Long-term HIV-1 infection without immunologic progression

Susan P. Buchbinder, Mitchell H. Katz, Nancy A. Hessol, Paul M. O'Malley and Scott D. Holmberg*

Objective: To identify and describe a subgroup of men infected with HIV for 10–15 years without immunologic progression, and to evaluate the effect of sexually transmitted diseases (STD) and recreational drug use on delayed HIV disease progression.
Design: Inception cohort study.
Setting: Municipal STD clinic.
Participants: A total of 588 men with well documented dates of HIV seroconversion and 197 HIV-seronegative controls.
Main outcome measures: AIDS, CD4+ count, rate of CD4+ cell loss, CD8+ count, β_2-microglobulin, complete blood count, p24 antigen and HIV-related symptoms.
Results: Of 588 men, 69% had developed AIDS by 14 years after HIV seroconversion (95% confidence interval, 64–73%). Of 539 men with HIV seroconversion dates prior to 1983, 42 men (8%) were healthy long-term HIV-positives (HLP), HIV-infected ≥ 10 years without AIDS and with CD4+ counts > 500 $\times 10^6$/l. When compared with progressors (men with HIV seroconversion prior to 1983 but with AIDS or CD4+ counts < 200 $\times 10^6$/l), HLP had a significantly slower rate of CD4+ decline (6 versus 85 $\times 10^6$/l cells/year), and less abnormal immunologic, hematologic and clinical parameters. However, when compared with HIV-uninfected controls, HLP demonstrated lower CD4+ counts and mild hematologic abnormalities. There were no consistent differences between HLP and progressors in prior exposure to recreational drugs or STD.
Conclusion: There are individuals with long-term HIV infection who appear clinically and immunologically healthy 10–15 years after HIV seroconversion, with stable CD4+ counts. Lack of exposure to STD or recreational drugs does not appear to explain the delayed course of disease progression in HLP.

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[For editorial comment, see pp 1179–1182]

Introduction

HIV infection leads to generalized immune system dysfunction and development of AIDS in the majority of HIV-infected individuals. However, because of the long latency period from HIV infection to the development of AIDS, estimated at a median of 10 years [1], it is unknown whether all HIV-infected individuals will ultimately develop AIDS. Few studies have documentation of incident HIV infection prior to 1984, when most prospective studies of HIV infection began. Therefore, very little is known about

From the AIDS Office, Department of Public Health, San Francisco, California and the *Division of HIV/AIDS, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

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Requests for reprints to: Dr Susan Buchbinder, Research Branch, AIDS Office, 25 Van Ness Avenue, Suite 500, San Francisco, CA 94102, USA.

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disease progression 10 years or more after HIV infection.

Moreover, there is a broad spectrum of progression times to AIDS; while some individuals develop AIDS within months of HIV infection [2], others are reported to remain healthy up to 10 years after infection [3].

Although older age at HIV seroconversion has been definitively associated with more rapid HIV disease progression [4–6], little is known about other factors mediating delayed HIV disease progression.

We estimated progression time to AIDS among men in the San Francisco City Clinic Cohort (SFCCC) with well documented dates of HIV seroconversion. We then evaluated participants who were HIV-infected prior to 1983 to identify a subset of men with long-term HIV infection but without immunologic progression. We compared immunologic and hematologic parameters of these healthy long-term HIV-positives (HLP) to progressors, men with long-term infection with advanced HIV disease, as well as to an HIV-uninfected control group. To evaluate the role of biologic and behavioral cofactors in disease progression, we compared the frequency of episodes of sexually transmitted diseases (STD) and use of recreational drugs between HLP and progressors.

Methods

Subjects

The characteristics of the SFCCC have been described fully elsewhere [1,7]. Participants were recruited from the municipal STD clinic from 1978–1980 for studies of the prevalence and incidence of hepatitis B (HBV); a subset of HBV seronegative men were recruited into a clinical trial of HBV vaccine from 1980 to 1983. Unused sera from these studies were frozen and stored. Beginning in 1983, men from the original HBV studies were recruited into prospective studies of AIDS and HIV infection, stored sera were tested for HIV, and participants were evaluated prospectively every 6–12 months. Both the HBV and AIDS studies were approved by the California State Committee for the Protection of Human Subjects and the Institutional Review Board for the Centers for Disease Control and Prevention (CDC).

Data collection

With the participants written informed consent, both stored and current sera were tested for HIV antibodies. Specimens repeatedly reactive by enzyme immunoassay (EIA) were confirmed by immunofluorescence assay or Western blot techniques. Date of HIV seroconversion was estimated as the midpoint between the last HIV-seronegative and first HIV-seropositive specimen, when this occurred within a known 24-month period. For men who were HIV-seropositive on entry into the cohort in 1978–1980, the date of HIV seroconversion was determined using a probability estimate based on men with 24 months or less between specimens. HIV-infected men without well documented dates of HIV seroconversion were excluded from this analysis.

Complete blood counts and T-lymphocyte subset testing were performed by a single laboratory from November 1988 through December 1992. Peripheral blood mononuclear cells were prepared using the whole blood lysis method (Q-Prep; Coulter Diagnostics, Hialeah, Florida, USA) and stained using monoclonal antibodies. Percentages of CD4+ and CD8+ cells were determined by flow cytometric procedures using an EPICS profile (Coulter); absolute counts were calculated based on total and differential white blood cell (WBC) counts. Serum β_2-microglobulin (β_2M) concentrations were measured by quantitative competitive EIA according to the manufacturer's protocol (Pharmacia Diagnostics, Piscataway, New Jersey, USA). The presence of p24 antigen was detected by commercial sandwich-type EIA using murine monoclonal antibody coated onto microwell strips (Coulter). Prior hepatitis B infection was determined by the presence of hepatitis B surface antigen or anti-hepatitis B core antibody by radioimmunoassay (RIA; Abbott Laboratories, North Chicago, Illinois, USA).

Date of initial AIDS diagnosis and death were determined by cross-matching with local and national AIDS and death registries; information was updated through 31 December 1992. AIDS was defined using the 1987 CDC surveillance definition.

Behavioral data were obtained from entry into the original study (1978–1980), including questions on tobacco, alcohol and recreational drug use, and STD. HIV-related signs and symptoms were ascertained by a study physician. Symptoms and signs were defined as the history on most recent examination of prolonged idiopathic fever, weight loss, night sweats, diarrhea or presence of oral candidiasis. History of zidovudine or other nucleoside analogue use was ascertained up to the date of the most recent clinical evaluation.

Statistical analysis

Kaplan–Meier techniques were used to determine the cumulative incidence of AIDS by duration of HIV infection for men with well documented dates of HIV seroconversion [8]. For participants who did not have an AIDS diagnosis before death (n = 17), data were censored at the date of death; all other participants without an AIDS diagnosis were censored on 1 January 1993.

The remaining analyses were limited to men evaluated in the last 3 years (1990–1992) who either had an estimated date of HIV seroconversion prior

to 1983 or remained HIV-uninfected. HLP were defined as men without AIDS with CD4+ cell counts $>500\times10^6$/l at their most recent visit, 10 years or more after HIV seroconversion. Progressors were men with AIDS or a CD4+ cell count $<200\times10^6$/l at their last evaluation. HIV-uninfected men served as a control group.

We compared HLP with progressors and controls using a variety of immunologic, hematologic and clinical measures, including most recent CD4+ and CD8+ count, CD4+/CD8+ ratio, β_2M, p24 antigen, WBC count, hemoglobin, platelet count, HIV-related symptoms and prior use of antiretroviral agents. We calculated the CD4+ slope using the least squares method [8] for men with three or more CD4+ cell measurements.

To assess the role of cofactors in delayed HIV disease progression, we compared HLP with progressors for the number of episodes of STD per year and the number of months of recreational drug use per year from the estimated date of HIV seroconversion. Exposure data for HLP was censored at the date of the most recent interview and for progressors at the interview prior to an AIDS diagnosis or CD4+ count $<200\times10^6$/l. To investigate time-dependent effects, we repeated the analysis censoring data at uniform intervals (annually from 5–10 years after seroconversion). For these analyses, we used χ^2 or Fisher's test for dichotomous variables, and t test or Mann–Whitney U test for continuous variables.

Results

We identified 588 men with well documented dates of HIV seroconversion. The proportion of men developing AIDS by 3 years after HIV seroconversion was small [3%; 95% confidence interval (CI), 2–4] (Fig. 1). This proportion increased over time with 51% developing AIDS by 10 years, and 69% developing AIDS by 14 years after HIV seroconversion (95% CI, 64–73).

Of the 588 men with well documented dates of HIV seroconversion, 539 had estimated dates of seroconversion prior to 1983. Figure 2 shows the clinical status of these men 10 or more years after HIV seroconversion. All 42 men (8%) with CD4+ counts $>500\times10^6$/l were evaluated in 1990–1992 and are defined as HLP. Of the 382 men with AIDS or a CD4+ count $<200\times10^6$/l, 177 were alive as of 1990; 102 of these men were evaluated in 1990–1992 and are defined as progressors for the remaining analyses. (The most likely reason for loss to follow-up of the remaining 75 eligible men is that all but eight died in the period from 1990 to 1992.) We also used

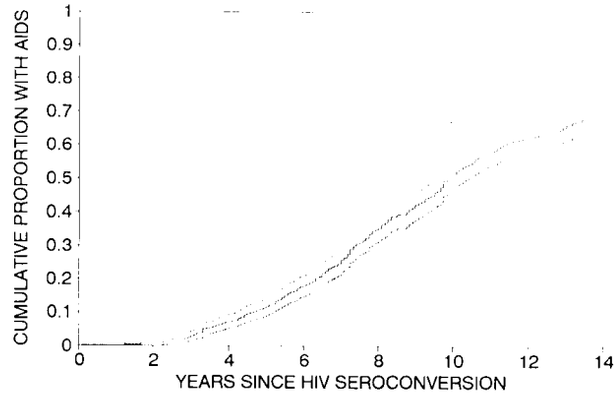

Fig. 1. Kaplan–Meier analysis of progression time from HIV seroconversion to AIDS in the San Francisco City Clinic Cohort. (———), estimated; (.....), upper 95% confidence interval (CI); (- - - -), lower 95% CI.

a group of 196 HIV-uninfected controls who had immunologic and hematologic data from 1990–1992.

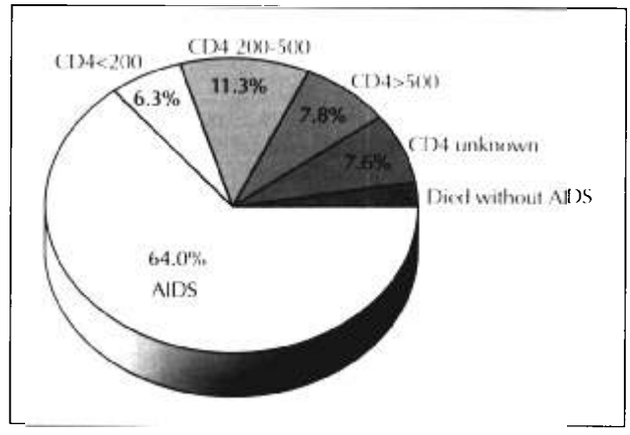

Fig. 2. Clinical and immunologic outcome in patients HIV-infected for 10–15 years in the San Francisco City Clinic Cohort. CD4 counts, $\times10^6$/l cells; n = 539.

HLP did not differ from progressors by age at seroconversion but were followed for a longer period of time after HIV seroconversion (Table 1). HLP had significantly higher CD8+ counts, CD4+/CD8+ ratios, WBC, hemoglobin, and platelet counts and significantly lower β_2M levels than progressors. However, when compared with controls, HLP had significantly lower CD4+ counts and WBC, indicating mild immunologic and hematologic abnormalities (Table 1). It is noteworthy that HLP had significantly higher CD8+ counts than either progressors or controls; this contributed to the lower CD4+/CD8+ ratio in HLP.

Although HLP had lower CD4+ counts than the uninfected control group, these counts appeared to be stable over time. Compared with 78 progressors with a median loss of 85×10^6/l per year over 4 years of study, 35 HLP lost only 6×10^6/l per year ($P<0.001$). Controls lost a median of 7×10^6/l per year over the same period.

HLP had significantly fewer clinical signs or symptoms than progressors (Table 1). Only 38% of the

Table 1. Immunologic, hematologic and clinical parameters in healthy long-term positives (HLP), progressors and uninfected men.

	HLP (n = 42)	Progressors (n = 102)	Uninfected (n = 196)
Mean (SD)			
Age at seroconversion§	27.8 (4.4)	28.4 (4.0)	NA
Duration of infection§	12.8 (1.0)	11.9 (1.5)***	NA
CD4+ ($\times 10^6$/l)	692 (148)	99 (134)***	984 (383)††
CD8+ ($\times 10^6$/l)	1077 (496)	689 (487)***	57 (252)††
CD4+ : CD8+	0.8 (0.4)	0.2 (0.2)***	1.9 (0.8)††
β_2M (mg/dl)	2.4 (1.0)	4.0 (1.7)***	ND
WBC ($\times 10^6$/l)	5.6 (1.8)	3.6 (1.4)**	6.2 (1.6)†
Hemoglobin (mg/dl)	14.6 (1.0)	12.3 (1.9)***	14.7 (0.8)
Platelets (k/$\times 10^6$/l)	230 (57)	199 (74)**	246 (57)
Percentage positive			
p24 antigen-positive	3	13*	
HIV signs/symptoms	12	39***	
Prior antiretroviral use	38	94***	

§Years. For comparisons of HLP with progressors, *$P<0.05$; **$P<0.01$; ***$P<0.001$. For comparisons of HLP with uninfected men, †$P<0.01$; ††$P<0.001$. β_2M, β_2-microglobulin; WBC, white blood cell count; NA, not applicable; ND, test not done.

HLP had ever used zidovudine or other nucleoside analogues, compared with 94% of the progressors.

Table 2. History of drug use and sexually transmitted diseases (STD) in healthy long-term positives (HLP) and progressors.

	HLP	Progressors	P*
Median months/year of drug use since seroconversion			
Cigarettes (≥ 7/day)	0.7	0.8	0.9
Marijuana (≥ 4 joints/month)	3.9	4.9	0.6
Alcohol (≥ 7 drinks/week)	3.5	2.2	0.7
Amyl nitrite (≥ 4 times/month)	2.6	2.9	0.3
Amphetamines (≥ 1 time/month)	0.2	0	1.0
Injection drug use (any)	0	0	0.9
Tranquilizers (≥ 2 times/month)	0	0.1	0.04
LSD (≥ time/month)	0	0	0.6
Cocaine (≥ 2 times/month)	0	0	0.2
Heroin (≥ 1 time/month)	0	0	0.3
Median number of episodes/year since seroconversion			
Syphilis	0	0	0.8
Gonorrhea	0.006	0.007	0.5
Enteric infections	0	0.07	0.08
Proportion ever having STD (%)			
Herpes	50	59	0.3
Hepatitis B (serologic testing)	86	75	0.2

*P value by Mann–Whitney U test and χ^2. LSD, lysergic acid diethylamide.

HLP reported fewer episodes of enteric infections and less tranquilizer use than progressors; there were no other differences in STD or drug use between the two groups (Table 2). The difference in enteric infections was most pronounced when data were censored at 10 years after HIV seroconversion for all participants ($P = 0.03$). This difference decreased with earlier censor dates and was no longer statistically significant at 8 or fewer years after HIV seroconversion. The difference in tranquilizer use was most significant when data were censored at 10 years ($P = 0.04$), but became non-significant when data were censored prior to 10 years. Censoring data at uniform time intervals did not significantly change the results for either STD or recreational drugs.

Discussion

We have identified a subset of men from the SFCCC with long-term HIV infection who have maintained high CD4+ counts 10–15 years after HIV infection. This group of 'non-progressors' represents 8% of men with well documented dates of HIV seroconversion prior to 1983; the true proportion could be somewhat higher because an additional 8% of the cohort have not had recent CD4+ cell testing or been reported to have AIDS through local and national surveillance.

The group of HLP appears to represent a distinct subgroup within the cohort. Compared with other men with long-term HIV infection, these men have more stable CD4+ cell counts, less abnormal immunologic and hematologic parameters and fewer significant HIV-related signs or symptoms. This is a conservative comparison; we would have expected to find even more dramatic differences between HLP and other HIV-infected men from the cohort if we had included men who had progressed to death prior to 1990.

However, when HLP were compared with the controls, they did not have normal immunologic parameters. This is consistent with the finding that viral activity and destruction occurring in the lymph nodes may not be fully represented by changes in the peripheral blood [9]. However, the fact that after an initial drop in CD4+ count HLP have stable CD4+ slopes more than 10 years after HIV infection, suggests that HIV-induced immunologic destruction may be slowed or arrested in HLP.

We have found that HLP have elevated CD8+ levels, both compared with progressors and HIV-uninfected men. The role of CD8+ cells in HIV disease progression has not been clearly defined. Most studies of laboratory markers have found that CD8+ counts do not add independent prognostic value to CD4+ counts [10–12]. Other studies have found that high CD8+ counts predict a rapid decline in CD4+ counts [13] or that increased levels of specific CD8+ cell subsets are correlated with more rapid progression to AIDS [14–17]. In contrast, in this study, the HLP had significantly higher CD8+ counts, suggesting that some subset of CD8+ cells may play a role in delayed progression in these men. This finding was confirmed in another study of long-term HIV-1 'non-progressors' [20]. Preliminary studies from the

SFCCC and other groups have found that CD8+ suppressor cell activity may be increased in HLP men, when compared with men with advanced HIV disease [18,19,21]. In addition, a number of studies have documented increased CD8+ cytotoxic lymphocyte activity in asymptomatic HIV-seropositive individuals [18,22] and in particular in HLP [19].

To investigate possible reasons for delayed HIV disease progression, we evaluated antiretroviral use in the cohort. The men who used antiretrovirals despite high CD4+ counts cited many reasons, including participation in early intervention clinical trials, a desire to maintain high CD4+ counts, and prior transient decreases in CD4+ counts. However, the majority of HLP had never used antiretrovirals, the only demonstrated method for slowing HIV disease progression. This suggests that other factors play a role in delayed HIV disease progression.

We were unable to demonstrate any consistent association between history of STD or recreational drugs and delayed HIV disease progression. Although HLP were less likely to report enteric infections than progressors, this association did not appear until 9 years after HIV seroconversion and was strongest at 10 years. Rather than being a cause of differences in progression rates, enteric infections may represent a symptom of immunodeficiency in the progressors, who may be both more susceptible to enteric infections and more likely to have cultures performed to diagnose infection. Alternatively, enteric infections may be associated with Kaposi's sarcoma as has been reported previously [23], rather than truly associated with the rate of HIV disease progression. Similarly, the association between tranquilizer use and progressors was only present at 10 or more years after HIV seroconversion. While it is difficult to postulate a biologically plausible mechanism for accelerated progression late in disease for this class of drugs (which included benzodiazepines and methaqualone), it is quite likely that progressors were being treated with and self-administering anxiolytics to cope with late-stage HIV infection.

Several factors may limit our ability to find differences in exposures between HLP and progressors, including sample size and homogeneity of risk behaviors in the cohort. Misclassification could have occurred in defining HLP based on a single (most recent) CD4 count, given the inherent variability of this measurement. However, all but four of the HLP had multiple CD4 counts $>500\times10^6$/l, making it unlikely that this misclassification significantly diluted these results. It is also possible that restricting our comparison to men with long-term HIV infection may have masked important differences in the very rapid progressors and HLP. For example, increasing age was not found to be significantly associated with progressors, although it has been associated with rapid progression in our cohort and in others [24]. It is also difficult to rule out the possibility that poor health in the progressors led to a decreased likelihood of exposures, thus diluting our ability to detect a difference between the groups. We attempted to control for this by censoring exposure data at the interview prior to AIDS diagnosis or a low CD4+ count and by censoring the analysis at several earlier intervals. We were unable to find a consistent difference between the groups using either of these techniques.

Several other published reports have also found no association between HIV disease progression and STD [25,26], recreational drugs [26,27], smoking [26,28], or alcohol [26,29]; however, only one of these studies controlled for duration of HIV infection [28]. One study of men with incident HIV infection found an association between sexual risk factors and very rapid HIV disease progression [30]. However, it does not appear that a simple absence of risk factors for rapid progression accounts for delayed HIV disease progression in our cohort.

In common with many other infectious diseases, there may exist a subset of individuals who become infected with HIV and never develop disease. Whether HLP belong to such a group or represent the tail of a random distribution of latency periods [20] cannot yet be determined. It does not appear that slower progression is due to decreased exposure to behavioral or sexual risk factors. The possibility exists that HLP have slowed or arrested HIV disease progression through effective immunologic responses, host genetic factors, viral factors, or as yet unidentified biologic or behavioral cofactors. The role of these mechanisms in delaying HIV disease progression deserves further investigation.

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