Does symptomatic primary HIV-1 infection accelerate progression to CDC stage IV disease, CD4 count below $200 \times 10^6/l$, AIDS, and death from AIDS?

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See editorial by Johnson
and pp 1537, 1549, 1550

Abstract

Objective—To investigate the prognostic significance of symptomatic primary HIV-1 infection.

Design—Prospective study of homosexual men seroconverting to HIV in 1985 and 1986. Patients were followed up at least three times yearly with clinical examinations and T cell subset determinations for an average of 7.2 years.

Setting—Research project centred on attenders for treatment and screening for HIV at the Karolinska Institute, Stockholm.

Subjects—19 patients presenting with a glandular-fever-like illness associated with seroconversion to HIV and 29 asymptomatic seroconverters.

Main outcome measures—Progression to Centers for Disease Control and Prevention stage IV disease, CD4 cell count below $200 \times 10^6/l$, AIDS, and death from AIDS.

Results—Symptomatic seroconverters were significantly more likely to develop Centers for Disease Control and Prevention stage IV disease (95% v 66%), CD4 cell counts below $200 \times 10^6/l$ (84% v 55%), and AIDS (58% v 28%) and die of AIDS (53% v 7%).

Conclusion—A glandular-fever-like illness associated with seroconversion to HIV-1 predicts accelerated progression to AIDS and other HIV related diseases.

Introduction

The clinical picture of primary HIV-1 infection ranges from asymptomatic seroconversion to a distinct and recognisable clinical syndrome characterised by fever, sore throat, lymphadenopathy, maculopapular rash, and mucocutaneous ulcers.^{1,2} About half of homosexual men with primary HIV infection develop this mononucleosis-like syndrome^{3,4} whereas a lower prevalence has been reported in seroconverting drug addicts.^{2,5}

We have reported on the clinical picture and laboratory confirmation of primary HIV infection in 20 homosexual men who presented in 1985 and 1986 with a glandular-fever-like illness.^{2,6,9} During the same period we identified another 29 homosexual men with asymptomatic seroconversion. Both groups have now been followed up for more than seven years and we present data on the progression of HIV infection as monitored by four end points—namely, Centers for Disease Control and Prevention (CDC) stage IV disease,¹⁰ CD4 cell count below $200 \times 10^6/l$, AIDS,¹¹ and death from AIDS.

Patients and methods

We included all incident cases of HIV infection in homosexual men between November 1984 (when

testing for HIV antibody became available in Sweden) and December 1986 for whom the date of HIV infection could be estimated. Date of onset of HIV infection was taken as the midpoint between the last HIV negative and first HIV positive test result in samples taken no more than 15 months apart. Patients who sought medical attention and were observed during a feverish illness of acute onset associated with seroconversion to HIV, with other causes of illness excluded by differential diagnostic methods, were classified as cases of symptomatic primary HIV infection. All other patients who had regularly presented for screening were classified as cases of asymptomatic primary HIV infection.

All HIV screening was performed by first generation enzyme linked immunosorbent assay (ELISA; Abbott or both Wellcozyme and Organon) and infection confirmed by western blotting. Methods and results from laboratory confirmation of primary HIV infection in patients with symptomatic seroconversion were as reported.^{6,9} Patients were clinically examined and peripheral blood samples collected for determination of T cell subsets at least three times yearly. Patients were treated according to hospital routines.

Levels of significance for differences between groups in attaining end points were calculated by the log rank test of Kaplan-Meier life table estimated disease progression rates.

Results

Symptomatic primary HIV infection—Nineteen homosexual men with a mean age of 32.8 years (range 19–49) presented with a glandular-fever-like illness a median of two weeks after HIV exposure. All seroconverted to HIV with a median of 15 days between the last HIV negative and first HIV positive test result. Eleven patients developed AIDS defining conditions during follow up—one Kaposi's sarcoma, two lymphomas, and eight opportunistic infections. One patient committed suicide after five years, when he had progressed to Centers for Disease Control and Prevention stage IV disease and a CD4 cell count below $200 \times 10^6/l$. Ten patients died of AIDS. Eight were still being followed up after a mean of 7.2 years (range 6.4–8.0).

Asymptomatic primary HIV infection—Twenty nine homosexual men with a mean age of 33.7 years (range 18–46) consulted for HIV testing. All were initially seronegative for HIV and seroconverted with a median of 250 days between the last HIV negative and first HIV positive test result. A few recalled having had fever and occasionally other symptoms during that period, but an association with HIV seroconversion could not be established as none had sought medical attention at the time. Eight patients developed AIDS

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defining conditions during follow up—four Kaposi's sarcoma and four opportunistic infections. Two patients died of AIDS. Twenty seven patients were still being followed up after a mean of 7.2 years (range 6.1-8.4).

Comparison of disease progression—A more rapid progression of HIV infection after symptomatic primary infection was indicated by all end points—Centers for Disease Control and Prevention stage IV disease (18 men (95%) *v* 19 (66%); $P < 0.001$), CD4 cell count $< 200 \times 10^6/l$ (16 (84%) *v* 16 (55%); $P < 0.01$), AIDS (11 (58%) *v* 8 (28%); $P < 0.02$), and death from AIDS (10 (53%) *v* 2 (7%); $P < 0.0001$) (figure).

Discussion

The prognostic significance of symptomatic seroconversion in HIV-1 infection has long been controversial. Interpretation of other studies has been complicated by differences in populations, follow up times, end points, and selection of patients. In two studies^{12,13} the diagnosis of symptomatic primary HIV infection was established retrospectively from interviews. Patients had been asked to recall symptoms during the three months before their first HIV positive test result, a method which is clearly open to bias.³ In a third study difficulty was evident in distinguishing between the influence of different presentations and transmission categories.⁵ All these studies were terminated early with an average follow up of two to three years and were therefore dependent on the use of surrogate markers, which may not always reflect true progress of HIV infection.¹⁴

We believe that our study clearly shows an association between symptomatic primary HIV infection and accelerated progression of the disease. Three main factors strengthen our conclusion. Firstly, there was a reliable history in all cases of symptomatic primary HIV infection, all patients having been observed during the acute illness. Secondly, the patients were followed up for a mean of 7.2 years, allowing us to record end points in most cases and also to employ definite markers of progression including the "final end point," death from AIDS. Thirdly, we studied subjects belonging to only one transmission category—namely, homosexual men. The possible validity of our findings for other transmission categories will need to be proved by other studies.

What factors determine whether an infected person develops symptomatic or asymptomatic primary HIV infection? The clinical picture is probably related to the host's response,¹⁵ which may be determined by

Kaplan-Meier graphs showing percentages of patients with symptomatic and asymptomatic primary HIV-1 infection progressing to Centers for Disease Control and Prevention stage IV disease, CD4 cell count $< 200 \times 10^6/l$, AIDS, and death from AIDS in relation to duration of infection. Open circles indicate results of most recent observations on subjects in whom progression to particular end point was not recorded

both virus specific and host factors as well as by the mode of acquisition. A high prevalence of symptomatic primary HIV infection has been reported for transmission categories associated with extravasally introduced HIV—for example, via mucous membranes at sexual transmission or into subcutaneous tissue by needle accidents.¹⁶ A lower prevalence of symptomatic primary HIV infection, except for a mild illness with few symptoms, may generally be expected when HIV is inoculated intravasally—for example, to recipients of blood products¹⁷ or by "microtransfusion" to drug users sharing injecting equipment.²³ A seven year progression rate to AIDS of 21% was found in a study of injecting drug users¹⁸ whereas four different studies of HIV infected homosexual men reported a seven year progression to AIDS of 28%, 28%, 32%, and 40%.¹⁹⁻²² These differences may be associated with a higher prevalence of both Kaposi's sarcoma and symptomatic primary HIV infection in homosexual men.

This study shows that prognosis may be determined at the onset of infection. This is supported by a report of long term symptomless subjects infected by a less virulent strain of HIV, suggesting that viral factors influence the rate of progression.²³ Furthermore, Murphy-Corb found that rhesus monkeys infected by identical simian immunodeficiency virus inoculates could be examined within 30 days of inoculation by several assays to identify animals with rapid, moderate, or slow progression, indicating that host related factors may be an important determinant of disease progression with the simian virus.²⁴ These reports suggest that information obtained during primary HIV infection will prove to be of value in identifying markers indicative of rapid progression as well as in studies of long term survivors.

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Key messages

- Seroconversion to HIV-1 is associated with a glandular-fever-like illness in about half of patients
- Patients presenting with this clinical illness have a much accelerated progression of HIV infection as compared with asymptomatic seroconverters
- Clinicians caring for these patients should know that within four years half progress to CD4 cell counts at which antiretroviral therapy and prophylaxis against opportunistic infections are recommended
- Randomised, placebo controlled trials of zidovudine during primary HIV-1 infection have been started but long term benefit remains to be established

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HIV disease progression in 854 women and men infected through injecting drug use and heterosexual sex and followed for up to nine years from seroconversion

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Abstract

Objective—To compare the progression of HIV-1 infection in men and women followed up for up to nine years after an accurately estimated date of seroconversion.

Design—Prospective observational study.

Setting—16 HIV outpatient clinics across Italy.

Subjects—321 women and 533 men infected with HIV through injecting drug use or heterosexual sex and with accurately estimated dates of seroconversion.

Main outcome measures—Progression to severe CD4 lymphocytopenia (CD4 lymphocyte count <200×10⁶/l), development of AIDS defining diseases, and death from AIDS.

Results—Thirty two women and 67 men developed AIDS at Kaplan-Meier progression rates of 25% (95% confidence interval 13.8% to 35.5%) and 23% (15.6% to 30.4%), respectively, 7 years after seroconversion. In a Cox proportional hazards model the relative hazard was 0.93 (that is, a slightly lower hazard in women) before and 1.10 (0.70 to 1.72) after adjusting for age, HIV exposure group, and year of seroconversion. When CD4 lymphocytopenia and death from AIDS were used as end points the results were similar, with adjusted relative hazards of 0.95 (0.63 to 1.42) and 0.72 (0.48 to 1.09) respectively. In both women and men the risk of developing AIDS before the CD4 lymphocyte count had declined below 200×10⁶/l was small (3% in women, 6% in men). The estimated median count at which AIDS developed in women (34×10⁶/l; 10×10⁶ to 44×10⁶) was similar to that for men (44×10⁶/l; 22×10⁶ to 60×10⁶).

Conclusion—There seems to be little evidence for appreciable differences in the natural course of HIV infection between men and women followed up from the time of seroconversion.

Introduction

Half of the HIV cases in the developing world are in women, and in industrialised countries the proportion of cases of HIV infection and AIDS reported in women is increasing.^{1,2} However, the natural course of HIV infection in women has not been studied extensively and little is known about markers and risk factors for disease evolution. Progression rates to AIDS and clinical manifestations of diseases associated with HIV infection might differ between women and men because of biological and socioeconomic factors. In several countries access to care and treatment is an important issue for HIV infected women, most of whom belong to ethnic or racial minorities.³ Moreover, diseases now indicative of AIDS, such as cervical cancer might determine an excess of morbidity and mortality in women as compared with men.

Several case reports and cross sectional and retrospective studies lacking detailed descriptions of research methodology have been published, but there are very few prospective studies of HIV progression among women.⁴ Furthermore, most workers have investigated gender as a cofactor in studies of survival with AIDS⁵⁻¹⁰ or in longitudinal studies of seroprevalent cohorts of HIV infected women without knowing the seroconversion date.¹¹⁻¹⁴ To our knowledge, with the exception of two preliminary reports coauthored by some of us^{15,16} the only incident cohort study addressing this issue was conducted in a population of women working as prostitutes in Nairobi without any referent male population.¹⁷ Recently a multicohort analysis project workshop held in Cambridge¹⁸ marginally considered gender differences in terms of disease progression and marker paths in five seroconverter cohorts, including our own.

To address these issues we followed up a large number of HIV infected women and men with accurately estimated dates of seroconversion to eval-