Do gender differences in CD4 cell counts matter?

AIDS 1999; 13: 2361-2364
CHAPTER 7

CONCISE COMMUNICATION

Do gender differences in CD4 cell counts matter?

Maria Prins\textsuperscript{a}, J. Roy Robertson\textsuperscript{b}, Raymond P. Brettle\textsuperscript{c}, Ildefonso Hernández Aguado\textsuperscript{d}, Barbara Broers\textsuperscript{e}, Faroudy Boufassa\textsuperscript{f}, David J. Goldberg\textsuperscript{g}, Robert Zangerle\textsuperscript{h}, Roel A. Coutinho\textsuperscript{a, i} and Anneke van den Hoek\textsuperscript{a}

\textbf{Objective:} To examine the effect of gender on disease progression and whether gender differences in CD4 lymphocyte counts persisted for the entire course from HIV seroconversion until (death from) AIDS.

\textbf{Methods:} CD4 lymphocyte counts were modelled in 221 female and 443 male seroconverters following seroconversion, backwards from AIDS and backwards from death using regression analysis for repeated measurements.

\textbf{Results:} In the period before use of highly active antiretroviral therapy (HAART), progression to AIDS and to death were marginally slower in women than in men as assessed by proportional hazards analysis. Women seroconverted for HIV, developed AIDS and died at higher CD4 cell counts than men (women: 815, 146 and \(44 \times 10^6\) cells/l, respectively; men: 727, 49 and \(22 \times 10^6\) cells/l, respectively), although differences were only statistically significant at AIDS onset. Declines in CD4 lymphocyte counts were not significantly affected by gender and absolute differences between men and women were stable, with exception for the trajectory close to AIDS when the decline became steeper for men than women.

\textbf{Conclusion:} These gender differences in CD4 lymphocyte counts suggest a delay of initiation of therapy in women compared with men (our model predicted that women reach the threshold of starting HAART at about 12 months later than men). If this delay unfavourably influences progression, treatment guidelines should be revised so that women can benefit equally from HAART. © 1999 Lippincott Williams & Wilkins

\textit{AIDS} 1999, \textbf{13}:2361–2364

\textbf{Keywords:} CD4 cell counts, gender differences, treatment guidelines

\textbf{Introduction}

Relative to their male counterparts, both HIV-negative and HIV-positive women tend to have higher CD4 lymphocyte cell counts \cite{1-6}. The difference in absolute CD4 counts was found to be about \(100 \times 10^6\) cells/l in HIV-negative subjects \cite{2} and in HIV-positive subjects shortly after HIV infection \cite{3, 4}. Since the absolute

From the \textsuperscript{a}Municipal Health Service, Division of Public Health and Environment, Amsterdam, The Netherlands, the \textsuperscript{b}Edinburgh Drug Addiction Study, Muirhouse Medical Group and the \textsuperscript{c}Infectious Diseases Unit, Western General Hospital, Edinburgh, UK, the \textsuperscript{d}Valencian HIV Seroconversion Study, Department of Public Health, Miguel Hernández University, Alicante, Spain, the \textsuperscript{e}Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland, the \textsuperscript{f}SEROCO Study Group, Inserm U 292, Hôpital de Bicêtre, Le Kremlin Bicêtre, France, the \textsuperscript{g}Scottish Centre for Infection and Environmental Health, Ruchill Hospital, Glasgow, UK, the \textsuperscript{h}AIDS Unit, University of Innsbruck, Innsbruck, Austria and the \textsuperscript{i}Academic Medical Centre, University of Amsterdam, Department of Human Retrovirology, Amsterdam, The Netherlands.

Sponsorship: Supported by the Dutch AIDS Foundation (Stichting AIDS Fonds), as part of the Stimulation Programme on AIDS Research of the Dutch Programme Committee for AIDS Research (2172) and by the grants of the original studies.

Requests for reprints to: Maria Prins, Municipal Health Service, Division of Public Health and Environment, Nieuwe Achtergracht 100, 1018 WT Amsterdam, The Netherlands.

Received: 23 February 1999; revised: 18 June 1999; accepted: 17 September 1999.
CD4 cell count is one of the markers most closely correlated with the stage of HIV infection, one could argue that once infected, women should experience a more favourable course of disease than men. However, most studies found only a very marginal effect of gender on disease progression [7—10], suggesting that the higher CD4 cell counts have no functional significance. Alternatively, gender differences in CD4 cell counts might diminish with ongoing time since HIV infection. A previous study concluded that gender differences were not lost, but this study only included data up to 5 years after infection [4].

Here, we report the results from a longitudinal study among seropositive individuals with documented intervals of seroconversion to investigate further the importance of higher levels of CD4 lymphocyte counts in women prior to and following HIV infection on subsequent disease progression. We evaluated the effect of gender on progression to different endpoints and whether gender differences in CD4 lymphocyte counts persisted for the entire course from seroconversion until (death from) AIDS.

Subjects and methods

The study population comprised 221 women and 443 men infected with HIV for whom the dates of a last negative and first positive HIV test were known. These individuals originated from eight ongoing cohort studies registered in the European Seroconverter Study among injecting drug users [11]. A group of 111 HIV-negative women and 240 HIV-negative men entered the original studies and seroconverted during follow-up; 110 women and 203 men were infected with HIV at study entry but had earlier negative blood samples available to determine HIV seroconversion. For the latter group, negative blood samples were mostly obtained for reasons unrelated to disease progression. The original studies started between 1982 and 1988. Briefly, participants underwent standardized clinical examination, blood testing and completed questionnaires every 3—6 months. T cell subsets were determined by flow cytometry.

The expected date of seroconversion was calculated for each individual conditional upon the last negative and first positive test using a cohort-specific estimate of the cumulative HIV seroincidence over calendar time [11]. Progression from HIV seroconversion to AIDS (1987 Centers for Disease Control AIDS case definition [12]) and to death from AIDS were studied using Cox proportional hazards analysis. For participants who were HIV positive at study entry, follow-up time was calculated from the estimated moment of seroconversion, but they entered the risk set at the date of enrolment. The effect of gender on the CD4 lymphocyte trajectory was assessed in two steps. First, the marker path was modelled by regression analysis for repeated measurements. A mixed linear approach was used [13] in which the rate of change of the CD4 cell count was allowed to differ from one time interval to another [14]. CD4 lymphocyte counts were modelled on the square-root scale up to 7 years after HIV seroconversion, backwards from AIDS diagnosis, and backwards from death from AIDS. A first-order autoregressive moving average within-person correlation structure (i.e. each CD4 cell count depended on the value of and the variation around the preceding count) was applied because compared with various other plausible correlation structures it showed the highest likelihood in all three models. Second, the influence of gender on the intercept and slope in each of the obtained models was estimated and adjusted for potential confounders. *P* values < 0.05 were considered statistically significant.

Results

The median follow-up time was 4.4 years [interquartile range (IQR) 2.1—7.5] and did not differ by gender (*P* = 0.290 by the Mann-Whitney U test). In addition, the frequency of study visits was similar for women and men. Median age at seroconversion was 24.3 years for women (IQR 21.2—28.9) and 25.5 years for men (IQR 22.4—29.0) (*P* = 0.019). The median interval between the last negative and the first positive HIV test (this interval is henceforth denoted as seroconversion interval) was smaller for women (0.9 years; IQR 0.4—2.4) than for men (1.2 years; IQR 0.6—2.3) (*P* = 0.025). At the end of the follow-up (maximally August 1995), 26 women and 61 men had developed AIDS and 31 women and 77 men had died, of whom 19 and 39, respectively, were without AIDS. The most frequently identified single AIDS-defining condition was *Pneumocystis carinii* pneumonia (PCP) (29.9% of the 87 patients with AIDS), followed by oesophageal candidiasis (28.7%) and HIV encephalopathy (11.5%). No differences were found in the distribution of AIDS-defining illnesses between men and women. Six months after their first CD4 cell count fell below 200 × 10⁶ cells/l, 27% of the AIDS-free subjects were receiving antiretroviral treatment (mainly zidovudine monotherapy) and 36% were on PCP prophylaxis. These proportions were comparable for men and women.

Accounting for pre-AIDS mortality from natural causes [14] and adjusting for age at seroconversion and site in Cox analysis, the relative hazard of AIDS for women compared with men was 0.89 [95% confidence interval (CI) 0.58—1.35] and the relative hazard of death from AIDS was 0.71 (95% CI 0.40—1.26). Relative hazards
estimated for individuals with a seroconversion interval of less than 2 years and recruited before or maximally 1 year after seroconversion (n = 372) were not substantially different from those for the group as a whole, though less accurate.

In total, 4702 CD4 lymphocyte measurements from 3 months prior to HIV seroconversion until the end of the HIV-positive follow-up were available for repeated-measurement regression analysis. Modelling the square root CD4 lymphocyte counts from seroconversion onwards, the slope did not appear to be approximately linear for the whole trajectory and a slope change was needed: the CD4 cell count appeared to decline rapidly for the first 7 months following seroconversion and more slowly thereafter. Modelling the decline prior to AIDS, the decline accelerated 18 months before AIDS. No notable change in decline was observed modelling the marker path prior to death from AIDS.

Figure 1 shows the CD4 cell marker paths by gender obtained from fitting the basic mixed models including gender. Back transforming the predicted square root counts, the CD4 cell count at seroconversion was estimated to be $815 \times 10^6$ cells/l for women and $727 \times 10^6$ cells/l for men ($P = 0.121$). Both the decline up to $(26 \times 10^6$ cells/l per month) and following 7 months from seroconversion $(5 \times 10^6$ cells/l per month) did not significantly differ by gender ($P = 0.709$ and 0.992, respectively). Restricting the analysis to those with a HIV-seroconversion interval of less than 2 years and recruited before or maximally 1 year after seroconversion did not alter these estimates appreciably. The CD4 cell count at onset of AIDS was estimated to be $146 \times 10^6$ cells/l for women and $49 \times 10^6$ cells/l for men ($P = 0.004$). The monthly decline was approximately $6 \times 10^6$ cells/l up to 18 months before AIDS and was not significantly affected by gender ($P = 0.920$). However, 18 months prior AIDS, the moment when the decline slightly accelerated, the slope became steeper for men $(10 \times 10^6$ cells/l per month) than for women $(7 \times 10^6$ cells/l per month) ($P = 0.021$). The CD4 count at death from AIDS was $44 \times 10^6$ cells/l for women and $22 \times 10^6$ cells/l for men ($P = 0.347$). The decline prior to death was $5-8 \times 10^6$ cells/l per month. The gender effect on this decline was not significant ($P = 0.956$), although the curves tended to converge slightly close to death (Fig. 1c). Finally, controlling for age at seroconversion, site and time since seroconversion (the latter only when modelling the marker path prior to AIDS and death) did not substantially change the results on the effect of gender.

Discussion

Women seroconverted for HIV, developed AIDS and died from AIDS at higher CD4 cell counts than men, although differences were only statistically significant at AIDS onset. The absolute difference did not appear to be stable close to AIDS and death from AIDS, which might be a consequence of the small number of observations. As progression rates to AIDS and death from AIDS were marginally slower in women than in men, this suggests that following the higher level prior to HIV infection [2] women continue to have higher CD4 cell counts with ongoing HIV infection; however, these higher counts seems to have no functional significance. Since our follow-up was limited, resulting in relatively small numbers of cases and observations prior to AIDS and death from AIDS, our results for later stages of HIV infection need to be confirmed by
studies with a longer follow-up period. Furthermore, CD4 lymphocyte counts may fluctuate depending on smoking, drug use, use of antiretroviral therapy, diurnal variation and the occurrence of splenectomy. However, because of the uniform study population (i.e. all drug users) and several additional analyses (data not shown), we think it is very unlikely that these sources of variability have seriously biased our results.

The main question is whether the gender differences in CD4 lymphocyte counts have implications for patient management, especially with regard to initiation of antiretroviral therapy since guidelines include CD4 cell counts as criteria for starting therapy. Before highly active antiretroviral therapy (HAART) became available, a CD4 count of 200 × 10^6 cells/l was regarded as the level below which antiretroviral therapy and PCP prophylaxis should be started. Because of this relatively late start and because antiretroviral therapy was less powerful, the potential later start of treatment in women than in men as a result of gender differences in CD4 lymphocyte counts was unlikely to have largely influenced disease progression. However, since the more powerful HAART, which is initiated much earlier in infection when the CD4 cell count drops below 500 × 10^6 cells/l (our model predicted that women reach this threshold about 12 months later than men), became generally available in 1996, the situation might be different. Moreover, recent studies have shown that women have lower levels of plasma HIV RNA than men [16–18], while a viral load of > 10 000 copies/ml plasma is nowadays also used as a criterion for initiating antiretroviral therapy. This again suggests a delay of initiation of treatment in women. Consequently, it is very important to study the effect of the later start of therapy in women compared with men on subsequent disease progression in the current era of HAART. If there is epidemiological evidence that women are going to do less well with HAART than men under current guidelines, treatment guidelines will need to be revised so women can benefit equally from HAART.

Acknowledgements

We thank A. M. Richardson (Edinburgh), B. Hirschel, V. Schiffer (Geneva), N. Carré, L. Meyer (Paris), J. McMenamin (Glasgow), R. B. Geskus, A. Krol, E. J. C. van Ameijden (Amsterdam) and the partners in the Valencian HIV Seroconversion Study (FIS 95/0228, 95/1688) for their contributions to this study. We also thank the laboratories collaborating with the original studies for determining lymphocyte subsets, the clinical and health workers who contributed by collecting data, and the participants for their ongoing participation.

References
