

Transmission of HTLV-I and HIV Among Homosexual Men in Trinidad

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Risk for human T-cell lymphotropic virus type I (HTLV-I) and human immunodeficiency virus (HIV) infection was evaluated in 100 homosexual or bisexual men from Trinidad. High seropositivity for HTLV-I (15% vs 2.4% in the general population) was linked to duration of homosexuality and numbers of partners, suggesting that HTLV-I, like HIV, can be transmitted by homosexual sex. Forty percent of homosexuals compared with 0.19% of the general population were seropositive for HIV, and sexual contact with US homosexual men and prior history of gonorrhea were major risk factors. The seroprevalence of HIV was three times higher than that for HTLV-I, suggesting that HIV is more efficiently transmitted, especially since HIV appears to have been recently introduced into Trinidad. Altered immune status was prominent in individuals infected with HIV and coinfecting with HIV and HTLV-I. Whether HIV/HTLV-I coinfection amplifies clinical effects is a hypothesis that will require further evaluation.

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THE CONTINUED spread of human immunodeficiency virus (HIV) (human T-cell lymphotropic virus type III [HTLV-III]/lymphadenopathy-associated virus), the etiologic agent of acquired immunodeficiency syndrome (AIDS), into new geographic areas via homosexual contact and the international distribution of blood products has been documented.^{1,2} The first cases of

AIDS in the homosexual community of Trinidad were recognized in February 1983.⁴

The current study was undertaken to evaluate the introduction of HIV into an otherwise healthy male homosexual or bisexual population in an HTLV-I-endemic area and to evaluate risk factors, outcomes, and the possible interaction of these two retroviruses.

PATIENTS AND METHODS

One hundred self-declared homosexual or bisexual men (mean age, 22 years; range, 15 to 42 years) were enrolled between November 1983 and February 1984 at a sexually transmitted disease clinic in Port of Spain, Trinidad. Two methods of ascertainment were used: (1) Study subjects were recruited from a register of homosexual men maintained

Table 1.—Prevalence of HIV* and HTLV-I* in Two Populations

Population	HTLV-I	HIV	HTLV-I and HIV
Homosexual males	15 (15%)†	40 (40%)†	6 (6%)‡
Comparison group	24 (2.44%)	2 (0.20%)	0 (0%)

*HIV indicates human immunodeficiency virus; HTLV-I indicates human T-cell lymphotropic virus type I.
 † $P < .001$ (significance level computed by the method of Mantel and Haenszel¹⁰ with adjustment for age in intervals of 15 to 20, 21 to 25, 26 to 30, and >30 years).
 ‡ $P < .001$. The unadjusted P value is twice the Fisher's exact one-sided P value. These six doubly infected patients were also counted in the two previous columns.

where is the location?

by the sexually transmitted disease clinic using the services of the contact tracer department. As very few of these men had telephones in their homes, there was a tendency to select volunteers whose homes were more readily accessible by the contact tracers. (2) Incident cases of gay men who appeared at the venereal disease clinic for treatment or follow-up were enrolled consecutively. At the end of the enrollment, there were 70 participants from Port of Spain and its environs and 30 from the rest of the island. No individuals with AIDS were included in the present study. After informed consent was obtained, each individual filled out a brief questionnaire designed to elicit information about age, race, how long they had engaged in homosexual or bisexual activity, their total number of lifetime male sex partners, whether they had ever practiced insertive and/or recep-

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...al intercourse, whether they had sexual contact with individuals outside Trinidad, and whether had a history of syphilis or gonorrhoea. A physical examination was performed with specific emphasis on oral lesions, skin lesions, and hepatosplenomegaly and the size and number of enlarged lymph nodes in each group was recorded. For the purposes of analysis, lymphadenopathy was defined as enlarged nodes of 1 cm or more in diameter in two noncontiguous lymph node groups.

Background seroprevalence rates of HTLV-I and HIV for a comparably aged population of Trinidadian men (whites and residents of Tobago were excluded) were obtained by testing 983 males from a larger island-wide survey for hepatitis B conducted between June and December 1982 (C. Bartholomew, MD, B. Hull-Drysdale, PhD, B. Blumberg, MD, PhD, et al, unpublished data, June 1982). In assembling the hepatitis survey, every tenth business was selected from the Register of Business Places of the Central Statistical Office of the Ministry of Finance of the Government of Trinidad/Tobago. Blood samples and basic demographic information were collected from all willing employees at a selected business place. The cooperating businesses covered a broad spectrum, from light manufacturing to agro- and petro-industrial companies. There was no difference in seroprevalence between Port of Spain and other areas of Trinidad for HTLV-I (C. Bartholomew, MD, unpublished data, July 1986).

Quantitative immunoglobulins (IgG, IgA, and IgM) were measured by single radial immunodiffusion of serum. Viral studies on the homosexual cohort included the determination of serum antibodies to cytomegalovirus, which was titrated by anticomplement immunofluorescence; the determination of serum antibodies to herpes simplex virus by complement fixation; and the determination of Epstein-Barr virus IgG antibodies to viral capsid antigen by complement fixation. Hepatitis B surface antigen and core antibodies were determined by radioimmunoassay.

Antibodies to HTLV-I and HIV were determined by the enzyme-linked immunosorbent assay (ELISA) using disrupted whole virus as a substrate in laboratory test kits developed in the laboratory of one of us (W.C.S.).^{4,6} The

ELISA ratio was defined as the mean absorbance for each pair of test sample wells divided by the mean absorbance of the eight negative control wells.⁶ For HIV, all samples with ELISA ratios less than 3.0 were considered negative,

Table 2.—Epidemiologic Correlates of HTLV-I* and HIV* Infection

Epidemiologic Correlate	No. of Subjects	% Positive	HTLV-I				HIV		
			Odds Ratio† (Unadjusted)	P	Odds Ratio† (Adjusted for Age)	P	% Positive	Odds Ratio† (Unadjusted)	P
Age, y									
>22	49	22	39	0.9	.8
≤22	51	8	3.4	.04	41
Race									
Asian	10	20	30	0.6	.5
Black	90	14	1.5	.8	1.7	.6	41
US contact									
Yes	15	8	0.3	.3	0.5	.5	73	5.3	.004
No	85	16	34
Duration of homosexuality, y									
≤10	70	9	4.4	.006	3.4	.05	39	1.2	.7
>10	30	30	43
Number of lifetime homosexual partners									
>20	62	23	44	1.5	.4
≤20	38	3	10.8	.007	7.1	.03	34
Receptive anal intercourse									
Yes	94	16	∞	.3	41	3.4	.2
No	6	0	17
Insertive anal intercourse									
Yes	60	12	0.6	.2	0.6	.6	47	2.1	.2
No	40	20	30
History of gonorrhoea									
Yes	49	14	0.9	.8	0.7	.6	51	2.5	.03
No	51	16	29
History of syphilis									
Yes	65	14	0.8	.7	0.8	.6	38	0.83	.7
No	35	17	43
Lymphadenopathy									
Yes	68	12	0.5	.2	0.8	.8	57	42	<.001
No	32	22	3
HTLV-I									
Yes	15	40
No	85	40	1.00	1.0
HTLV-III									
Yes	40	15	1.0	1.0	1.4	.6
No	60	15

*HTLV-I indicates human T-cell lymphotropic virus type I; HIV indicates human immunodeficiency virus.

†See "Patients and Methods" section for information on how odds ratios were determined.

‡Not calculable because none of the six subjects answering "yes" were positive for HTLV-I.

and samples with ratios greater than or equal to 3.0 required confirmation by Western blot analysis to be called positive.⁷ For HTLV-I, samples with ELISA ratios less than 3.0 were considered negative, and samples with ratios greater than 3.0 were confirmed by competitive binding assays by the method of W.C.S.⁸ No tests for HTLV-II were made.

Total numbers of T cells (Leu 4), T-helper/inducer cells (Leu 3), and T-suppressor/cytotoxic cells (Leu 2) were determined by direct immunofluorescence with the use of human monoclonal antibodies on Ficoll-Hypaque-separated mononuclear cells. Absolute numbers of T cells were calculated with the use of the total white blood cell

count and differential.

The Mantel-Haenszel procedure¹⁰ was used to test the equality of proportions between the homosexual study population and the historic hepatitis survey study group (Table 1) with adjustment for age. Unadjusted comparisons of proportions within the male homosexual study population (Table 2) were made with standard χ^2 tests.⁹ To see whether various factors in Table 2 added to age in predicting HTLV-I infection, logistic models¹¹ were fitted, in which the presence of HTLV-I was the dependent variable and in which the independent variables included age plus one other factor. Age was stratified into two levels by coding age as 1 if the subject was older than 22 years and 0

Table 3.—Laboratory Markers Associated With HTLV-I* and HIV† (no AIDS) see intro

Laboratory Markers by Infection Group	No. of Subjects	Median	Range	Unadjusted P	Adjusted P
T4/T8 ratio‡					
HTLV-I only	9	1.20	0.60-1.94	.40	.580
HIV only	32	0.70	0-2.45	.004	.004
HTLV-I and HIV	5	0.30	0.30-1.20	.02	.020
No HTLV-I or HIV	43	1.00	0.30-2.75
T4 cells/mm³ (× 10⁹/L)					
HTLV-I only	9	560 (0.56)	290-1560 (0.29-1.56)	.60	.94
HIV only	31	510 (0.51)	0-2790 (0-2.79)	.59	.51
HTLV-I and HIV	5	490 (0.49)	130-1210 (0.13-1.21)	.45	.312
No HTLV-I or HIV	43	560 (0.56)	220-1660 (0.22-1.66)
T8 cells/mm³ (× 10⁹/L)					
HTLV-I only	9	620 (0.62)	320-990 (0.32-0.99)	.90	.85
HIV only	31	890 (0.89)	410-1970 (0.41-1.97)	.002	.003
HTLV-I and HIV	5	1000 (1.00)	470-1740 (0.47-1.74)	.08	.085
No HTLV-I or HIV	43	570 (0.57)	120-2480 (0.12-2.48)
Herpes simplex (titers)					
HTLV-I only	9	32	8-64	.281	.497
HIV only	34	32	0-64	.101	.064
HTLV-I and HIV	6	64	32-128	.002	.003
No HTLV-I or HIV	51	16	0-64
Cytomegalovirus (titers)					
HTLV-I only	9	32	8-64	.342	.326
HIV only	34	32	0-128	.040	.040
HTLV-I and HIV	6	57	16-128	.020	.020
No HTLV-I or HIV	51	16	0-128
IgG level, mg/dL (g/L)					
HTLV-I only	9	2160 (21.60)	1184-2261 (11.84-22.61)	.273	.167
HIV only	32	2340 (23.40)	1316-3350 (13.16-33.50)	.001	.001
HTLV-I and HIV	6	2662 (26.62)	2045-3860 (20.45-38.60)	.002	.002
No HTLV-I or HIV	49	1942 (19.42)	1096-3520 (10.96-35.20)
IgA level, mg/dL (g/L)					
HTLV-I only	9	452 (4.52)	179-498 (1.79-4.98)	.046	.104
HIV only	32	389 (3.89)	159-689 (1.59-6.89)	.036	.039
HTLV-I and HIV	6	469 (4.69)	173-655 (1.73-6.55)	.152	.834
No HTLV-I or HIV	49	288 (2.88)	55-618 (0.55-6.18)

*HTLV-I indicates human T-cell lymphotropic virus type I; HIV indicates human immunodeficiency virus.

†Unadjusted P values are based on a two-sided Wilcoxon test comparing one of the three infected groups with the uninfected group. Age-adjusted P values are obtained from age-stratified Wilcoxon tests as described in the "PATIENTS AND METHODS" section. Titers of hepatitis B and Epstein-Barr virus and levels of IgM were not significantly associated in any of the comparisons, so those data are not shown.

‡Comparing the T4/T8 ratio in those five patients with coinfection to those 32 patients with HIV infection alone, P = .244 unadjusted and P = .282 adjusted for age.

otherwise, based on the fact that age 22 years was the median and mean age of the population, so that half of study subjects were over and half under age 22 years. Unadjusted comparisons for quantitative variables (Table 3) were based on two sample Wilcoxon tests. Age-adjusted P values were obtained by calculating Wilcoxon numerators and variances separately in two age strata (≤ 22 years and > 22 years) and then calculating a standardized normal deviate by dividing the square root of the sum of the variances into the sum of the numerators.

RESULTS

Seroprevalence

Among the 100 homosexual men, 15 were HTLV-I seropositive, 40 were HIV seropositive, and, of these, six were both HTLV-I and HIV seropositive (Table 1). For HTLV-I, the 15% rate of seropositivity among the gay male

population was sixfold higher than that recorded in the comparison population ($P < .001$). Two (0.19%) confirmed HIV positives were observed in the comparison group in contrast to 40 among the 100 homosexual men ($P < .001$).

Risk Factors for HTLV-I

Among members of the homosexual study group, there was a significant correlation between HTLV-I seropositivity and age (odds ratio = 3.4; $P = .04$) (Table 2). Persons of African descent accounted for 90 of the 100 cohort members, and 13 (14%) of these were seropositive for HTLV-I, while two of the ten (20%) Asian study subjects were HTLV-I seropositive (odds ratio = 1.5; $P = .6$) (Table 2).

Number of lifetime sexual partners (odds ratio = 10.8; $P = .007$) and duration of homosexuality (odds ratio = 3.1; $P = .02$) were both significantly associated with HTLV-I seropositivity even

when adjusted for age (Table 2). Ever having performed receptive or insertive anal intercourse was not linked to HTLV-I seropositivity, but number of lifetime specific sexual acts was not obtained. A history of gonorrhea or syphilis was not associated with HTLV-I seropositivity.

Risk Factors for HIV

Age and race were not associated with HIV seropositivity (Table 2). The major risk factor for HIV seropositivity was homosexual contact with a partner from a foreign country, primarily the United States (odds ratio = 5.3; $P = .004$). Duration of homosexuality (odds ratio = 1.2; $P = .7$) and number of lifetime partners (odds ratio = 1.5; $P = .4$) were not significantly associated with HIV seropositivity. Ever having engaged in anal intercourse, either receptive or insertive (94% reported having been receptive partners and 60% were insertive), was associated with a nonsignificant increased risk (odds ratio = 3.4; $P = .2$ [receptive]; odds ratio = 2.1; $P = .2$ [insertive]). Self-reported gonorrhea (odds ratio = 2.5; $P = .03$), but not syphilis (odds ratio = 0.83; $P = .7$), was significantly associated with HIV seropositivity. There is no association between HTLV-I seropositivity and being seropositive for HIV or vice versa. None of the clinical variables was independently associated with dual HTLV-I/HIV infection (data not shown).

Outcomes of Infections

Effects of HTLV-I and HIV infection were measured clinically and through a number of ancillary laboratory investigations (Tables 2 and 3). Lymphadenopathy was not associated with HTLV-I infection (odds ratio = 0.5; $P = .2$), but was strongly associated with HIV infection (odds ratio = 42.0; $P < .001$). Fifty-seven percent of persons with lymphadenopathy were HIV seropositive compared with 3% of those without lymphadenopathy.

As summarized in Table 3, depression of the T4/T8 ratio was significantly associated with HIV infection alone (median ratio = 0.70; $P = .002$), but the lowest median ratio (0.30 [$P = .02$]) was observed in persons coinfecting with HTLV-I and HIV. The low ratio in HIV-infected study subjects was due to elevated T8 cells (median count [HIV alone] = 890 [$P = .002$]; median count [coinfection] = 1000 [$P = .08$]), while there were no differences in T4-cell counts when compared with uninfected study subjects. The difference in T4/T8 ratio and T8 count between coinfecting and singly infected persons

control accelerated the transformation of premalignant HTLV-I-infected T cells in this patient. Already there is evidence that the immunosuppressive effects of HIV augment the pathogenic effects of other viruses, including the induction of B-cell lymphoma, reflecting a postulated deregulation of immunologic control of Epstein-Barr virus.^{28,29}

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References

- Melbye M, Biggar RJ, Ebbesen P, et al: Seroepidemiology of HTLV-III antibody in Danish homosexual men: Prevalence, transmission, and disease outcome. *Br Med J* 1984;289:573-575.
- Melbye M, Froebel KS, Madhok R, et al: HTLV-III seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the U.S.A. *Lancet* 1984;2:1444-1446.
- Rinaldo C, Lyter D, Kingsley L, et al: Virologic, immunologic, and epidemiologic associations with AIDS among gay males in a low incidence area. *Ann NY Acad Sci* 1984;437:544-548.
- Bartholomew C, Charles W, Saxinger C, et al: Racial and other characteristics of human T cell leukaemia/lymphoma (HTLV-I) and AIDS (HTLV-III) in Trinidad. *Br Med J* 1985;290:1243-1246.
- Saxinger C, Gallo RC: Application of the indirect ELISA microtest to the detection and surveillance of human T-cell leukemia-lymphoma virus (HTLV). *Lab Invest* 1983;49:371.
- Weiss SH, Goedert JJ, Sarngadharan MG, et al: Screening test for HTLV-III (AIDS agent) antibodies: Specificity, sensitivity, and applications. *JAMA* 1985;253:221-225.
- Sarngadharan MG, Popovic M, Bruch L, et al: Antibodies reactive with human T-lymphotropic retrovirus (HTLV-III) in the serum of patients with AIDS. *Science* 1984;224:506-508.
- Saxinger C, Blattner WA, Levine P, et al: HTLV-I antibodies in Africa. *Science* 1984;225:1473-1476.
- Snedecor GW, Cochran WG: *Statistical Methods*, ed 6. Ames, Iowa State University Press, 1967.
- Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959;22:719-748.
- Cox DR: *The Analysis of Binary Data*. Andover, England, Methuen & Co Ltd, 1970.
- Goedert JJ, Sarngadharan MG, Biggar RJ, et al: Determinants of retrovirus (HTLV-III) and immunodeficiency conditions in homosexual men. *Lancet* 1984;2:711-715.
- Blattner WA, Gallo RC: Human T-cell leukemia/lymphoma viruses: Clinical and epidemiologic features. *Curr Top Microbiol Immunol* 1985;115:67-88.
- Tajima K, Tonunaga S, Suchi T, et al: Epidemiologic analysis of the distribution of antibody to adult T-cell leukemia virus associated antigen: Possible horizontal transmission of adult T-cell leukemia virus. *Gann* 1982;73:893-901.
- Tedder RS, Shanson DC, Jeffries DJ, et al: Low prevalence in the UK of HTLV-I and HTLV-III infection in subjects with AIDS, with extended lymphadenopathy, and at risk of AIDS. *Lancet* 1984;2:125-128.
- Robert-Guroff M, Weiss SH, Giron JA, et al: Associations of antibodies to HTLV-I, -II, and -III with soft tissue infections in intravenous drug abusers from an AIDS endemic region. *JAMA* 1986;255:3133-3137.
- Fauci AS, Macher AM, Longo DL, et al: NIH Conference, Acquired immunodeficiency syndrome: Epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984;100:92-106.
- Goedert JJ, Biggar RJ, Winn DM, et al: Decreased helper T lymphocytes in homosexual men: II. Sexual practices. *Am J Epidemiol* 1985;121:637-644.
- Polk BF, Fox R, Brookmeyer R, et al: Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. *N Engl J Med* 1987;316:61-66.
- Blattner WA, Biggar RJ, Weiss SH, et al: Epidemiology of human T-lymphotropic virus type III and the risk of the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:665-670.
- Kobayashi M, Yoshimoto S, Fujishita M, et al: HTLV-positive T-cell lymphoma/leukemia in an AIDS patient. *Lancet* 1984;1:1361-1362.
- Essex M, McLane MF, Tachibana N, et al: Seroepidemiology of human T-cell leukemia virus in relation to immunosuppression and the acquired immunodeficiency syndrome, in Gallo RC, Essex ME, Gross L (eds): *Human T-Cell Leukemia/Lymphoma Virus*. Cold Spring Harbor (NY) Laboratory, 1984, pp 355-362.
- Popovic M, Flomenberg N, Volkman DJ, et al: Alteration of T-cell functions by infection with HTLV-I or HTLV-II. *Science* 1984;226:459-462.
- Clark JW, Robert-Guroff M, Ikehara O, et al: Human T-cell leukemia-lymphoma virus type I and adult T-cell leukemia-lymphoma in Okinawa. *Cancer Res* 1985;45:2849-2852.
- Harada S, Koyanagi Y, Yamamoto N: Infection of HTLV-III/LAV in HTLV-I-carrying cells MT-2 and MT-4 and application in a plaque assay. *Science* 1985;229:563-566.
- Koyanagi Y, Harada S, Yamamoto N: Correlation between high susceptibility to AIDS virus and surface expression of OKT-4 antigen in HTLV-I-positive cell lines. *Jpn J Cancer Res* 1985;76:799-802.
- Harper ME, Kaplan MH, Mansell L: Concomitant infection with HTLV-I and HTLV-III in a patient with T8 lymphoproliferative disease. *N Engl J Med* 1986;315:1073-1078.
- Ziegler JL, Beckstead JA, Volberding PA, et al: Non-Hodgkin's lymphoma in 90 homosexual men: Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. *N Engl J Med* 1985;311:565-570.
- Birx DL, Redfield RR, Tosato G, et al: Defective regulation of Epstein-Barr virus infection in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related disorders. *N Engl J Med* 1986;314:874-879.