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Human T-Cell Lymphotropic Virus Type III Infection in a Cohort of Homosexual Men in New York City

Cladd E. Stevens, MD; Patricia E. Taylor, PhD; Edith A. Zang, PhD; John M. Morrison, MA; Edward J. Harley, MS; Santiago Rodriguez de Cordoba, PhD; Carlos Bacino, MD; Robert C. Y. Ting, PhD; Anne J. Bodner, PhD; M. G. Sarngadharan, PhD; Robert C. Gallo, MD; Pablo Rubinstein, MD

• **Using blood samples collected since 1978, we investigated the epidemiology of human T-cell lymphotropic virus type III (HTLV-III), the etiologic agent of the acquired immunodeficiency syndrome, in a group of 378 homosexually active men who have resided in New York City since the acquired immunodeficiency syndrome epidemic began. The anti-HTLV-III prevalence was 6.6% in sera from 1978 or 1979, and the subsequent annual incidence of seroconversion among susceptible men ranged between 5.5% and 10.6%. The highest incidences were in recent years, even though these men reported a decrease in their sexual activity during this time. These data demonstrate the continuing risk of HTLV-III infections in the homosexual population studied and emphasize the need for more effective prevention of transmission. The year during which antibody was first present was the only factor identified that was associated with altered cell-mediated immunity in antibody-positive men. Men who became antibody positive in 1981 or earlier currently had significantly lower OKT4/OKT8 ratios than did those who seroconverted more recently. Further follow-up will be necessary to establish the reasons for this association.**

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THE ACQUIRED immunodeficiency syndrome (AIDS), manifested by Kaposi's sarcoma and infections considered indicative of cellular immune deficiency, was first recognized in 1980.[1-11] The majority of AIDS cases in the United States have occurred in homosexually active men. In an effort to control the spread of infection with the AIDS virus in this group, public health officials have recommended that homosexual men limit their numbers of male sex partners and avoid the types of sexual activity associated with a risk of infection, especially receptive rectal intercourse.[12]

In early 1984, we began a prospective study of AIDS in a cohort of homosexual men in New York City, one of the major foci of the disease in the United States. The men who volunteered for this project had participated in earlier studies of the epidemiology of hepatitis B virus (HBV) or a hepatitis B vaccine efficacy trial that began in 1978.[13-15] Many of these men had been followed up continuously since that time, and the sera collected from them had been kept frozen in storage. After this study began, the etiologic agent of AIDS was identified as a retrovirus (designated human T-cell lymphotropic virus type III [HTLV-III], lymphadenopathy-associated virus, or AIDS-associated retrovirus), and serologic tests for antibody to the virus were developed.[16-26] In testing sera from men in our cohort for antibody to the virus, we have been able to follow the spread of infection within this group throughout the entire epidemic and to assess the impact, if any, of changes in sexual activity. For comparison, we also examined the incidence in this population of infection with hepatitis A virus (HAV), a virus that is well documented to be transmitted by homosexual activity.[27] These studies further allowed us to examine the

From the Wolf Szmuness Laboratory of Epidemiology (Drs Stevens, Taylor, and Zang and Messrs Morrison and Harley) and the Laboratory of Immunogenetics (Drs Rodriguez de Cordoba, Bacino, and Rubinstein), Lindsley F. Kimball Research Institute, New York Blood Center, New York; the Biotech Research Laboratories, Inc, Rockville, Md (Drs Ting and Bodner); Litton Bionetics, Inc, Kensington, Md (Dr Sarngadharan); and the National Cancer Institute, Bethesda, Md (Dr Gallo).

Reprint requests to New York Blood Center, 310 E 67th St, New York, NY 10021 (Dr Stevens).

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relationship between the duration of infection and its immunologic consequences. We report herein preliminary results of this study.

SUBJECTS AND METHODS

Study Population

Volunteers for a prospective study of AIDS were sought in 1984 from among a cohort of 4,394 men who had participated in studies of HBV beginning in 1978.[14,15] Of the 378 men included in this report, 212 had previously taken part in a hepatitis B vaccine trial and had had serial blood specimens drawn every three to six months from 1978 or 1979 until they entered the current project. The remaining 166 men had participated only in a survey for HBV markers and had a previous specimen collected only in 1978 or 1979. To be eligible for the study, a volunteer could not have already been diagnosed as having AIDS. Otherwise, volunteers were not selected by either symptoms or by risk factors for AIDS other than homosexuality. When compared with men who did not join the current study, volunteers tended to be older and more sexually active (data not shown).

Prospective Study Protocol

At the time of entry early in 1984, the participants completed a self-administered questionnaire detailing their medical history (including sexually transmitted diseases), use of recreational drugs, sexual activity, and known contact with AIDS cases. Questions about sexual activity focused on three time periods: the six months before entry into the AIDS study, the period just before the individual became aware of AIDS, and the period of peak sexual activity. A physical examination for lymphadenopathy and signs of AIDS was performed by a physician's assistant. Blood specimens were taken for viral serology, for quantitation of β_2-microglobulin, immunoglobulins, and circulating immune complexes, for counts of peripheral blood cells and T-lymphocyte subsets, and for in vitro assessment of lymphocyte function.

Laboratory Tests

Sera were tested under code for anti-HTLV-III by an enzyme-linked immunosorbent assay (ELISA) and by Western blot analysis.[17,26] The ELISA results were expressed as the ratio of absorbance (at a wavelength of 410 nm) of the sample to the mean absorbance of the normal controls. An individual was considered positive for anti-HTLV-III if his serum ELISA ratio was 3.0 or higher and antibody to the 41-dalton molecular weight protein (p41) was detected by Western blot. When there was a discrepancy between the ELISA and Western blot, the specimen was retested by both methods, and a subsequently drawn specimen from the same individual was also tested by both methods. Individuals who had a specimen initially positive for anti-HTLV-III by either ELISA or Western blot but not confirmed on testing of the same or a subsequent sample were considered unconfirmed and counted as negative for this report. Eleven men had unconfirmed serology.

Sera collected in 1978 or 1979 and in 1984 from each participant were tested for anti-HTLV-III. Interim sera from men who had been part of the hepatitis B vaccine efficacy trial and who developed anti-HTLV-III between 1978 or 1979 and 1984 were tested to determine the time of seroconversion.

Antibody to HAV (anti-HAV) was detected by radioimmunoassay (HAVAB). β_2-Microglobulin levels were measured by radioimmunoassay and expressed in micrograms per liter. Immunoglobulin (IgG, IgA, and IgM) levels were measured by ELISA.[28] Circulating immune complex levels were measured by their capacity for binding C1q.

Total white and red blood cell and platelet counts, hemoglobin, and hematocrit levels were determined using automated counters. White blood cell differential counts were carried out under light microscopy, using Wright-Giemsa-stained smears of freshly collected peripheral blood. The numbers of T lymphocytes and the helper/inducer and suppressor/cytotoxic subsets were measured using cells labeled with monoclonal anti-T-cell antibodies (OKT3, OKT4, and OKT8, respectively) on mononuclear cells separated from peripheral blood by Ficoll-Hypaque and counted in a fluorescence-activated cell sorter (FACS IV). T-cell blastogenic responses were detected by the incorporation of radioisotope-labeled thymidine in lymphocytes stimulated by pokeweed mitogen (PWM) or phytohemagglutinin in the presence of T-cell growth factor and measured as counts per minute and as the percentage of thymidine incorporated after 18 hours of incubation. Results were also compared with the responses by cells from a panel of healthy donors as controls. For purposes of analysis, we used the peak response to varying mitogen concentrations.

Table 1.—Reported Sexual Activity in a Cohort of Homosexual Men in New York City*

Activity	% of Homosexual Men, by Period of Sexual Activity: Peak (1976-1980)†	Before Aware of AIDS (1981-1982)†	Current (1984)
No. of male sex partners in 6 mo			
≥2 steady	55.8	41.7	24.9
≥20 nonsteady	63.9	46.4	18.5
Practice of receptive sex			
Oral-genital	97.1	94.1	78.6
Rectal	80.1	72.8	46.0
Oral-rectal	67.3	58.6	33.4
Practice of insertive sex			
Oral-genital	98.1	95.4	82.9
Rectal	88.1	80.9	59.1
Oral-rectal	57.1	49.5	27.8

*Differences in numbers of sex partners and in the practice of receptive and insertive sexual techniques between peak and before awareness of acquired immunodeficiency syndrome (AIDS) periods and between before awareness of AIDS and current periods were statistically significant ($P<.05$ by χ^2) except for receptive oral-genital sex between the peak and before awareness of AIDS periods.

†Range of years reported by most men.

Statistical Analysis

Comparisons involving categorical variables and continuous variables grouped categorically were made using contingency tables and the χ^2 statistic. The strength of associations of continuous variables with anti-HTLV-III was estimated individually using simple logistic regression and in combinations through stepwise, multiple logistic regression.[29] The incidence of anti-HTLV-III seroconversion for each calendar year was calculated as the number of seroconversions that occurred during the year divided by the sum of the length of follow-up in person-years among the participants while they were antibody negative during the year, and expressed as a percentage. The same procedure was used to calculate the incidence of HAV infection by calendar year.

RESULTS

Men participating in this study reported decreases in sexual activity from their period of peak activity to the current period, especially in the numbers of sex partners and in rectal

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intercourse and oral-rectal sex (Table 1). The largest proportion of these decreases occurred after the men became aware of AIDS, which occurred in 1981 or 1982 for most men.

Among the men tested, 6.6% already had detectable anti-HTLV-III in 1978 or 1979. The antibody prevalence reached 43.7% by early 1984. Exactly when anti-HTLV-III seroconversion occurred was of particular interest, in view of the reported decrease in sexual activity. Accordingly, we determined the incidence of anti-HTLV-III seroconversion among those men for whom serial samples were available (the hepatitis B vaccine efficacy trial participants) for each year since 1979 (Fig 1). The annual incidence of seroconversion ranged from 5.5% to 10.6%. The incidence was highest in 1982 and 1983 through early 1984, despite the reported decrease in sexual activity among the participants during this period. In contrast, the annual incidence of anti-HAV seroconversion decreased dramatically beginning in 1982 (Fig 1). The data on the incidence of HAV seroconversion provided objective verification of the sexual history reported to us. Because the period of viremia and fecal shedding for HAV is brief, one would expect infection rates to be more readily affected by the kinds of changes reported in sexual behavior than might be seen for an agent like HTLV-III, which has a prolonged period of infection.

Anti-HTLV-III prevalence correlated with numbers of different sex partners, the frequency of various types of sexual practices, history of common sexually transmitted diseases, use of recreational drugs (including intravenous drugs), and known sexual contact with a person with AIDS. Because many of these variables correlated with each other, stepwise, multiple logistic regression analysis was used to identify those that had an independent, predictive relationship with antibody prevalence. In this analysis, only receptive rectal intercourse, douching, rectal bleeding, sexual contact with a person known to have AIDS, and use of intravenous drugs were significant predictors ($P<.05$) of anti-HTLV-III positivity. The numbers of times a man had had sex with a person with

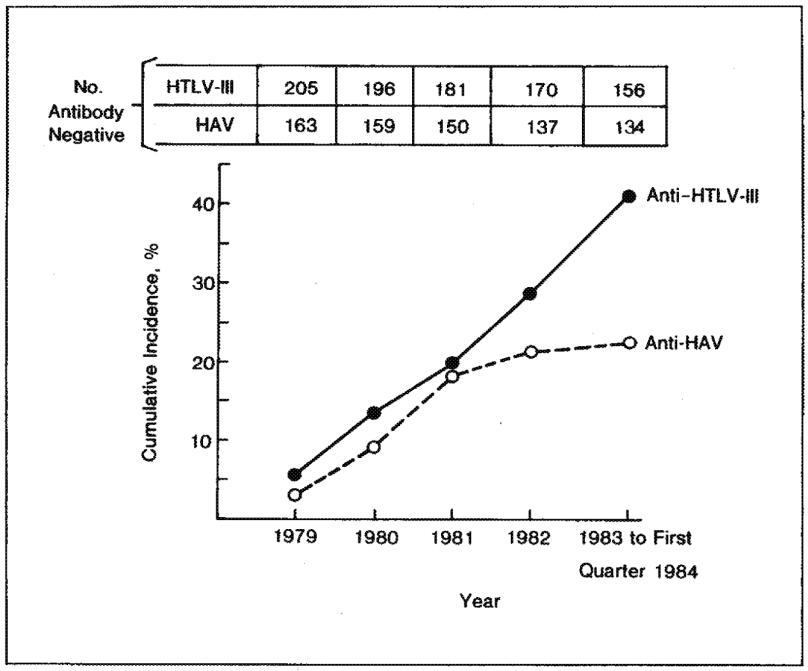

Fig 1.—Incidence of human T-cell lymphotropic virus type III (HTLV-III) and hepatitis A virus (HAV) antibody seroconversion among hepatitis B vaccine trial participants, by year. Note that length of period 1983 to early 1984 is increased proportionately in figure to include first quarter of 1984.

AIDS (whether before or after the diagnosis) was also associated with anti-HTLV-III positivity: 93.7% of 32 men who knew they had had sex with a person with AIDS at least ten times were anti-HTLV-III positive, compared with 48.1% of men who had sex with a person with AIDS from one to nine times and only 37.4% of men who had no knowledge of having had sex with a person with AIDS. Use of condoms was too infrequent in this study to assess its effectiveness as a barrier against HTLV-III infection.

Clinical Features

None of the participants had evidence of a specific disease associated with AIDS on entry into the study, although many reported experiencing some of the nonspecific symptoms associated with AIDS. Lymphadenopathy, cough, malaise, fever, night sweats, diarrhea, or unexplained weight loss was reported significantly more often among the anti-HTLV-III-positive men than among the antibody-negative men (37.4% vs 17.1%, respectively, $P<.001$). The majority of anti-HTLV-III-positive men, however, reported having no symptoms.

Although few participants reported a history of lymphadenopathy, most (82.8%) had palpable lymph nodes at one or more of seven sites examined on entry. Among anti-HTLV-III-positive men, lymph nodes were detected at various sites twofold to tenfold more often than among antibody-negative men. Of antibody-positive men, 50.9% had lymph nodes of 1 cm in diameter or larger at two or more extrainguinal sites, compared with only 8.0% of anti-HTLV-III-negative men ($P<.001$).

Laboratory Features

The presence of anti-HTLV-III was associated with abnormalities in several hematologic indexes, with alterations of in vitro measures of cell-mediated immunity (CMI) (OKT4 and OKT8 counts, OKT4/OKT8 ratio, and lymphocyte responsiveness to PWM or phytohemagglutinin) and with increased levels of IgG, IgA, β_2-microglobulin, and circulating immune complexes. Stepwise multiple logistic regression analysis indicated that, of these variables, the OKT4/OKT8 ratio had the strongest predictive value for anti-HTLV-III status. Responsiveness to PWM had no independent predictive value for anti-HTLV-III positivity, probably because it was so

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closely associated with the OKT4/OKT8 ratio. Figure 2 shows the correlation between OKT4/OKT8 ratio and anti-HTLV-III positivity. The geometric mean OKT4/OKT8 ratio in anti-HTLV-III-positive men was 0.76 (with 95% of values falling between 0.25 and 2.34), while the geometric mean in antibody-negative men was 1.80 (with 95% of values between 0.85 and 3.83). Among anti-HTLV-III-positive men, there was no statistically significant correlation between the OKT4/OKT8 ratio and the degree of lymphadenopathy.

Determinants of Altered CMI Among Anti-HTLV-III-Positive Men

In an effort to identify factors that might be related to altered CMI among men who were anti-HTLV-III positive, we examined the relationship between OKT4/OKT8 ratio and various exposure factors (history of sexually transmitted disease, numbers of sex partners and type of sexual activity, sexual exposure to a known AIDS case, and recreational drug use) and duration of antibody positivity. The only factor significantly associated with a low OKT4/OKT8 ratio in anti-HTLV-III-positive men was the duration of positivity. Men who were antibody positive for a longer period of time were more likely to have a low OKT4/OKT8 ratio than were those with a relatively short period of positivity (Table 2).

AIDS Cases

In the year and a half since the study began, ten of the men in this study have developed AIDS: seven with *Pneumocystis carinii* pneumonia, one with Kaposi's sarcoma, one with toxoplasmosis of the central nervous system, and one with a progressive, fatal dementia. Each of these men was anti-HTLV-III positive on entry. Nine had been antibody positive since 1981 or earlier. The other case was anti-HTLV-III negative in 1978, but the onset of antibody positivity could not be determined precisely because no interim sera were available. Nine of the ten patients had an OKT4/OKT8 ratio of less than 0.5 on entry. The other patient had an OKT4/OKT8 ratio of 0.93 on entry, but the ratio decreased to 0.46 by one year later, two months before the diagnosis of AIDS. Table 3 shows the incidence of AIDS during 18 months of follow-up among anti-HTLV-III-positive men according to their OKT4/OKT8 ratio on entry into the project in early 1984.

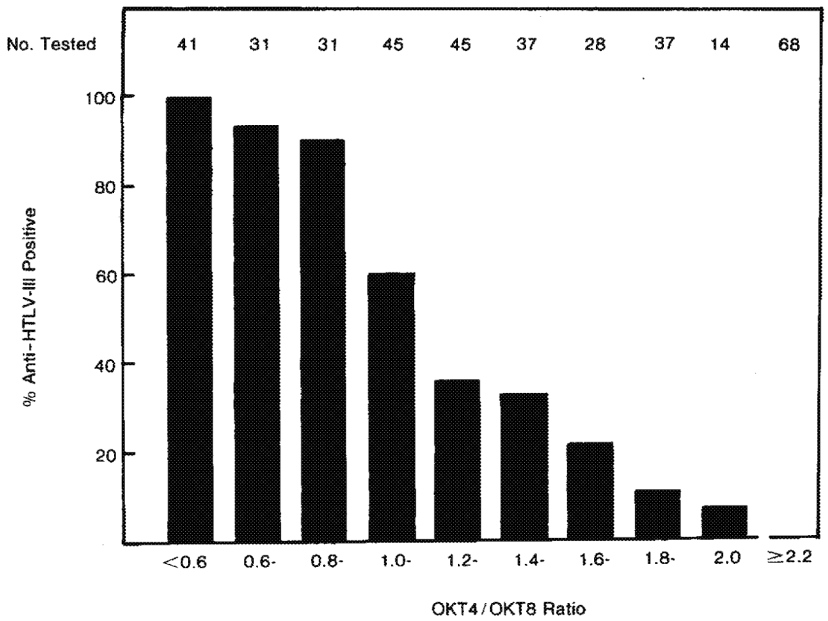

Fig 2.—Prevalence of antibody to human T-cell lymphotropic virus type III (anti-HTLV-III) among homosexual men according to their ratio of OKT4-positive to OKT8-positive lymphocytes (OKT4/OKT8 ratio).

Table 2.—Ratio of OKT4/OKT8 at the Time of Entry (1984), by Year When Anti-HTLV-III* Was First Detected†

Year of First Anti-HTLV-III Positivity	No. Tested	% With OKT4/OKT8 Ratio <1.0 in 1984
1981 or earlier	42	71.4
1982 or later	33	36.4

*Anti-HTLV-III indicates antibody to human T-cell lymphotropic virus type III.
†$\chi^2=9.2$, $P<.01$.

Table 3.—Incidence of AIDS* During 18 Months Follow-up of Anti-HTLV-III*-Positive Men, by Their OKT4/OKT8 Ratio on Entry in Early 1984

Ratio of OKT4/OKT8 Lymphocytes in 1984	No. of Men	No. (%) With AIDS
<0.5	37	9 (24.3)
0.5-0.9	54	1 (1.9)
≥1.0	74	0 (0.0)
Total	**165**	**10 (6.1)**

*AIDS indicates acquired immunodeficiency syndrome; anti-HTLV-III, antibody to human T-cell lymphotropic virus type III.

COMMENT

The most disturbing observation from this study was that the incidence of anti-HTLV-III seroconversion remained persistently high throughout the five-year study period, suggesting that HTLV-III continued to be transmitted in this population. Recent seroconversions could be due to early exposure if the interval between exposure and the appearance of antibody is prolonged in some individuals. However, experimental data in chimpanzees suggest that this interval is only weeks to months rather than years.[30,31] It thus seems most likely that recent seroconversion reflects recent infection. A continuing occurrence of new HTLV-III infections, despite considerable curtailment of homosexual activity, would imply that the risk of exposure from a sexual encounter is now much greater than it was early in the epidemic, and indicates that precautions taken by many homosexual men thus far are not adequate to prevent transmission. Data from this and previous studies have shown that receptive rectal intercourse, for example, is an important risk factor for HTLV-III infection.[32-37] Yet, at the time of entry into this project, nearly

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half of the participants still practiced this technique. We found no evidence that other forms of sexual activity contributed to the risk. However, these data should not be taken to indicate that other forms of sex are safe. It is possible that the virus may be transmitted by sexual activities other than receptive rectal intercourse, although probably with lower efficiency and therefore not detectable in the present study. Our retrospectively collected data on sexual activity also might not accurately reflect the specific activities practiced at the time of exposure. Data collected prospectively on new HTLV-III infections may provide more reliable information on current risk-related sexual activity and a stronger basis for making future recommendations to minimize the risk of infection.

The most consistent immunologic alteration among anti-HTLV-III-positive men was in the T-lymphocyte subsets, with decreased OKT4 and increased OKT8 counts resulting in low OKT4/OKT8 ratios, a pattern similar to that seen in AIDS cases.[38-41] The length of time since antibody seroconversion was the only factor we identified that was associated with a low OKT4/OKT8 ratio; men infected earliest were those most likely to have ratios below the normal range, a relationship also reported among anti-HTLV-III-positive hemophiliacs.[42] Theoretically, this relationship with duration of antibody positivity could have occurred through chronic HTLV-III infections producing progressive deterioration in CMI. This possibility may be likely in view of reports that HTLV-III is related to visna and other lentiretroviruses that characteristically produce chronic infections and repeated viral mutation.[43] It is reassuring, however, that even among men found to have been exposed five years ago or longer, some still have normal CMI, suggesting that the development of immune deficiency and AIDS may not be an inevitable consequence of exposure. Repeated exposure over time to variants of HTLV-III or to other infectious agents or environmental factors that affect the immune system could also explain the association between the duration of anti-HTLV-III positivity and altered CMI. The recent isolation of more than one HTLV-III variant from a single individual might support this concept.[44] A third explanation for our findings could be that passage of HTLV-III in the human population has produced viral attenuation, resulting in milder infections among those most recently infected, a phenomenon postulated for myxoma virus among Australian rabbits.[45] A final explanation might be that recently infected individuals may be more resistant to HTLV-III than were those infected early in the epidemic. For example, exposure to other immunosuppressive infectious agents, such as cytomegalovirus, before HTLV-III may have been more common among the more sexually active men infected with HTLV-III early in the epidemic than among those recently exposed. Until one or more of these possibilities is proved, attack rates for AIDS among individuals infected with HTLV-III early in the epidemic should not be considered predictive of the outcome for recent infections.

Unlike some other studies, participants in this project were not preselected for signs or symptoms thought to be AIDS related. Our data demonstrate that men who are anti-HTLV-III positive exhibit a broad range of clinical findings, from no symptoms and no detected physical or immunologic abnormalities to features of the AIDS-related complex with generalized lymphadenopathy and altered CMI to frank AIDS. What proportion of antibody-positive men will progress to the development of AIDS is not yet clear.[46] Although 6.1% of the antibody-positive men in this study developed AIDS within 18 months of entry into the project, this rate may not be representative. Some of these patients had nonspecific symptoms on entry and may have volunteered for the study because they suspected they might be developing AIDS. Moreover, nine of the ten patients were known to have had serologic evidence of HTLV-III infection at least four to seven years before AIDS was diagnosed. None of the men known to have been antibody positive for less than four years has yet developed AIDS. This could simply relate to the incubation period, if four years or longer is typical, or may be compatible with the concept that recently acquired infections generally produce milder consequences than the earlier infections. Further prospective evaluation should provide the data needed to accurately describe the long-term risk for developing AIDS, the rate of progression to AIDS, and what, if any, viral factors and host or environmental cofactors affect progression.

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