Effect of highly active antiretroviral therapy on diagnoses of sexually transmitted diseases in people with AIDS

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Summary

Background There has been an increase in high-risk sexual behaviour and sexually transmitted diseases (STD) during the time period when highly active antiretroviral therapy (HAART) became widely available. We examined whether taking HAART increased the risk of acquiring an STD—an epidemiological marker of unsafe sex—in people with AIDS.

Methods We did a computerised match of people in the San Francisco STD and AIDS registries. People with AIDS who were diagnosed before 1999 and alive in November, 1995, or later, were classified as having had an STD after AIDS diagnosis or not having had an STD after AIDS diagnosis. We used a Cox proportional hazards model to see whether use of antiretroviral therapy was associated with acquiring an STD after AIDS, after adjustment for sex, age, race, HIV-1 risk category, and CD4 count at AIDS diagnosis.

Findings People with AIDS who had had HAART showed an independent increase in the risk of developing an STD (hazard ratio 4·10; 95% CI 2·84–5·94). Americans of African origin, younger age, and higher CD4 count at AIDS diagnosis were also associated with acquiring an STD after AIDS. The number of people living with AIDS who acquired an STD increased over time from 60 (0·66%) in 1995 to 113 (1·32%) in 1998 ($p<0·001$).

Interpretation We have shown that people on HAART are more likely to develop an STD, an epidemiological marker of unsafe sex. More intensive risk-reduction counselling and STD screening for people with AIDS is needed.

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Introduction

The use of highly active antiretroviral therapy (HAART) has substantially lowered morbidity and mortality from HIV-1 infection[1,2] and has improved the quality of life of HIV-1 infected people.[3,4] These newer treatments have also been effective in decreasing serum[5] and genital fluid concentrations of HIV-1,[5–8] thereby potentially reducing sexual transmission of HIV-1.[9–11]

Several reports have documented increases in high-risk sexual behaviour and sexually transmitted diseases (STD) with the increased availability of HAART.[12–14] There is also evidence that uninfected individuals are less worried about acquiring HIV-1 infection,[15–20] and that there has been a decrease in the perceived risk of sexual activity with HIV-1 infected people on HAART.[21–23] Additionally, the presence of STDs has been shown to increase genital HIV viral load[24] and could affect the resistance pattern of genital HIV-1.[25]

Non-HIV-1 STDs are epidemiological markers for unprotected sexual activity that may also transmit HIV-1.[26] Moreover, presence of an ulcerative or inflammatory STD increases the likelihood of HIV-1 transmission and acquisition.[27] We have therefore assessed whether taking HAART increases the risk of acquiring an STD in people with AIDS.

Methods

Selection of participants

AIDS surveillance in San Francisco is done by active and passive reporting, and has been reported to be more than 95% complete.[28] We did a computerised match of people in the San Francisco STD and AIDS registries. Adults (13 years or older) who were diagnosed with AIDS before 1999 and were alive in November, 1995, or later (the time that HAART became available) were included.[29] The Centers for Disease Control and Prevention, USA, 1993 AIDS case definition was used. The vital status of AIDS cases was mainly established by weekly review of local death certificates and matches yearly with the National Death Index. The date antiretroviral therapy began, type of therapy used, and CD4 test results were recorded from medical records at the time of initial case report and every year thereafter. HAART was defined as use of a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor before an STD diagnosis. People not receiving HAART before an STD diagnosis were classified as having received antiretroviral therapy other than HAART or as having received no antiretroviral therapy before the STD.

We included people who were reported to the San Francisco Department of Public Health with gonorrhoea, chlamydia, syphilis (primary, secondary, and early latent), or non-gonococcal urethritis, between Nov 1, 1995, and Dec 31, 1998. California law requires that laboratories and health-care providers report these STDs.

Analyses

People in the STD and AIDS registries who had the same last name, first name, date of birth, and sex were matched by the SAS SQL procedure. The University of California

	STD after AIDS	No STD after AIDS	Bivariate relative hazard (95% CI)	Adjusted relative hazard (95% CI)
Total	233 (100%)	11 283 (100%)	. .	. .
Risk category				
Men who have sex with men	213 (91%)	9779 (87%)	1·34 (0·85–2·12)	1·17 (0·66–2·08)
Other risk categories	20 (9%)	1504 (13%)	Referent	Referent
Race/ethnicity				
White	160 (69%)	7860 (70%)	Referent	Referent
Americans of African origin	41 (17%)	1645 (15%)	1·36 (0·97–1·92)	1·56 (1·09–2·23)
Other	32 (14%)	1778 (16%)	1·03 (0·71–1·51)	0·89 (0·61–1·32)
Sex				
Male	226 (97%)	10 696 (95%)	1·58 (0·74–3·35)	1·64 (0·65–4·11)
Female	7 (3%)	587 (5%)	Referent	Referent
Age at AIDS diagnosis (years)				
<25	11 (5%)	269 (2%)	3·11 (1·62–5·99)	4·09 (2·10–7·95)
25–29	37 (16%)	1118 (10%)	2·68 (1·76–4·08)	3·01 (1·97–4·60)
30–34	65 (28%)	2496 (22%)	2·14 (1·49–3·07)	2·38 (1·65–3·43)
35–39	67 (29%)	2626 (23%)	2·09 (1·46–2·99)	2·20 (1·53–3·16)
40+	53 (23%)	4774 (42%)	Referent	Referent
CD4 count at AIDS diagnosis (cell/μL^3)				
0–50	9 (4%)	1392 (12%)	Referent	Referent
51–200	123 (53%)	5923 (52%)	1·95 (0·99–3·84)	2·17 (1·10–4·27)
201+	72 (31%)	2678 (24%)	2·07 (1·04–4·16)	2·42 (1·20–4·86)
Missing	29 (12%)	1290 (11%)	1·44 (0·68–3·08)	2·19 (1·01–4·72)
Use of antiretroviral therapy‡				
No therapy	96 (11%)	10 071 (21%)	Referent	Referent
Used HAART§	144 (17%)	7809 (17%)	3·66 (2·57–5·22)	4·10 (2·84–5·94)
Used any other antiretroviral therapy	621 (72%)	28 760 (62%)	1·35 (0·94–1·95)	1·36 (0·94–1·97)

*STDs reported in November, 1995, or later. †Living with AIDS in November, 1995, or later. ‡For the therapy variables only, numbers=person-years. §Any protease inhibitors or non-nucleotide reverse transcriptase inhibitors.

Association between demographic and treatment characteristics and acquisition of an STD* in people with AIDS†

Committee for Protection of Human Subjects exempted the study protocol from review because the data were matched and analysed within the Department of Public Health as part of routine disease surveillance. Thereby, no one outside the department had access to the data. Infection control practitioners consulted medical records to confirm whether possible matches, including typographical errors in the name or variation on names, were true matches. People with AIDS were classified as either having an STD after AIDS diagnosis or not having an STD after AIDS diagnosis. STD rates by year were determined by dividing the number of people with AIDS reported with an STD by the number living with AIDS in every year. If someone had more than one STD after an AIDS diagnosis, we used the most recent STD to assess the effect of antiretroviral treatment on development of an STD.

We used a Cox proportional hazards model to identify whether use of antiretroviral treatment was associated with acquiring an STD after AIDS, after adjustment for sex, age, race, HIV-1 risk category, and CD4 count at AIDS diagnosis. We characterised treatment use by summing person-time spent in each treatment category (no treatment, antiretroviral treatment other than HAART, HAART use). Time-dependent variables for treatment were used so patients could be reclassified if they moved into a different treatment category during follow-up. People who did not develop an STD were censored at the time of their death, last known follow-up, or Dec 31, 1998, whichever was most recent. People with no follow-up information were excluded from the analysis.

Results

There were 11 832 people living with AIDS in San Francisco between 1995 and 1999. We excluded 316 people who did not have any follow-up information in the AIDS registry. The race, age, and sex of those excluded did not differ significantly from those included. Of the remaining 11 516 people, 233 (2%) were diagnosed with an STD after the date of their AIDS diagnosis. Most STD diagnoses were in men who have sex with men. The most common STDs were gonorrhoea, diagnosed in 196 cases (84%) and non-gonococcal urethritis, diagnosed in 17 (7%) people. 12 cases of chlamydia (5%) and eight cases of syphilis (3%) were identified. Of the gonorrhoea cases, 128 (65%) were urethral, 39 (20%) rectal, and four (2%) were pharyngeal gonorrhoea. The remaining gonorrhoea cases were other types of gonorrhoea such as cervical or from a non-specified site.

The number of people living with AIDS who had acquired an STD increased over time from 60 (0·66%) of 9043 in 1995, 60 (0·70%) of 8542 in 1996, 74 (0·89%) of 8315 in 1997, to 113 (1·32%) of 8551 in 1998 ($p<0·001$).

In bivariate and multivariate analyses, having ever been on HAART was associated with an increased risk of STD (table 1). In the multivariate model, younger age, Americans of African origin, and a higher CD4 count at AIDS diagnosis were also independently associated with developing an STD after AIDS. Interaction terms between HAART use and other variables in the multivariate model were not significant.

Discussion

Several studies have reported increases in unsafe sex with the advent of HAART.[12–14] We have confirmed these findings and shown that people on HAART are actually more likely to develop an STD.

One possible reason that HAART is associated with developing an STD is that people on such treatment are likely to feel better and have an increased interest in sex,[3,4,30] which lent support to our finding that a higher CD4 count at time of AIDS diagnosis (a marker of better health) was also associated with increased risk of acquiring an STD after AIDS. Additionally, people on HAART and their partners might feel that HAART makes HIV-1 transmission less likely. Also, patients with AIDS being reated with HAART might seem healthy, causing others to assume that they are HIV-1 negative.

Our findings in a population of mainly homosexual men is in accord with other STD trends in San Francisco. As the availability of HAART was increasing there was a

doubling in male rectal gonorrhoea in San Francisco—from 72 cases in 1994, to 158 cases in 1998. The largest outbreak of syphilis in homosexual men in San Francisco since the early 1980s was in 1999.[31] The increased risk of STDs among Americans of African origin in our study is consistent with the four to ten times higher rate of STDs seen among Americans of African origin in San Francisco than in white people.[32]

Younger age was also significantly associated with acquisition of an STD after AIDS, corresponding to reports that young people are less concerned about HIV-1 infection and AIDS.[33,34]

Our study had several limitations. As with any observational study, causality cannot be assumed. However, we required that development of the STD was after the initiation of HAART. Moreover, our finding that rates of STDs among people with AIDS increased each year despite an overall decrease in STDs in San Francisco[32] strongly suggests that HAART or some other factor associated with HIV/AIDS explains this rise in STDs among people with AIDS. Because most STD diagnoses were in men who have sex with men, our results might not be generalisable to areas in which most AIDS cases are among people in other risk groups. Since some physicians, especially those in the private sector, treat some people empirically without diagnostic testing or reporting, our study probably underestimates STDs in the community. But, since patients treated by private physicians are also most likely to be on HAART (unpublished data), underestimation of STDs among patients in the private sector would diminish the association between diagnosis of an STD and ever having been on HAART. In addition, in 1998, screening practices for chlamydia were changed. Public STD clinics began screening homosexual men without symptoms for chlamydia. To assess whether these changes in screening could have biased our results, we repeated our analysis excluding all chlamydia cases (n=12). Results were unchanged (data not shown).

Unfortunately, we do not know what proportion of sexual partners of people with AIDS are also HIV-1 infected. However, in a multisite study, which included San Francisco, investigators noted that in newly HIV-1 infected homosexual men, most seroconverters reported their most risky sexual activity as unprotected sex with partners of unknown HIV-1 status.[35] Moreover, unprotected sex with another HIV-1-positive person could result in superinfection with a drug-resistant strain of the HIV-1 virus.[36,37] Finally, STDs themselves cause morbidity, especially among individuals who are immunocompromised, and many studies have shown that having an ulcerative or inflammatory STD increases the likelihood of HIV transmission and acquisition.[27]

By definition, patients with AIDS receiving HAART know their HIV status and have continuing contact with the health-care system. To enhance HIV-1 prevention, more intensive risk-reduction counselling and routine STD screening for people with AIDS is needed.

Contributors

Susan Scheer contributed to the study conception and design, analysed and interpreted the data, and wrote the paper. Priscilla Lee Chu did the computerised match and contributed to data analysis and drafting of the paper. Jeffrey Klausner contributed to interpretation of the data, drafting the paper, and provided the data from the STD registry. Mitchell Katz contributed to study design, interpretation of the data, and drafting of the paper. Sandra Schwarcz contributed to study conception and design, interpretation of data, and drafting of the paper.

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