Impact of Highly Active Antiretroviral Treatment on HIV Seroincidence Among Men Who Have Sex With Men: San Francisco

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Objectives. This study assessed the countervailing effects on HIV incidence of highly active antiretroviral treatment (HAART) among San Francisco men who have sex with men (MSM).

Methods. Behavioral risk was determined on the basis of responses to cross-sectional community interviews. HIV incidence was assessed through application of an enzyme-linked immunoassay testing strategy.

Results. Use of HAART among MSM living with AIDS increased from 4% in 1995 to 54% in 1999. The percentage of MSM who reported both unprotected anal intercourse and multiple sexual partners increased from 24% in 1994 to 45% in 1999. The annual HIV incidence rate increased from 2.1% in 1996 to 4.2% in 1999 among MSM who sought anonymous HIV testing, and the rate was high (5.3%) but stable in a blinded survey of MSM seeking sexually transmitted disease services.

Conclusions. Any decrease in per contact risk of HIV transmission due to HAART use appears to have been counterbalanced or overwhelmed by increases in the number of unsafe sexual episodes. (*Am J Public Health.* 2002;92:388–394)

Since 1995, dramatic decreases in morbidity and mortality have occurred among people infected with HIV, primarily as a result of highly active antiretroviral therapy (HAART).[1,2] Indirect evidence suggests that use of HAART by HIV-infected individuals decreases sexual transmission of HIV to uninfected persons.[3] Specifically, antiretroviral treatment decreases serum[4,5] and genital fluid viral load.[6–11] Serum viral load predicts sexual[12-16] and perinatal[17] transmission of HIV. HAART has also been found to decrease perinatal transmission of HIV,[18] and in one small study,[19] it was associated with lower incidence rates of heterosexual transmission.

Unfortunately, availability of HAART paradoxically may increase sexual practices that lead to HIV transmission. Community surveys indicate that, as a result of the availability of HAART, HIV-negative men who have sex with men (MSM) are less concerned about contracting HIV,[20–23] HIV-infected MSM are less concerned about transmitting HIV,[21,22,24] and both groups are more likely to engage in unsafe sex.[21,22,24,25] Also, because HAART decreases mortality and improves the quality of life of persons with AIDS,[26,27] it has increased the number of persons living with HIV/AIDS who are engaging in sexual relations.

To date, there have been no published studies on how the availability of HAART has affected HIV incidence at the population level. Therefore, we conducted an ecological study to assess the potentially conflicting effects of HAART on seroincidence among MSM in San Francisco. Recognizing that seroincidence would be affected by both the size of the infected population and the sexual behaviors of MSM, we tracked changes in AIDS prevalence, sexual risk behavior, and seroincidence among MSM who sought HIV testing at an anonymous testing site or who sought sexually transmitted disease (STD) services at the county STD clinic during the time after HAART became available.

METHODS

Estimates of AIDS incidence, AIDS deaths, AIDS prevalence, and HAART use were derived from the San Francisco Department of Public Health AIDS registry (Figure 1). Vital status was determined through weekly reviews of local death certificates, monthly reports provided by the California State Office of AIDS, and annual matches with the National Death Index. Date of initiation and type of antiretroviral therapy were obtained through medical chart reviews conducted at the time of the initial case report and annually thereafter. Individuals were considered to be receiving HAART if they had ever been prescribed at least 1 protease inhibitor or nonnucleoside reverse transcriptase inhibitor. Evaluations of AIDS surveillance in San Francisco have shown it to be timely (median period of 1 month between date of diagnosis and report) and more than 95% complete.[28]

Trends in sexual behavior among MSM were determined from cross-sectional surveys conducted by the Stop AIDS Project, a San Francisco community-based organization.[29] MSM were interviewed in a variety of community settings (e.g., neighborhoods, clubs, bars, gay-oriented events, streets with large amounts of pedestrian traffic). Two markers of sexual risk were tracked from 1994 to 1999: percentage of respondents reporting that they "always" used condoms when engaging in anal sex (either insertive or receptive) and percentage of respondents reporting unprotected anal sex and multiple partners.

During the study period, 26 176 first-time interviews with MSM were conducted. There were no substantive changes in recruitment over the study period; however, fewer interviews were conducted in later years (decreasing from 6235 in 1994 to 3303 in 1999) owing to fewer volunteers and less interest among the target population in discussing HIV issues. Condom use rates were calculated among those reporting sex in the past year. Because we asked participants whether they had been previously inter-

viewed, we were able to exclude repeated interviewees and thus to have independent samples for statistical testing. Reanalyzing the data to include individuals who had previously participated in the survey did not change the results. Because surveys were anonymous, we could not link them to gather longitudinal data.

Incidence rates of rectal gonorrhea were taken from the San Francisco Department of Public Health's STD registry.[29] We report both the absolute number of cases (Table 1) and the rate per 100 000 men 15 years or older (Figure 2). Although sexual orientation was not recorded in all reported cases, rectal gonorrhea among men is assumed to reflect unprotected receptive anal sex with another man. Physicians and laboratory directors are required by law to report cases of gonorrhea to health departments. However, negative tests are not reported, making it impossible to assess from STD surveillance the impact of changes in screening practices on number of reported cases. Thus, we also report the number of cases of rectal gonorrhea diagnosed at the municipal STD clinic, for which the number of tests performed was available.

Trends in HIV incidence were determined via the serological testing algorithm for recent HIV seroconversion (STARHS). This algorithm identifies recent HIV seroconversion using 2 enzyme-linked immunoassays, one sensitive to low levels of antibody and one less sensitive. On the basis of the slow increase in antibodies during early infection,[30] the algorithm distinguishes people who have recently seroconverted (within the previous 129 days on average) from people with long-standing infection (greater than 129 days on average). Because the algorithm estimates the length of time recently infected individuals have been infected (i.e., duration), we were able to use the results to estimate incidence rates from cross-sectional serosurveys. Specifically, we used the epidemiological relation equating prevalence with the product of incidence and duration. We estimated HIV incidence as the prevalence of recent infection among persons tested and calculated annualized rates.[30]

Using the STARHS, we determined HIV incidence rates for 2 groups: MSM seeking HIV testing at the publicly funded anonymous testing site in San Francisco[31] and MSM who were seen at the county STD clinic during an annual blinded serosurvey.[32] Although no subjects were excluded from the study, approximately 1% of specimens from the anonymous testing site and 3% from the STD clinic were of a quantity insufficient for testing or could not be found. STARHS results were available for 11 347 MSM seeking HIV testing at the anonymous testing site from 1996 to 1999 (an average of 2837 tested each year) and for 4669 MSM seeking STD treatment services from 1995 to 1999 (an average of 778 per year).

During the annual blinded survey of the STD clinic, tests were performed on sera remaining from routine syphilis screenings (after removal of identifiers). Because persons with advanced HIV, especially those receiving HAART, may be falsely classified by the STARHS as having a recently acquired HIV infection,[30,33] we assumed that 29 patients from the blinded STD sample who reported an earlier positive test had a long-standing HIV infection, and we excluded these patients from the analysis. Including these individuals in the analysis increased the HIV incidence rate slightly in the latter years, but the estimated incidence remained within the 95% confidence intervals reported here. Previous self-reported

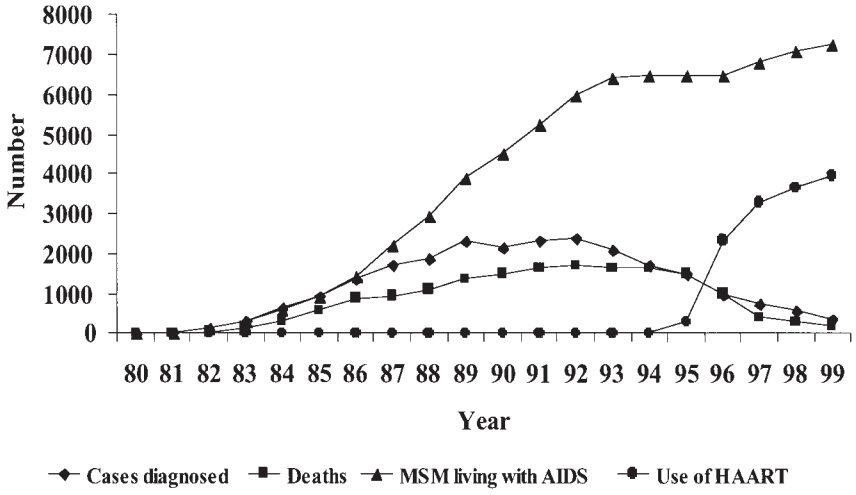
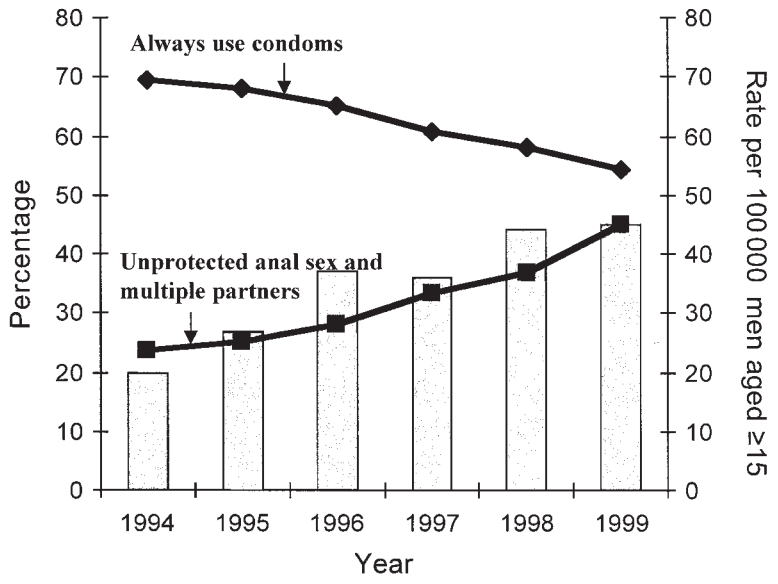


FIGURE 1—AIDS incidence, mortality, prevalence, and use of highly active antiretroviral therapy (HAART) among men who have sex with men (MSM): San Francisco, 1980–1999.

TABLE 1—Reported Cases of Male Rectal Gonorrhea: San Francisco, 1994–1999

Year	No. of Reported Cases of Male Rectal Gonorrhea	No. of Cases of Male Rectal Gonorrhea Diagnosed at STD Clinic (No. of Tests Performed)	Positivity Rate, %
1994	72	49 (531)	9.2
1995	97	61 (576)	10.6
1996	134	54 (660)	8.2
1997	129	85 (803)	10.6
1998	158	113 (1111)	10.2
1999	160	111 (1474)	7.5

Note. STD = sexually transmitted disease.



Note. Bars express male rectal gonorrhea incidence per 100 000. Lines express percentages.

FIGURE 2—Reported sexual behaviors among men who have sex with men and male rectal gonorrhea cases: San Francisco, 1994–1999.

HIV test results were available only for those who attended the STD clinic between 1997 and 1999.

Results presented from the community behavioral surveys and from the STD registry have been updated by 2 years from an earlier report,[29] while STARHS results from the anonymous testing and STD sites have been updated by 1 year from previous reports.[31,32]

Laboratory Analyses

A full description of the methods for using the STARHS has been provided elsewhere.[30] All batches are analyzed with positive and negative controls. The data of the San Francisco Public Health Laboratory, where these specimens were tested, were calibrated against those of the Blood Centers of the Pacific and the Centers for Disease Control and Prevention.

Statistical Analysis

Confidence intervals for HIV incidence rates were based on a Poisson assumption for the number of early seroconverters (via a Bonferroni procedure described in Appendix 1 of the study by Janssen et al.[30]). Chi-square trend tests were used to assess the statistical significance of time trends in the behavioral data. Odds ratios, confidence intervals, and *P* values for trends in seroincidence were based on a linear trend analysis (via logistic regression) with calendar year as the independent variable. SAS (version 6.12) was used in conducting analyses.

RESULTS

AIDS Incidence, Mortality, and Prevalence and Use of HAART

The incidence of AIDS among MSM was highest in 1992 and declined steadily thereafter (Figure 1). The number of deaths among MSM with AIDS increased somewhat from 1992 through 1995, followed by a dramatic decline through 1999. The decline in AIDS mortality corresponded to the period of availability of HAART. The number of MSM living with AIDS who were using HAART increased from 278 (4%) in 1995 to 3959 (54%) in 1999 (Figure 1). Because the decline in AIDS deaths was greater than the decline in AIDS incidence, the number of MSM living with AIDS increased between 1994 (6509) and 1999 (7272).

Indicators of Increases in Unsafe Sex and STDs

Cross-sectional interviews showed that the percentage of MSM who reported always using condoms in the preceding 6 months when engaging in anal intercourse decreased from 70% in 1994 to 54% in 1999 ($P<.001$; Figure 2). Over the same period, the percentage of MSM reporting both unprotected anal sex and multiple sexual partners increased from 24% to 45% ($P<.001$). The decreases in respondents' reports of always using condoms and the increases in their reports of unprotected anal intercourse and multiple partners seen between 1994 and 1999 were statistically significant ($P<.05$) within all 4 age groups and 5 ethnic groups of MSM, with the exception that the decrease in condom use among Native American MSM did not achieve statistical significance (data not shown) owing to the small sample size.

Rates of Rectal Gonorrhea

The number of male rectal gonorrhea cases reported in San Francisco increased from 72 in 1994 to 160 in 1999 (Table 1), with a concomitant increase in the rate of gonorrhea per 100 000 men 15 years or older (Figure 2). There was a similar increase in cases of rectal gonorrhea among persons seen at the STD clinic. The positivity rate of gonorrhea tests performed at the STD clinic remained stable, despite an increased frequency of testing, from 1994 to 1998 but decreased in 1999.

Trends in Estimated HIV Incidence

Among MSM tested for HIV at the anonymous site between 1996 and 1999, the estimated HIV annual incidence rate (according to the STARHS) was 2.2%. The annual number of serological HIV tests declined during this time period. Annual estimated HIV incidence rates (Table 2) were lowest in 1997 (1.3%) and highest in 1999 (4.2%; $P<.015$). Among the STD clinic patients, annual estimated HIV incidence was 5.3%, and this rate remained

TABLE 2—Incidence of HIV Among Men Having Sex With Men (MSM): San Francisco, 1994–1999

	Seeking HIV Testing at Anonymous Testing Site			Seeking Care at STD Clinic		
Year	No. Tested	No. of Recent HIV Infections	HIV Incidence per Year, % (95% CI)	No. Tested	No. of Recent Infections	HIV Incidence per year, % (95% CI)
1994	...	...	...	539	14	7.3 (3.1, 15.7)
1995	...	...	...	642	13	5.7 (2.3, 12.5)
1996	3489	27	2.2 (1.1, 4.0)	664	10	4.3 (1.5, 10.0)
1997	3123	14	1.3 (0.5, 2.7)	936	20	6.0 (2.9, 11.8)
1998	2909	22	2.1 (1.0, 4.1)	817	13	4.5 (1.8, 9.8)
1999	1826	27	4.2 (2.2, 7.6)	1071	18	4.7 (2.2, 9.5)
Odds ratio (per year)			1.27 (1.05, 1.54)			0.93 (0.82, 1.05)
P			.015			.26

Note. STD = sexually transmitted disease; CI = confidence interval.

stable (Table 2) between 1994 and 1999 (P=.26) despite an increased number of tests performed.

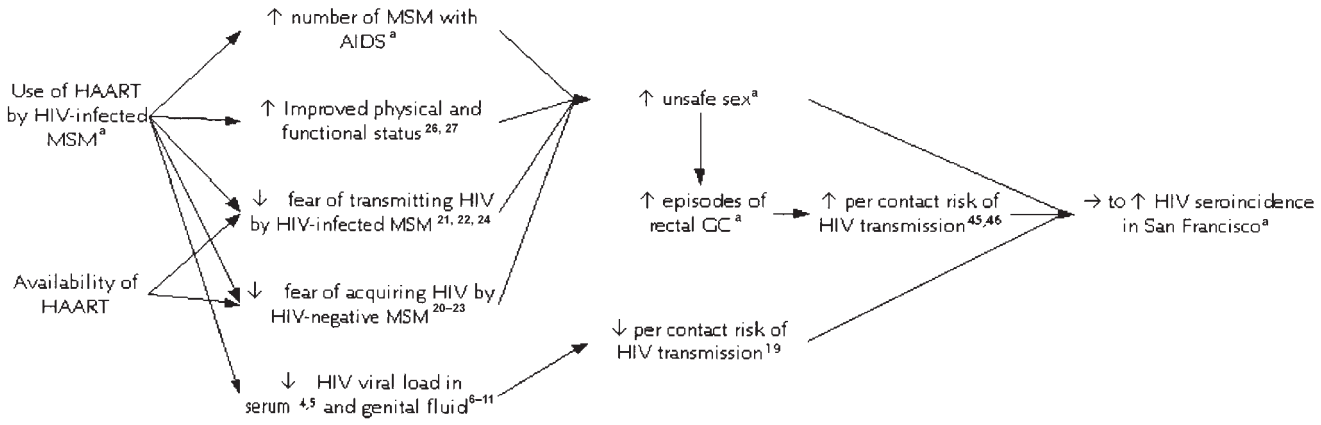
DISCUSSION

To design effective interventions to decrease HIV seroincidence, it is important to determine how individual factors (e.g., use of treatment, risk behavior) affect transmission dynamics at a community level. The results of our ecological study are consistent with the hypotheses (illustrated in Figure 3) that (1) the availability and increased use of HAART have resulted in an increased number of unsafe sexual contacts and (2) the impact of the increased number of unsafe contacts on seroincidence has been equal to or greater than the impact of HAART use on per contact transmissibility of HIV.

As indicated in Figure 3, a weakness of our study is that we measured only some of the features of the model, whereas other aspects are supported by published studies. In addition, measured aspects of the model have significant weaknesses and potential biases. Therefore, it is important to consider the strengths and weaknesses of each aspect of the model as well as the model as a whole.

Our data show a substantial increase in HAART use among persons with AIDS in San Francisco. Unfortunately, we do not have a measure of HAART use among MSM with HIV but not AIDS. However, a nationally representative sample showed an increase in HAART use from less than 10% in 1996 to almost 50% in 1998 among persons with HIV and high CD4 counts (above 0.5×10^9/L).[34]

The increase in the number of MSM living with AIDS is a direct result of the increased



[a]Measured directly or indirectly in this study.

FIGURE 3—Hypothesized effect of highly active antiretroviral therapy (HAART) on HIV seroincidence among men who have sex with men (MSM) in San Francisco. GC = gonorrhea.

survival with AIDS resulting from use of HAART.[1,2] As is the case with our measure of HAART use, we do not have data on changes in the size of the population of MSM with HIV but not AIDS. However, given that antiretroviral treatment decreases progression to AIDS in people who are infected,[2] we believe that this group has also increased in size in San Francisco. In addition to increases in the size of the infected population, improvements in functional status among persons with AIDS treated with antiretroviral treatment,[26,27] as well as the use of pharmacological approaches for erectile dysfunction,[35,36] probably increase the opportunities for transmission of HIV.

Studies have shown that with the advent of HAART, some HIV-infected persons are less concerned about transmitting HIV and some HIV-negative persons are less concerned about acquiring HIV. Among MSM, these attitudinal changes may be due either to the belief that HIV transmission is less likely (because the HIV-infected person is using HAART) or the belief that contracting HIV is no longer as serious a problem because of the availability of HAART. Although surveys show that these changes in perception are occurring in only a minority of MSM, even a small proportion of individuals engaging in substantially more unsafe sex will perceptibly increase seroincidence.

The reported decrease in the use of condoms during anal intercourse and the increase in unprotected anal sex and multiple partners parallel increases in unsafe sex reported in numerous other studies of MSM in San Francisco and elsewhere.[37–40] Unfortunately, our data on unsafe sexual behavior do not distinguish between HIV-concordant and HIV-discordant partners. However, other studies have shown that unprotected anal sex occurs in the context of both seroconcordant and serodiscordant relationships.[37,41] Another weakness of our community behavioral data is that they are based on a nonrandom sample. Although attention has been given to keeping the methods similar from year to year, subtle changes in sampling may have affected the time trends.

The increases in gonorrhea among MSM in San Francisco serve as epidemiological confirmation of the reported rise in unsafe sex. Data from the municipal STD clinic substantiate that such growth is not only the result of increased screening for gonorrhea; the positivity rate of cultures was constant between 1994 and 1998. Higher rates of incidence of rectal gonorrhea and other STDs have been reported among MSM in Seattle, Portland, and Los Angeles.[42–44] Because the presence of inflammatory STD raises the likelihood of HIV transmission,[45,46] a higher prevalence of gonorrhea is likely to increase HIV transmission in the community.

We found a substantial increase in estimated HIV incidence rates among MSM seeking anonymous testing but not among MSM seeking care at the STD clinic. This discrepancy cannot easily be resolved. It is possible that changes in the clientele of the anonymous testing site or the STD clinic during the years we studied biased the trends in annual seroincidence. For example, a decrease in the number of low-risk persons undergoing HIV testing could have resulted in an increase in HIV incidence at the anonymous testing site. Indeed, there was a decrease in the number of serum specimens tested at the site, in large part owing to an increase in client preference for available HIV saliva tests.

Unfortunately, we do not have the ability to use the STAHRS algorithm with saliva tests. However, analysis of saliva test results produced the same overall HIV prevalence as the serological tests (3%), and so it is unlikely that persons who chose these tests represented a significantly lower-risk population. To generate a conservative assessment of the potential bias introduced by an increasing number of saliva tests, we reestimated the HIV incidence rate after adding all of the saliva tests (n=1585) to the denominator and kept the numerator the same; the temporal increase in HIV incidence from 1997 to 1999 was still significant (P=.02), although the increase between 1996 and 1999 was not (P=.35). It is also possible that no increase in incidence was seen among MSM at the STD clinic because the baseline estimated seroincidence in this group was so high (average rate: 5.3%). An important limitation of our seroincidence data is that we do not have an estimate for the anonymous testing site during 1994 or 1995. However, only 4% of persons living with AIDS were receiving HAART in 1995, and the benefits of treatment were not widely appreciated until 1997.

In support of an increase in HIV incidence rates in San Francisco among MSM, the San Francisco Young Men's Health Study reported an increase in HIV incidence from 0.81% in the 1997–1998 wave to 1.8% in the 1998–1999 wave (D. Osmond, personal communication, 5 May 2000). Also, use of a different methodology for determining HIV incidence among MSM undergoing testing at the anonymous testing site revealed a similar increase between 1997 and 1998.[47]

A recently published theoretical model projected that the presumed benefits of HAART in decreasing HIV transmissibility could be cancelled out by an increase in rates of unsafe sex of only 10%.[48] Given that our behavioral risk data show a greater than 10% increase in unsafe sex, it is not surprising that there was no decrease in HIV incidence in either sample despite the increase in HAART use. We cannot rule out the possibility that HAART is ineffective in decreasing per contact HIV transmission; were this the case, however, we would have expected a substantial increase in estimated HIV incidence rates in both samples.

Because this was an ecological study, we cannot establish that the relationship between availability of HAART, increased risk behavior, and flat or increasing seroincidence is causal. For example, it is possible that individuals receiving HAART are not the ones exhibiting increased rates of unsafe sex. However, a linkage of the AIDS registry in San Francisco with the STD registry showed that MSM with AIDS who were treated with HAART were more likely to acquire an STD than were MSM not treated with HAART.[49] Also, the increases in unsafe sex parallel the increases in HAART use,[50] and other studies have established that perceptions and behaviors of MSM have been influenced by HAART.[20–25]

In conclusion, our study implies that the availability of HAART has resulted in increases in rates of unsafe sexual behavior equal to or greater than the beneficial impact of HAART on per contact HIV transmission rates. Our results suggest the need for MSM-focused prevention campaigns that take into

account changes in perceived risk of HIV owing to HAART. ■

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Contributors

M.H. Katz participated in the planning and analysis of the data and wrote the paper. S.K. Schwarcz, T.A. Kellogg, and W. McFarland participated in the planning and analysis of the data and edited the paper. J. Klausner participated in the planning and analysis of the sexually transmitted disease data and edited the paper. J.W. Dilley participated in the planning and analysis of the anonymous testing site data and edited the paper. S. Gibson participated in the planning and analysis of the community survey data and edited the final paper.

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