Prevalence of Kaposi Sarcoma–Associated Herpesvirus Infection in Homosexual Men at Beginning of and During the HIV Epidemic

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Context Some studies have inferred that an epidemic of Kaposi sarcoma–associated herpesvirus (KSHV) infection in homosexual men in the United States occurred concurrently with that of human immunodeficiency virus (HIV), but there have been no direct measurements of KSHV prevalence at the beginning of the HIV epidemic.

Objectives To determine the prevalence of KSHV infection in homosexual men in San Francisco, Calif, at the beginning of the HIV epidemic in 1978 and 1979 and to examine changes in prevalence of KSHV at time points from 1978 through 1996 in light of changes in sexual behavior.

Design, Setting, and Participants Analysis of a clinic-based sample (n=398) derived from the San Francisco City Clinic Cohort (ages 18–66 years) (n=2666 for analyses herein) and from population-based samples from the San Francisco Men’s Health Study (MHS) (ages 25–54 years) (n=825 and 252) and the San Francisco Young Men’s Health Study (YMHS) (ages 18–29 years) (n=428–976, and 557); behavioral studies were longitudinal and KSHV prevalence studies were cross-sectional.

Main Outcome Measures Antibodies against KSHV and HIV; sexual behaviors.

Results The prevalence of KSHV infection in 1978 and 1979 was 26.5% of 235 (overall weighted for HIV infection) vs 6.9% (128/1842) for HIV in the San Francisco City Clinic Cohort sample. The prevalence of KSHV infection remained essentially unchanged between an MHS sample of 252 in 1984 and 1985 (29.6%) and a YMHS sample of 557 in 1995 and 1996 (26.4%), while HIV prevalence dropped from 49.5% of 825 in 1984 and 1985 (MHS) to 17.6% of 428 in 1992 and 1993 (YMHS). The proportion of men practicing unprotected receptive anal intercourse with 1 or more partners declined from 54% to 11% during the 1984 through 1993 period (MHS) with similar though slightly higher values in the YMHS in 1992 and 1993; whereas for unprotected oral intercourse it ranged between 60% and 90% in the 1984 through 1996 period (MHS and YMHS).

Conclusions Infection with KSHV was already highly prevalent in homosexual men when the HIV epidemic began in San Francisco, and its prevalence has been maintained at a nearly constant level. Any declines in the incidence of Kaposi sarcoma do not appear to be caused by a decline in KSHV transmission.

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epidemic. It has also been suggested that a decline in new KS diagnoses, even before the highly active antiretroviral therapy (HAART) era, may have been due to decline in transmission of the “KS agent.”

We investigated KSHV prevalence at the beginning of and during the HIV epidemic, representing the period 1978 through 1996. We also compared KSHV prevalence with that of HIV at different points in the light of changes in sexual behavior.

METHODS
Cohorts and Sampling
We tested serum from stored samples for antibodies against KSHV from 3 cohort studies. For the study involving the group now known as the San Francisco City Clinic Cohort, 6705 homosexual and bisexual men ages 18 through 66 years and attending a sexually transmitted disease (STD) clinic in 1978 through 1980, were screened for hepatitis B virus infection to identify potential vaccine trial participants; of 4043 remaining alive who could be located several years later, 2877 (71%) consented to retrospective HIV testing. Also, samples from 675 of 699 persons who had died were tested, resulting in a total of 3552 samples tested for HIV.11 For the current study, we sampled specimens at random from four 6-month periods, the first and last 6 months of the 1978-1980 period and two 6-month blocks in between, representing 2666 HIV-tested men. Sampling was stratified by age (<25 years, 25-34 years, and ≥35 years) and by HIV infection status. We randomly sampled within these age and HIV-status strata a target of approximately 100 in each time period in the proportion of 70% HIV-uninfected to 30% HIV-infected. Due to constraints of numbers of available subjects in each stratum and available serum specimens for those sampled, some oversampling was performed to achieve the target number of specimens. We obtained results on 398 specimens distributed 105, 130, 85, and 78 by the 4 time periods, of which 74.6% were HIV-uninfected. However, in the first period, only 9 HIV-infected persons were available.

The second study was the San Francisco Men’s Health Study (MHS), a population-based probability sample of unmarried men, ages 25-54 years, living in the 19 San Francisco census tracts with the highest AIDS incidence in 1983.12 In 1984 and 1985, 1034 men (39.1% of eligible men), 823 of whom were self-identified as homosexual, entered the study, which continued as a cohort study of incidence, determinants (eg, sexual practices), and natural history of HIV infection. A random sample of 252 stored baseline serum specimens from an available 799 specimens from the homosexual participants was used for KSHV testing stratified by HIV infection.

The third study, the San Francisco Young Men’s Health Study (YMHS), using the same household survey methodology as the MHS, obtained a population-based probability sample of unmarried men, ages 18 to 29 years, from the same 19 census tracts plus 2 additional tracts.13 In a 1992 through 1993 period, 1076 men (77.6% of eligible men) completed an interview; of these, 428 were self-identified as homosexual. This sample was followed prospectively for HIV infection rates and monitoring of sexual and drug use behavior. In the first year of follow-up the sample was augmented by enrolling homosexual men referred by survey participants (a total sample of 976, including 83% of the initial 428). All 557 homosexual men participating in follow-up and having an available blood sample in a 1995 through 1996 period (when storage of serum began) were tested for KSHV antibodies. The human subjects procedures for this work were approved by the University of California, San Francisco institutional review board.

KSHV Antibody Assay
All samples were tested for KSHV antibodies with a whole virion enzyme immunoassay whose performance characteristics have been described, using an optical density cutpoint with an estimated 100% specificity against a panel of likely uninfected persons.14

Sexual Behavior
Interviews about sexual behavior were conducted confidentially using a structured interview at regularly scheduled clinic visits at about 6-month intervals for the San Francisco MHS12,13 (except only 1 measurement was performed in 5/84-4/85 [period of cohort recruitment] and in 9/91-9/92) (only data from the second half of each year interval are reported herein for simplified presentation) and approximately annually for the YMHS.13 Some analyses based on these data have been reported.12,13,16-18 Information on sexual behavior from the San Francisco City Clinic Cohort participants was not obtained during the 1978 through 1980 period.

Statistical Analyses
Because the prevalence of KSHV is related to HIV infection,1-5 we estimated overall KSHV prevalence in the 2 sampled cohorts (all samples were tested in the YMHS) by weighting for the proportion with HIV in each cohort. Differences in the weighted proportions positive for KSHV antibodies were tested using a weighted logistic regression procedure. All analyses were performed using STATA, version 6.0 (STATA Corp, College Station, Tex).

RESULTS
Seroprevalence of KSHV at the Beginning of the HIV Epidemic
In the San Francisco City Clinic Cohort, during the first 6 months of 1978, KSHV prevalence was 24.9% (26/105) vs an HIV prevalence of 1.8% (14/794) in the entire cohort. Between the earlier and later halves of the 1978 through 1980 period, HIV prevalence increased from 6.9% to 24.0% (P<.001) vs a statistically nonsignificant increase in KSHV prevalence from 26.5% to 33.4% (P=.15) (TABLE 1). Overall KSHV prevalence in the 1978 through 1980 period, after weighting for HIV status, was 28.4%: 25.6% in HIV-uninfected men and 48.2% in HIV-infected men (P<.001) (TABLE 2).
Seroprevalence of KSHV During the HIV Epidemic

Estimates of KSHV prevalence were also derived from the MHS in the 1984 through 1985 period and the YMHS in the 1995 through 1996 period. Overall prevalence of KSHV was similar in the 3 cohorts in the 3 periods: 28.4% in the 1978 through 1980 period, 29.6% in the 1984 through 1985 period, and 26.4% in the 1995 through 1996 period (P = .58) (Table 2). Seroprevalence of KSHV was strongly related to HIV infection (P < .001) but not to age in all 3 cohorts (D. H. O., unpublished data, 2001). When stratified by HIV status, prevalence over time in the 3 cohorts was similar in HIV-infected men (P = .81) and was similar in HIV-uninfected men in the City Clinic Cohort and the YMHS but somewhat lower in the MHS (P = .01) (Table 2).

Prevalence of HIV declined from 49.5% of a sample of 825 in the 1984 through 1985 period in the MHS to 17.6% of a sample of 428 in the 1992 through 1993 period in the YMHS. Restricting comparison to the groups of 25- to 29-year-olds sampled by both studies, HIV prevalence declined from 48.6% of a sample of 179 to 21.9% of 292. Overall KSHV prevalence remained about the same in the 2 cohorts during this period when restricting comparisons to those 25 to 29 years of age (21.8% of a sample of 78 and 25.8% of 292, respectively).

Temporal Changes in Sexual Behavior

A steep decline was seen in the MHS in the prevalence of being the receptive partner in anal intercourse without a condom with 1 or more partners (in the prior 6 months), from 54% in the 1984 through 1985 period to 13% in the 1987 through 1988 period, and to 11% in the 1992 through 1993 period. Prevalence of unprotected receptive anal intercourse remained at a low level throughout follow-up into the 1990s and was similar in the YMHS (in the prior year) in the 1992 through 1993 period (for which we have data from both cohorts) (FIGURE). Unprotected insertive anal in-

### Table 1. Prevalence of KSHV and HIV in the San Francisco City Clinic Cohort, 1978-1980*

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<tr>
<td>KSHV</td>
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<tr>
<td>HIV uninfected, No./total (%)</td>
<td>42/184 (22.8)</td>
<td>29/113 (25.7)</td>
<td>.98†</td>
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<tr>
<td>HIV infected, No./total (%)</td>
<td>20/51 (39.2)</td>
<td>29/50 (58.0)</td>
<td>.06†</td>
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<tr>
<td>Overall (weighted for HIV infection), %</td>
<td>26.5</td>
<td>33.4</td>
<td>.15‡</td>
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*From weighted logistic regression; percentages for the San Francisco City Clinic Cohort and San Francisco Men’s Health Study are estimated for the entire cohort weighting for proportions of the cohort that were HIV infected and HIV uninfected.
‡From weighted logistic regression; percentages for the San Francisco City Clinic Cohort and San Francisco Men’s Health Study are estimated for the entire cohort weighting for proportions of the cohort that were HIV infected and HIV uninfected.

### Table 2. Prevalence of KSHV Stratified by HIV Status in 3 San Francisco Studies, 1978-1996*

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<tr>
<td>HIV uninfected, No./total (%)</td>
<td>38/101 (37.6)</td>
<td>24/171 (14.0)</td>
<td>42/81 (51.9)</td>
<td>.81†</td>
</tr>
<tr>
<td>HIV infected, No./total (%)</td>
<td>16/64 (24.6)</td>
<td>30/58 (51.7)</td>
<td>30/81 (37.0)</td>
<td>.06†</td>
</tr>
<tr>
<td>Overall (weighted for HIV infection), %</td>
<td>28.4</td>
<td>29.6</td>
<td>31.8</td>
<td>.58‡</td>
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*From weighted logistic regression; percentages for the San Francisco City Clinic Cohort and San Francisco Men’s Health Study are estimated for the entire cohort weighting for proportions of the cohort that were HIV infected and HIV uninfected.

### Figure. Changes in Sexual Behavior in 2 Population-Based Cohorts of Homosexual Men in San Francisco, 1984-1996

Unprotected Receptive Intercourse
- Oral
- Anal

Men’s Health Study
- Young Men’s Health Study

Follow-up rate for the Men’s Health Study (MHS) was 64%; 87% for those alive in the 1992-1993 period. Follow-up rate for the Young Men’s Health Study (YMHS) was 65%; 66% for those alive in the 1995-1996 period. The sample at the second YMHS time point was augmented by a referral sample, resulting in a total of 976 (including 83% of the initial 428). Data were not collected for the first 2 oral intercourse time points. Data were collected at about 6-month intervals (except in 5/84-4/85 [the cohort was being assembled] and in 9/91-9/92 in the MHS but only data from the second part of a year interval are reported (see text); data were collected approximately annually in the YMHS. Intervals shown represent 1 measurement per subject.

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tercourse showed a nearly identical decline (D. H. O., unpublished data, 2001). In contrast, receptive oral intercourse with at least 1 partner without a condom was highly prevalent in both cohorts throughout the 1984 through 1996 period, ranging between 60% and 90% of participants (Figure). Unprotected insertive oral intercourse showed a nearly identical pattern (D. H. O., unpublished data, 2001). The mean total number of male sexual intercourse partners in the 12 months prior to enrollment was similar in the 2 cohorts: 21 in the MHS and 18 in the YMHS and, when restricted to the 25- to 29-year-old age group, 16 and 14, respectively.

COMMENT

We report several new findings about the relationship of KSHV and HIV in homosexual men in San Francisco: KSHV was highly prevalent in 1978 when HIV was at low levels; KSHV prevalence was relatively stable from 1978 to 1996; KSHV is strongly associated with HIV; and, at an ecological level, reductions in unprotected anal intercourse were accompanied by a decline in HIV prevalence but not in KSHV prevalence.

One study has reported concurrent epidemics of KSHV and HIV from 1982 onward in homosexual men from New York City and Washington DC. The prevalence of KSHV and of HIV in New York City in 1982 similar to our San Francisco data from the 1984 through 1985 period: 48.8% vs 49.5%, respectively, for HIV, and 34.1% vs 29.6% for KSHV. That report, which lacked samples from prior to 1982, was based on high seroincidence for both viruses at their initial time point, which dropped off after 1984. Our data are not inconsistent with some increase in KSHV prevalence with the first wave of HIV infection but over a longer period of time are more compatible with a steady rather than an epidemic rate of KSHV transmission in homosexual men in the 1980s. There may have been some increase in KSHV transmission during the period of rapid HIV spread from 1978 through 1980, but 25% of samples we tested were positive for KSHV antibodies at the start of that period when HIV prevalence was close to zero. Investigation of genomic strain variability has determined that KSHV is an ancient virus. How long it has been prevalent in homosexual men is unknown, but it could have been endemic in these men for a long period without attracting notice since HIV-uninfected persons in the United States with KSHV rarely develop KS (D. H. O., unpublished data, 2001).

Reports that AIDS-associated KS incidence declined in the United States prior to the HAART era are based on a decline in the overall KS incidence rate or in the proportion of incident AIDS cases that are KS diagnoses. It has been inferred this decline resulted from reduced transmission of the “KS agent” that accompanied behavior change in the 1980s in homosexual men. Our data suggest the perceived decline did not result from a decline in KSHV transmission. An overall KS incidence decline could be caused by reduced HIV transmission alone (fewer immunocompromised persons available to develop KS). A decline in KS as a proportion of new AIDS cases could be caused by a decline in the proportion of new cases occurring in homosexual men since KS is uncommon in other risk groups. The overrepresentation early in the HIV epidemic of KS relative to other AIDS diagnoses, because it occurs at higher CD4 lymphocyte counts, may also explain a decline in KS as a proportion of initial AIDS diagnoses. This effect is particularly relevant in a closed cohort. The most useful data on KS incidence comes from examining homosexual men seroconverting for HIV in different time periods. A study examining KS incidence in 407 men seroconverting for HIV throughout the 1980s in North America, Europe, and Australia found no change in incidence prior to 1996, concluding there was no evidence for a decline in a KS cofactor.

The association of KSHV with HIV could reflect partner selection patterns (sexual mixing), but may also be influenced by the effect of HIV on KSHV transmission. If HIV infection results in increased KSHV shedding, sexual partners coinfected with both viruses might be more infectious. Assuming HIV-infected persons more likely have HIV-infected sexual partners, they would also be at higher risk for KSHV. Alternatively, HIV infection may be a marker for increases in sexual behavior that are not completely accounted for by number of partners and STD history.

There is no consensus as to the route of KSHV transmission in homosexual men. Penile-oral intercourse, penile-anal intercourse, oral-anal contact, and kissing have all been implicated. Our comparison of prevalence in 3 time periods is ecological and does not demonstrate the route of transmission. Transmission dynamics and survival time after infection are complex and any or all of the behaviors listed above could account for transmission. Our primary observation is that KSHV prevalence did not decline during a time when HIV prevalence did decline, in parallel with a sharp decline in prevalence of unprotected anal intercourse in homosexual men in San Francisco in 2 similar population-based samples. The inference is that behaviors remaining highly prevalent during this period, such as unprotected penile-oral intercourse (and presumably kissing [not evaluated]), seem more likely transmission routes. If kissing is a route of KSHV transmission, KSHV would likely be widespread in heterosexual populations but actual prevalence estimates range from 0% to 9%. Low prevalence in heterosexual groups would be plausible if KSHV were recently introduced but our data do not support this. An association between penile-oral intercourse and incident KSHV infection in homosexual men in Amsterdam was reported, as was little reduction in unprotected oral intercourse concurrent with large reductions in unprotected anal intercourse. Other reports have not found an association with penile-oral intercourse, but have found an association with penile-anal intercourse. Thus, while the route or routes of sexual transmission of KSHV are unclear, our finding that KSHV prevalence dropped off after 1984, in contrast to HIV prevalence, suggests intimate contact during unprotected anal intercourse is a major route of transmission.
KSHV remain to be determined, if penile-oral intercourse has an important role in transmission, the risk may be greatest for the insertive partner with contact with KSHV-infected saliva. DNA of KSHV has been detected frequently in saliva but rarely in semen of seropositive persons. Acquisition of KSHV via insertive penile-oral intercourse could explain the concentration of infection in homosexual men without ready spread to heterosexual groups.

Author Contributions: Study concept and design: Osmond, Buchbinder, Martin. Acquisition of data: Osmond, Buchbinder, Graves, Cossen, Forghani, Martin. Analysis and interpretation of data: Osmond, Buchbinder, Cheng, Vittinghoff, Martin.

REFERENCES


