The Acquired Immunodeficiency Syndrome in a Cohort of Homosexual Men
A Six-Year Follow-up Study

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A cohort of 6875 homosexual men, initially seen at the San Francisco City Clinic between 1978 and 1980, were studied to determine the incidence and prevalence of the acquired immunodeficiency syndrome (AIDS), related conditions, and infection with the human T-lymphotropic virus, type III (HTLV-III/LAV). Of 474 cohort members seen in 1984, 7.5% had generalized lymphadenopathy, 1.1 had other prodromal findings, and 0.8 had hematologic abnormalities. Prevalence of serum antibodies to HTLV-III/LAV, measured by an enzyme-linked immunosorbent assay, increased from 4.5% in 1978 to 67.4% in 1984. Of 31 persons who were seropositive and without the syndrome between 1978 and 1980, 2 developed the syndrome and 8 developed related conditions during a median follow-up of 61 months. Over a 6-year period, two thirds of cohort members were infected with HTLV-III/LAV and almost one third developed related conditions.

The acquired immunodeficiency syndrome is a major public health problem in the United States. By the end of 1984, nearly 8000 patients who met a surveillance definition of the syndrome (1) had been reported to the Centers for Disease Control (CDC), and almost half of these patients were known to have died. Approximately 94% of reported cases can be classified into one of four groups: homosexual or bisexual men, intravenous drug users, persons born in Haiti, and men with hemophilia.

Although homosexual and bisexual (gay) men account for more of the reported cases than any other group, attempts to estimate the incidence of the syndrome in gay men have been hampered by the lack of accurate denominator data. For that reason, census data on single (never-married) men aged 15 years or older were used in a recent study to approximate the number of gay men in various urban populations (2).

Physicians have reported seeing gay men who do not have the life-threatening illnesses included in the surveillance definition for the acquired immunodeficiency syndrome yet have conditions that appear to be related. Such conditions include generalized lymphadenopathy, oral candidiasis, chronic fever, diarrhea, or weight loss, and hematologic abnormalities (3-8). Although these conditions are believed to be commoner than the syndrome, the frequency of their occurrence relative to the syndrome is poorly defined.

Recent evidence has indicated that a retrovirus, which has been given several names including lymphadenopathy-associated virus (LAV) and human T-lymphotropic virus, type III (HTLV-III), is the cause of the acquired immunodeficiency syndrome. (9, 10)
The acquired immunodeficiency syndrome (9, 10). Serologic surveys have shown that many asymptomatic persons in groups at increased risk for the syndrome have been infected with this virus (11-13). However, data on the incidence of HTLV-III/LAV infections in risk groups and the outcome in infected persons are limited.

The San Francisco Health Department and CDC undertook a collaborative study of a cohort of homosexual and bisexual male clinic patients followed for up to 6 years. Specifically, we studied the incidence of the acquired immunodeficiency syndrome in the cohort, the prevalence of the syndrome and related conditions in a representative sample of cohort members, the incidence of HTLV-III/LAV infections in the sample, and the outcome in persons infected with the virus.

Methods

Between 1978 and 1980, a cohort of approximately 6875 homosexual and bisexual men treated for sexually transmitted diseases at the San Francisco City Clinic were enrolled in studies of the prevalence, incidence, and prevention of hepatitis B virus infections (14, 15). At the time of enrollment, basic demographic data and a blood specimen were obtained from each participant. Sera were frozen at -20°C and stored at the CDC.

To find the prevalence of the acquired immunodeficiency syndrome in the cohort, the San Francisco Health Department ascertained which members of the cohort had been reported as having the syndrome in San Francisco. No formal procedures were available to determine if patients who were reported to other health departments were cohort members. However, when the Health Department learned that a cohort member had had the diagnosis in another city, that information was verified with the health department of that city.

In 1984, we attempted to enroll a representative sample of men in the cohort, as well as all other cohort members with the syndrome not included in the sample, in a follow-up study. The sample had two components: The first component was a 50% random sample of 833 men admitted consecutively from January through May 1978 into a study of the prevalence of hepatitis B virus infections. The second component was a 6% random sample of the 6042 men screened from June 1978 through December 1980 for markers of hepatitis B virus infection.

Cohort members selected for follow-up were invited to participate in a study of the acquired immunodeficiency syndrome. After written informed consent was obtained, participants were interviewed and examined for signs of the syndrome or related conditions. Blood specimens were also obtained. Conditions that were considered to be possibly related to the syndrome were defined as follows:

- Generalized lymphadenopathy—palpable nodes of at least 1 cm in diameter in two or more extraglandular sites, not more than one of which was cervical.
- Other signs or symptoms suggesting predomestic illness—fever or diarrhea lasting at least 2 weeks or weight loss of at least 4.5 kg in the last 4 months; oral candidiasis on examination.
- Hematologic abnormalities—hematocrit less than 40%, absolute lymphocyte count less than 1500/mm³, or absolute neutrophil count less than 1200/mm³.
- Serum samples from the participant's initial blood specimen, collected between 1978 and 1980, and his follow-up specimen, collected in 1984, were tested for antibodies to HTLV-III/LAV by an enzyme-linked immunosorbent assay (ELISA) (Guthrell JP, Kalyanaraman VS. Unpublished method). Interpretation of ELISA results, based on optical density values, was as follows: less than 0.150, negative; between 0.150 and 0.250, equivocal; and over 0.250, positive. The assay was repeated on all sera with equivocal results. Repeatedly equivocal results
Of the 166 patients, 111 (66.9%) had serum specimens available from 1978 to 1980; 24 (21.6%) of these were positive for HTLV-III/LAV antibody shown by ELISA. At the time these specimens were collected, none of these 24 men had the syndrome. The median interval between specimen collection and diagnosis for these men was 43 months (range, 17 to 60 months).

Of the 785 men included in the representative sample, 492 (62.7%) participated in the follow-up study. Reasons for nonparticipation included: inability to locate (23.3%), inability to participate (1.3%), refusal to participate (9.7%), death from causes other than the acquired immunodeficiency syndrome (1.3%), and enrollment pending (1.8%). Because nonparticipants did not give permission for serologic testing of the serum samples obtained from them on entry to the cohort, they were omitted from further analysis.

Overall, 28.5% of the men sampled either had the syndrome or developed related conditions (Table 1). For each man in the sample with the syndrome, there were 7.5 with lymphadenopathy, 1.1 with other signs or symptoms suggesting the prodrome of the syndrome, and 0.8 with hematologic abnormalities. In addition to the 13 men who had the syndrome at the time of examination, 14 more men from the sample were diagnosed with the syndrome by the end of 1984. Findings in men from the 50% and 6% samples were similar, with the exception of generalized lymphadenopathy, which was present significantly more often in members of the 50% sample (p = 0.004).

The epidemic of the acquired immunodeficiency syndrome in the sample of cohort members was preceded by an epidemic of HTLV-III/LAV infection (Figure 2). From 1978 to 1984, the prevalence of antibodies to HTLV-III/LAV in serum specimens collected from men in the sample increased from 4.5% in 1978 to 67.4% in 1984 (Table 2). In 1984, rates of seropositivity were similar for members of the 50% sample (67.8% seropositive) and the 6% sample (66.7% seropositive). At the time of follow-up specimen collection, the rate of seropositivity was significantly higher for persons with the syndrome or related conditions (91.9%) than for persons who appeared to be well (57.7%) (p < 0.001). Among the men who were seropositive on follow-up specimens, 3.4% had the syndrome and 35.2% had related conditions.

Paired serum specimens were available for 397 of the men in the sample. Of the 360 men who were seronegative on their initial specimen, 239 (66.4%) were seropositive on their follow-up specimen. Of the men who seroconverted, 40.6% developed the syndrome or related conditions as compared with 8.4% of those who did not seroconvert (relative risk, 4.8). The proportion of men who seroconverted was significantly higher for those who developed the syndrome or related conditions (90.7%) than for those who did not (56.6%) (p < 0.001).

Thirty-one men from the sample who were initially seropositive entered the follow-up study. Of these 31 men, 2 (6.4%; 95% confidence interval, 0.8% to 21.4%) had developed the syndrome, and 8 (25.8%; 95% confidence interval, 11.9% to 44.6%) had developed related conditions over a median follow-up period of 61 months (range, 41 to 76 months). Outcomes in members of the 50% and 6% samples were not significantly different (p = 0.85).

Discussion

The acquired immunodeficiency syndrome is now the major health problem for gay men in San Francisco, particularly those who are members of the City Clinic cohort. Over 2% of men in the cohort are reported to have the syndrome. Because cohort members who develop the syndrome in other cities may not be known to the San Francisco Health Department, this proportion is a minimum estimate. Another 21% of a representative sample of cohort members had generalized lymphadenopathy, a condition reported to progress to the acquired immunodeficiency syndrome in up to 20% of cases (3, 4, 6).

Furthermore, men who entered the cohort in early 1978 (50% sample) were significantly more likely to have developed lymphadenopathy than those who entered later

![Figure 2. Percent of men in the sample with the human T-lymphotropic virus, type III/lymphadenopathy-associated virus antibody (solid line) and cumulative number with the acquired immunodeficiency syndrome (broken line) by year of diagnosis, San Francisco City Clinic Cohort, 1978-1984.](image-url)
Table 2. Prevalence of Antibodies to Human T-Lymphotropic Virus, Type III/Lymphadenopathy-Associated Virus by the Enzyme-Linked Immunosorbent Assay in Serum Specimens from a Representative Sample of Homosexual Men, San Francisco City Clinic Cohort, 1978-1984

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<td>Acquired immunodeficiency syndrome</td>
<td>2/12 (16.7)</td>
<td>0/1</td>
<td>0/0</td>
<td>10/10 (100)</td>
<td></td>
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<td>Related conditions†</td>
<td>3/86 (3.5)</td>
<td>5/19 (26.3)</td>
<td>0/6</td>
<td>10/13 (76.9)</td>
<td></td>
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<tr>
<td>Apparently well</td>
<td>8/102 (4.2)</td>
<td>6/67 (9.0)</td>
<td>7/23 (30.4)</td>
<td>180/312 (57.7)</td>
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<tr>
<td>Total</td>
<td>13/290 (4.5)</td>
<td>11/87 (12.6)</td>
<td>7/29 (24.1)</td>
<td>293/435 (67.4)</td>
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* Excludes equivocal results; 1978, 1979, and 1980 are initial specimens; 1984, follow-up specimens.
† Excludes persons with generalized lymphadenopathy, either prodromal signs or symptoms, or hematologic abnormalities.

(6% sample), suggesting that lymphadenopathy may be associated with a longer duration of infection. Mortality attributable to the syndrome among cohort members in 1984 (600 per 100,000) substantially exceeded that attributable to all causes of death among white men in the United States between ages 25 and 34 years (157 per 100,000) and between ages 35 and 44 years (238 per 100,000) in 1982 (17).

Because HTLV-III/LAV appears to be sexually transmissible, it is likely that cohort members, men enlisted from a sexually transmitted diseases clinic, are at a higher risk for the acquired immunodeficiency syndrome than other gay men in San Francisco. However, the proportion of all patients in San Francisco with the syndrome that are from the cohort has been slowly decreasing. In part, this trend may reflect the spread of HTLV-III/LAV infections into populations of gay men who have fewer sexual partners than men in the cohort. Additionally, most cohort members have now been exposed to the virus, and the rate of the syndrome in those exposed may be stabilizing.

Data from both this study and studies of transfusion-associated acquired immunodeficiency syndrome indicate that the incubation period of the syndrome is long. In 18 patients with the transfusion-associated syndrome, the median time between transfusion and diagnosis was 28 months (18). In 24 men from the cohort study, the median time between collection of a serum that, in retrospect, had antibodies to HTLV-III/LAV and diagnosis of the syndrome was 43 months. Because these 24 men were seropositive on their initial serum specimen, it is likely that many of them had been infected months before the specimen was collected. Thus, their true incubation periods must be even longer.

Several recent reports have described the development of the acquired immunodeficiency syndrome in gay men with serologic evidence of HTLV-III/LAV infections. Melbye and associates (19) found that of 22 seropositive volunteers from a gay organization in Denmark, 2 developed the syndrome over a 14-month observation period. Goedert and coworkers (20) followed 35 seropositive homosexual males residents of New York City for 2 years and found that 5 developed the syndrome, an incidence of 6.9% per year. Compared with these studies, we found that a similar proportion of seropositive men developed the syndrome, but over a considerably longer follow-up period. In part, differences in outcome could be the result of differences in the populations studied. For example, Goedert and coworkers (20) studied patients who visited the private office of an internist in Manhattan in mid-1982. When enrolled, approximately one third of the men had lymphadenopathy, which was significantly associated with HTLV-III infection at follow-up. On the other hand, City Clinic cohort patients were men who visited a sexually transmitted diseases clinic between 1978 and 1980. Although these men were not examined specifically for conditions that could, in retrospect, be related to the acquired Immunodeficiency syndrome, it is unlikely that many were affected.

We can also examine the risk of the syndrome in another way. During the time when 2.4% of the 6875 men in the cohort had been diagnosed with the syndrome, 67% of the 435 men in the follow-up sample developed serologic evidence of HTLV-III/LAV infection. If the sample is representative of the entire cohort, we can estimate that approximately 3.6% of the infected men had developed the syndrome by January 1985.

The findings from either the City Clinic sample or other study samples must be applied to larger populations with caution. Nonetheless, these results can be used to approximate the magnitude of the problem created by HTLV-III/LAV infections. As an example, for each person in the cohort sample with the syndrome, approximately 30 had serologic evidence of past or present infection with the virus. Thus, the 8000 reported cases of the syndrome in the United States could indicate that about 240,000 Americans have already been infected with HTLV-III/LAV. An appreciable proportion of seropositive persons will develop the syndrome or related conditions after a prolonged incubation period. Thus, even if all transmission of the virus were to stop immediately, the acquired immunodeficiency syndrome would continue to be a major public health problem for the foreseeable future.

ACKNOWLEDGMENTS: The authors thank the San Francisco City Clinic staff, especially Tim Morris, Jack Campbell, Carol Badron, Paulea Franklin, Terrence Shu, Carmen Litte, and Dr. Thomas Wilson; Drs. Steve Russell and Larry Drew, Mt. Zion Hospital, San Francisco, for processing serum samples; Barbara Kilbourne and Lynn Barashick for specimen handling; Dan Hicks for serologic testing; and Ann Rumph and Martha Mayes for data entry.

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References