-III seropositivity associated with sexual partners and age at initiation of regular sex with men in 150 seropositive men and 297 controls

Variable	No. (and %) of subjects (n = 150)	No. (and %) of controls (n = 297)	Relative risk (and 95% confidence interval [CI])	Adjusted relative risk (and 95% CI)*
More than 100 male sexual partners in lifetime	114 (80)	158 (57)	3.0 (1.9–4.7)†	—
More than 20 male sexual partners in previous year	92 (64)	118 (42)	2.4 (1.6–3.7)†	1.7 (1.0–2.8)
Initiation of regular sex with men at 19 years or younger	74 (52)	164 (59)	0.8 (0.7–1.8)	0.8 (0.6–1.3)

\*Adjusted for number of male sexual partners in lifetime.

† $p < 0.001$ .

## Use of illicit drugs

The use of methylene-dioxy amphetamine (MDA), lysergic acid diethylamide (LSD) or cocaine was significantly associated with HTLV-III seropositivity, both before ( $p < 0.001$ ) and after ( $p < 0.01$ ) adjustment for lifetime number of sexual partners (Table V). Few participants ever used heroin. As most used marijuana and amyl or butyl nitrite inhalants, there were wide estimates of risk for these variables. Further analysis of the use of nitrite inhalants failed to show any dose-response relation.

## Sexual contact in other cities

Sexual contact with more than 10 partners in the preceding 5 years in Los Angeles ( $p < 0.05$ ), San Francisco ( $p < 0.01$ ), Seattle ( $p < 0.001$ ) or New York ( $p < 0.01$ ) was associated with an elevated risk of HTLV-III seropositivity (Table VI). This association remained significant after adjustment except for Los

Angeles; however, the numbers were small for both Los Angeles and New York. Sexual contact in other cities did not occur often enough for analysis.

## Multivariate analysis

More than 100 male sexual partners in one's lifetime, frequent receptive anal intercourse, fisting, a history of gonorrhea or hepatitis, and frequent sexual contact in clubs were significantly associated with HTLV-III seropositivity in the final model (Table VII). Use of illicit drugs and sexual contact in other cities were no longer significantly associated with seropositivity. To account for possible differences in age and medical practice between subjects and controls, we entered these variables into the model; neither was significant.

## Discussion

Our data suggest an overall prevalence rate of HTLV-III seropositivity of 34% among the 448 men

**Table III—Relative risk for HTLV-III seropositivity associated with sexual practices**

Practice*	No. (and %) of subjects	No. (and %) of controls	Relative risk (and 95% CI)	Adjusted relative risk (and 95% CI)†
<b>Oral-genital contact‡</b>				
Insertive	95 (67)	180 (64)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
Receptive	109 (77)	221 (79)	0.9 (0.5–1.4)	0.8 (0.5–1.3)
<b>Anal intercourse‡</b>				
Insertive	79 (56)	144 (51)	1.2 (0.8–1.8)	1.0 (0.7–1.6)
Receptive	92 (65)	112 (40)	2.8 (1.8–4.2)	2.7 (1.8–4.2)
<b>Oral-anal contact‡</b>				
Insertive	59 (42)	83 (39)	1.6 (1.1–2.6)¶	1.6 (1.0–2.5)
Receptive	74 (52)	111 (39)	1.7 (1.6–2.6)¶	1.6 (1.0–2.4)¶
<b>Fisting§</b>				
Insertive	68 (48)	68 (24)	2.8 (1.9–4.4)	2.2 (1.4–3.5)
Receptive	38 (27)	23 (8)	4.1 (2.3–7.1)	3.6 (1.9–6.4)
<b>Sexual contact in clubs‡</b>	128 (90)	209 (77)	3.0 (1.7–5.4)	3.1 (1.6–5.9)
<b>Sexual contact in bathhouses‡</b>	90 (63)	121 (44)	2.2 (1.5–3.3)	1.6 (1.1–2.6)¶

\*Proportion of sexual encounters that included this practice: ‡more than 25%; §any.

†Adjusted for number of male sexual partners in lifetime.

||  $p < 0.001$ .

¶  $p < 0.05$ .

**Table IV—Relative risk for HTLV-III seropositivity associated with history of infectious disease**

Disease	No. (and %) of subjects	No. (and %) of controls	Relative risk (and 95% CI)	Adjusted relative risk (and 95% CI)*
Gonorrhea	125 (87)	171 (61)	4.5 (2.7–7.3)†	3.6 (2.1–6.5)†
Hepatitis	108 (76)	150 (53)	2.7 (1.8–4.2)†	2.1 (1.3–3.3)‡
Infestation with pubic lice	135 (94)	237 (84)	3.1 (1.5–6.4)†	2.5 (0.8–4.7)§
Syphilis	50 (35)	67 (24)	1.7 (1.1–2.7)§	1.3 (0.8–2.1)
Nonspecific urethritis	76 (53)	121 (43)	1.5 (1.1–2.3)§	1.4 (0.8–2.1)
Gay bowel syndrome	32 (22)	45 (16)	1.5 (0.9–2.5)	1.4 (0.8–2.4)

\*Adjusted for number of male sexual partners in lifetime.

†  $p < 0.001$ .

‡  $p < 0.01$ .

§  $p < 0.05$ .

tested. This estimate may be slightly low, as there were 121 men who were seronegative at the first test but did not undergo a second test; in some cases the serum may have converted. One might argue that the increase in prevalence between the first and second visits (from 29% to 38%) could have been due to a tendency to more frequently retest men who were seropositive or symptomatic. However, this was not possible, as the serologic results were not available until long after the second visit had occurred. Furthermore, the prevalence rate was identical (38%) among the 96 men who were tested at the second visit only. While it is tempting to infer from this change in prevalence that seropositivity is increasing over time, the initial and second visits did not correspond to particular points in time. Because of staggered recruitment, both first and second visits were being carried out throughout the study period. On the other hand, seroconversion in 14 of the 130 men who had been seronegative and for whom follow-up information was available suggests that a real increase in population prevalence may be taking place. The crude annual seroconversion rate of 15% within this interval is similar to that reported in smaller studies.<sup>11,12</sup>

That the prevalence of HTLV-III seropositivity within this population was of this magnitude is not surprising. First, we have already established a prevalence of persistent generalized lymphadenopathy of approximately 24% in this population. The association between

this syndrome and HTLV-III seropositivity has previously been reported.<sup>11,13</sup> Second, during the recruitment period, when the blood samples were taken, cases of AIDS began to appear in this community. Third, high prevalence rates of antibody to HTLV-III and LAV have been reported in other asymptomatic homosexual populations. In particular, antibody to HTLV-III was found in 35 (53%) of 66 homosexual men in New York City in 1982<sup>11</sup> and in 22 (8.8%) of 250 Danish homosexual men in 1981.<sup>12</sup> Among male homosexuals visiting a sexually transmitted disease clinic in San Francisco the prevalence rate of HTLV-III seropositivity rose from 1% to 25% and then 65% in 1978, 1980 and 1984 respectively.<sup>14</sup> The fact that our observed prevalence rate was only 34% may be accounted for by the later introduction of the virus into the Canadian homosexual community; moreover, as our study was general-practice-based, we may have avoided some of the bias associated with tertiary-care- or clinic-based studies.

Our study confirms that several risk factors for AIDS<sup>1</sup> and persistent generalized lymphadenopathy (part 1) are indeed risk factors for HTLV-III seropositivity. In particular, an elevated lifetime number of male sexual partners and receptive anal intercourse are established risk factors for AIDS.<sup>1</sup> Our data suggest similar associations with HTLV-III seropositivity and support the hypothesis that the observed associations between these risk factors and both persistent general-

**Table V—Relative risk for HTLV-III seropositivity associated with use of illicit drugs**

Drug*	No. (and %) of subjects	No. (and %) of controls	Relative risk (and 95% CI)	Adjusted relative risk (and 95% CI)†
Methylene-dioxyamphetamine (MDA)	93 (65)	124 (44)	2.4 (1.6–3.6)‡	2.0 (1.3–3.1)§
Lysergic acid diethylamide (LSD)	83 (59)	116 (42)	2.0 (1.3–3.0)‡	1.8 (1.2–2.8)§
Cocaine	68 (48)	88 (32)	2.0 (1.3–3.1)‡	1.8 (1.1–2.8)§
Marijuana	130 (91)	237 (84)	1.9 (1.0–3.5)¶	1.8 (0.9–3.5)
Nitrite inhalants	136 (97)	242 (89)	4.4 (1.8–10.7)§	3.9 (1.3–11.7)¶
Heroin	6 (4)	8 (3)	1.5 (0.5–4.5)	1.3 (0.4–4.0)

\*Ever used.  
†Adjusted for number of male sexual partners in lifetime.  
‡p < 0.001.  
§p < 0.01.  
¶p < 0.05.

**Table VI—Relative risk for HTLV-III seropositivity associated with sexual contact in other cities**

City*	No. (and %) of subjects	No. (and %) of controls	Relative risk (and 95% CI)	Adjusted relative risk (and 95% CI)†
Los Angeles	14 (9)	13 (4)	2.2 (1.0–4.9)‡	1.6 (0.7–3.6)
San Francisco	44 (29)	36 (12)	3.0 (1.8–4.9)§	2.4 (1.4–4.0)§
Seattle	57 (38)	41 (14)	3.8 (2.4–6.0)¶	3.0 (1.8–4.9)¶
New York	18 (12)	12 (4)	3.2 (1.5–6.8)§	2.4 (1.1–5.3)‡

\*More than 10 sexual partners in city in previous 5 years.  
†Adjusted for number of male sexual partners in lifetime.  
‡p < 0.05.  
§p < 0.01.  
¶p < 0.001.

ized lymphadenopathy and AIDS may be mediated solely by their association with HTLV-III. Both these risk factors were found to be associated with HTLV-III seropositivity by Goedert and colleagues,<sup>11</sup> but number of sexual partners was not found to be a risk factor in a recent Danish study.<sup>12</sup> Our univariate analysis showed both insertive and receptive fisting to be associated with seropositivity. As these variables are virtually collinear, results of regression models in which they are treated separately may be misleading. Goedert and colleagues,<sup>11</sup> in multivariate analysis of their data, found insertive fisting to be highly associated with seropositivity and found no association with receptive fisting. However, it seems most biologically plausible that receptive fisting, with resultant disruption of mucosal integrity, would facilitate viral transmission. At any rate, we chose to consider fisting as a single variable and found that it was a significant risk factor for HTLV-III seropositivity, independent of its association with number of sexual partners and receptive anal intercourse.

We found a history of gonorrhoea to be significantly associated with HTLV-III seropositivity and have previously found it to be associated with persistent generalized lymphadenopathy. As well, we detected significant associations with a history of hepatitis and with frequent sexual contact in clubs. Non-B hepatitis has been found to be associated with AIDS,<sup>1</sup> and hepatitis has been proposed as a model of disease transmission for the etiologic agent of AIDS.<sup>1</sup> It is our impression that these three variables exert an independent effect on seropositivity by virtue of their association with lifestyle variables not represented in the model.

It is noteworthy that we detected no association between HTLV-III seropositivity and either age or age at which regular sex with men was initiated. Normally with an endemic agent such as hepatitis B one expects to find an increased prevalence of seropositivity with age. In fact, in our analysis of hepatitis B seropositivity in this population we found that both age and age at which regular sex with men was initiated were strongly associated with hepatitis B seropositivity (unpublished data, 1985). These observations are consistent with the hypothesis that HTLV-III has only recently been introduced into the homosexual population.

In our univariate analysis we found sexual contact in AIDS-endemic areas to be a significant risk factor. Similar results have been reported in Denmark,<sup>12</sup> where sexual contact with men in the United States was the

most significant risk factor for HTLV-III seropositivity. Although this variable was not significant in our multivariate analysis, this might have been due in part to collinearity with other variables. Sexual contact in endemic areas may, in time, decline in importance as the prevalence of the virus rises within the surveyed populations.

While the observed prevalence of HTLV-III antibody of 34% in our study population is high, it must be recognized that the majority of the homosexual population, as represented by our study group, were still seronegative at the time of this analysis. As no vaccine is currently available to prevent HTLV-III infection, efforts must be made to prevent transmission. We and others<sup>11,12</sup> have identified risk factors for HTLV-III seropositivity. Resources should be directed at disseminating this information throughout the homosexual population while relatively large numbers of men remain uninfected.

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**Table VII—Results of logistic regression analysis**

Risk factor	Coefficient	Relative risk
More than 100 male sexual partners in lifetime	0.572	1.8*
Receptive anal intercourse	0.701	2.0†
Fisting	0.680	2.0†
History of gonorrhoea	1.009	2.7‡
History of hepatitis	0.603	1.8†
Sexual contact in clubs	0.660	1.9*

\*p < 0.05.

†p < 0.01.

‡p < 0.001.