Association between the Rate of CD4+ T Cell Decrease and the Year of Human Immunodeficiency Virus (HIV) Type 1 Seroconversion among Persons Enrolled in the Swiss HIV Cohort Study

Philippe Vanhems,[1] Jean Lambert,[3] Marta Guerra,[3] Bernard Hirschel,[2] Robert Allard,[3] and the Swiss HIV Cohort Study[a]

[1]Laboratoire d'Epidémiologie et de Santé Publique, INSERM Unité 271, Université Claude Bernard, Lyon, France, for the Coordinating Center of the Swiss HIV Cohort Study, CHUV, Lausanne; [2]Division of Infectious Diseases, University Hospital, Geneva, Switzerland; [3]Department of Social and Preventive Medicine, University of Montreal, Montreal, Canada

The aim of this study was to investigate the early CD4+ T cell response among human immunodeficiency virus type 1 (HIV-1) seroconverters in relation to their year of seroconversion. Study participants were enrolled in the Swiss HIV Cohort Study between 1985 and 1995 and had not received antiretroviral treatment. The slope of the CD4+ T cell count within 2 years after seroconversion was significantly associated with the year of seroconversion, by sex and by use of injection drugs, when controlling for initial CD4+ cell count. These results show that the loss of CD4+ cells might be associated with the year of seroconversion, suggesting a change in the pathogenesis of HIV across the years. If these results are confirmed, they could have important implications for the pathogenesis of and therapeutic strategies for HIV-1 infection.

CD4+ T cell count is associated with human immunodeficiency virus type 1 (HIV-1) disease progression and survival [1, 2] among patients infected by HIV from an unknown date and among seroconverters [3, 4]. Recently, the prognostic value of the CD4+ cell count was confirmed independently of the virus load [5]. Two studies done in the US Navy reported that the initial CD4+ cell count was <500/mm^3 in nearly 40% and <200/mm^3 in nearly 4% of HIV-1 seroconverters 1 year after seroconversion [6, 7]. These results suggest that host or viral factors (or both) are associated with a faster loss of CD4+ cells early in the course of HIV infection. The emergence of more virulent strains has also been suggested as a factor influencing the rate of CD4+ cell loss. Holmberg et al. [8] did not find that recently infected persons lost their CD4+ cells faster by year of seroconversion, and this finding was confirmed among patients from the Multicenter AIDS Cohort Study [9]. In addition, no major change, such as a more rapid loss of CD4+ T cells, seems to have occurred in the natural history of HIV-1 infection in US patients.

In Europe, analysis of data from the Italian Seroconversion Study [10] did not show a secular trend by year of seroconversion for the initial CD4+ cell measurement obtained within 24 months of seroconversion. Keet et al. [11] suggested a prolongation of the AIDS-free period for patients in the Amsterdam Cohort Study, a finding in contrast to those from the Tricontinental Seroconverters Study, which showed a more rapid progression to AIDS in homosexual men who seroconverted between 1982 and 1987 [12]. In addition, Sinicco et al. [13] showed that HIV-1 seroconversion after 1989 was an independent predictor of disease progression.

Additional studies are needed of the natural history of HIV-1 infection for regional public health interventions and comparisons between countries. The Swiss HIV Cohort Study (SHCS) provides an opportunity for such investigation [14, 15]. We studied the slope of CD4+ cell decrease among HIV seroconverters enrolled in SHCS between 1985 and 1995, to identify any association between the loss of CD4+ cells and the year of seroconversion.

Methods

Study population. The SHCS is a prospective study based on voluntary participation of persons infected by HIV-1; persons infected by HIV-2 were not included. The rationale of the study, the organization of the study, and the baseline characteristics of the SHCS have been described in detail elsewhere [14, 15]. In brief, this multicenter project was implemented in 7 university hospitals

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[a] Study group members are listed after the text.

Reprints or correspondence: Dr. Philippe Vanhems, Laboratoire d'Epidémiologie et de Santé Publique, Université Claude Bernard Lyon 1, 8, av. Rockefeller, 69373 Lyon Cedex 08, France (philipva@lyon-sud.univ-lyon1.fr).

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in Switzerland: Basel, Bern, Geneva, Lausanne, Lugano, St-Gall, and Zurich. Study participants are from both sexes, belong to various groups at risk for HIV infection, and have a physical and blood sample examination every 6 months.

In the first part of the study, we investigated HIV seroconverters with a lag time for seroconversion of <12 months ($n = 266$). The lag time for seroconversion was defined as the time elapsed between the last HIV-negative screening test and the first HIV-positive screening test. The date of infection was estimated as the midpoint between these 2 tests, to facilitate comparisons with other investigations [9, 10].

To determine secular trends for the initial $CD4^+$ cell measurement by year of seroconversion, we compared the first count among patients after stratification by the year of seroconversion. This approach is similar to that of Galai et al. [10], except that we restricted the lag time of the first $CD4^+$ cell determination to 1 year after the date of HIV seroconversion, whereas Galai et al. used 2 years. The lag time for the initial $CD4^+$ cell measurement was the time elapsed from the estimated date of infection to the first $CD4^+$ cell measurement. The mean lag time of the first $CD4^+$ cell determination was 5.6 months (median, 5.5 months; SD = 2.9 months). No patient had received antiretroviral therapy before the first $CD4^+$ cell count.

In the second part of the study, we estimated secular trends of $CD4^+$ cell slopes within 2 years after HIV seroconversion. To do this, we restricted the study population to patients with at least 4 $CD4^+$ cell determinations within 2 years since the date of HIV seroconversion ($n = 69$). This inclusion criterion was chosen so that there would be enough reliable data for assessing a slope. To explore the natural history of $CD4^+$ cell response early after HIV infection, we analyzed data from persons who did not receive any antiretroviral drug during the 2 years after seroconversion or whose treatment began <30 days before the last $CD4^+$ cell measurement (1 month of treatment is unlikely to have an effect on the CD4 cell count).

Laboratory methods. HIV seroconversion was assessed by ELISA, and Western blot was used to confirm the presence of HIV-1 antibodies. $CD4^+$ cell counts were done similarly in each center [16]. All participating centers used cytofluorometry and fluorescein isothiocyanate– or phycoerythrin-labeled antibodies.

Statistical analysis. The baseline characteristics of the patient population were reported by use of means, medians, and SDs for continuous variables and percentages and frequencies for categorical variables.

In the first part of the study ($n = 266$), we performed one-way analyses of variance (ANOVA) to compare age, $CD4^+$ cell count, lag time for seroconversion, and lag time for the first $CD4^+$ cell count by year of seroconversion. The χ^2 test was used to compare sex and risk factors of HIV-infection distributions. The proportions of patients having baseline $CD4^+$ cell counts $<500/mm^3$, $<350/mm^3$, and $<200/mm^3$ by year of seroconversion were compared by use of the χ^2 test for trend [17].

In the second part of this study ($n = 69$), we analyzed individual repeated measures of $CD4^+$ cell counts, to identify a secular trend of these values over the years. We have included in the analysis the data of persons with at least 4 determinations within 2 years from seroconversion, with at least 2 measurements in the first year and 2 in the second year. The analysis was done in 2 steps. First, the slopes of the $CD4^+$ cell counts, with respect to time, were estimated for each patient. In the second step, these slopes were entered as dependent variables in a linear regression model including years of seroconversion and adjusted for center, age, sex, risk factors, initial $CD4^+$ cell count, time elapsed between the seroconversion and the first $CD4^+$ cell count, and the following factors in relation to years since seroconversion: center × year of seroconversion, age × year of seroconversion, sex × year of seroconversion, and risk factors × year of seroconversion. We used a backward stepwise method to identify the appropriate model. To check the adequacy of the model and to identify influential cases, studentized deleted residuals, leverages, and Cook distances were computed. The statistical analyses were done by use of SPSS (version 6.1; SPSS, Chicago) and Epi Info (version 6.04; Centers for Disease Control and Prevention, Atlanta). $P < .05$ was considered statistically significant.

Results

First part of study. A total of 266 patients were included in the first part of the study: 181 were male (68%), 93 (35%) were exposed to HIV by homosexual contact, 86 (32%) were exposed by heterosexual contact, 42 (16%) were exposed by injection drug use (IDU), and 45 (17%) were exposed by sexual contact and IDU or by another route. The mean age was 30.3 ± 8.7 years (range, 17–60; median, 28.0).

The overall median lag time for seroconversion was 6.0 months (range, 0.2–12.0), and the median lag time for the first $CD4^+$ cell measurement was 5.5 months (range, 0.1–11.7). The baseline characteristics did not differ by center (data not shown). The overall median of the first $CD4^+$ cell count after seroconversion was $546/mm^3$ (range, 4–$2100/mm^3$). The overall proportions of patients with CD4 cell counts $<500/mm^3$, $<350/mm^3$, and $<200/mm^3$ were 38.6%, 20.1%, and 3.6%, respectively.

Age, median lag times, and characteristics of $CD4^+$ cell counts, by calendar year of seroconversion, are shown in table 1. There were no statistically significant differences for age, lag for seroconversion, lag for $CD4^+$ cell measurement, and $CD4^+$ cell counts between years of seroconversion. Similarly, sex and risk factor distributions did not show statistically significant differences among years of seroconversion (data not shown). The χ^2 tests for linear trend of these proportions, by year of seroconversion, were not statistically significant.

Second part of study. Sixty-nine patients were included in the second part of the study (table 2): 71% were male, 43.5% were exposed to HIV by homosexual contact, 29% were exposed by heterosexual contact, 12% were exposed by IDU, and 16% were exposed by other routes. The mean age was 31.6 ± 10.4 years (range, 18–60). ANOVA was done on the initial $CD4^+$ cell counts, to identify possible differences among years of seroconversion; the results were nonsignificant ($P = .42$). In addition, there was no difference in the lag time for

Table 1. First CD4+ cell count of 266 Swiss HIV Cohort Study participants who seroconverted for HIV between 1985 and 1995.

Year	No. of patients	Median age, years	Median lag for seroconversion, months[a]	Median lag for CD4+ cell count, months[b]	Median no. of CD4+ cells/mm³	Mean (SD) no. of CD4+ cells/mm³	% with CD4+ cells/mm³ <500[c]	% with CD4+ cells/mm³ <350[d]	% with CD4+ cells/mm³ <200[e]
⩽1987	11	27.0	5.08	7.11	600	721 (400)	27	18	0
1988	29	28.0	5.50	6.59	540	676 (410)	34	14	7
1989	50	26.5	6.29	5.49	540	617 (350)	36	24	12
1990	40	26.0	4.81	4.85	528	518 (270)	45	32	15
1991	36	28.0	5.13	5.42	519	627 (300)	42	14	3
1992	39	29.5	6.21	5.96	571	615 (370)	28	18	15
1993	21	32.0	6.22	5.40	740	712 (279)	33	5	0
1994	19	35.0	8.95	6.85	560	684 (300)	26	16	0
1995	21	31.0	6.65	5.01	450	435 (230)	62	38	14
Total	266	28.0	6.01	5.49	546	612 (330)	38.6	20.1	3.6

NOTE. Represents first part of current study. HIV, human immunodeficiency virus.
[a] Time midpoint between last HIV-negative and first HIV-positive ELISA.
[b] Time between estimated date of infection and date of first CD4+ T cell count.
[c] $P = .42$, χ^2 for linear trend.
[d] $P = .83$, χ^2 for linear trend.
[e] $P = .98$, χ^2 for linear trend.

seroconversion ($P = .60$) or the lag time for the first CD4+ cell measurement by year of seroconversion ($P = .14$).

The overall mean of the individual CD4+ cell count slopes was −46 cells/mm³ per semester. The results of the statistical analysis relating individual CD4+ cell count slopes to prognostic factors are shown in table 3. The initial CD4+ cell count was strongly associated with the slope ($P = .001$): the higher the initial count, the steeper the negative slope. As an example, an increase of 100 cells/mm³ for the initial count was associated with a supplementary loss of 9.4 cells/mm³ per semester.

There were 2 significant interactions: year of seroconversion by sex ($P = .011$) and year of seroconversion by IDU ($P = .007$). Owing to the presence of these interactions in the model, the regression coefficients associated with the main effects included in these interactions should be interpreted with caution. Our objective was to study the impact of year of seroconversion on the CD4+ cell count slopes, and this effect can be obtained for each sex by combining with IDU in the linear regression model shown in table 3. The results are shown in table 4.

As shown in table 4, year of seroconversion was positively associated with the CD4+ cell count slope for men using injection drugs ($b = 27.9$ cells/mm³ per semester) and negatively associated with the CD4+ cell count slope for women not using injection drugs ($b = -17.6$ cells/mm³ per semester). These results mean that, after controlling for the initial CD4+ cell count, the rate of CD4+ cell count loss is less important during the recent years for men using injection drugs and more important during the recent years for women not using injection drugs.

Discussion

The objective of this study was to explore the relationship between the CD4 cell response early in the course of HIV in-

Table 2. Descriptive statistics of the 4 CD4+ cell determinations performed within 2 years of seroconversion among 69 participants of the Swiss HIV Cohort Study, 1985–1995.

	1st year				2d year			
	1st measure (initial)		2d measure		3d measure		4th measure	
Year of seroconversion *(n)*	No. of CD4+ cells/mm³	Lag time for CD4+ cell count, months[a]	No. of CD4+ cells/mm³	Lag time for CD4+ cell count, months[b]	No. of CD4+ cells/mm³	Lag time for CD4+ cell count, months[b]	No. of CD4+ cells/mm³	Lag time for CD4+ cell count, months[b]
⩽1987 (5)	562.0	7.43	676.0	6.66	693.0	16.05	649.6	23.40
1988 (5)	682.2	6.51	637.6	4.30	558.4	16.56	514.8	21.98
1989 (16)	646.2	5.75	657.2	6.35	503.1	16.57	531.3	20.07
1990 (9)	542.3	3.26	455.1	4.80	390.9	15.70	330.5	20.43
1991 (8)	652.3	5.08	555.2	5.12	480.4	15.12	508.0	18.40
1992 (14)	766.1	6.15	882.6	4.08	594.1	16.53	568.6	21.02
1993 (8)	871.8	5.97	608.1	5.43	673.5	17.25	599.1	21.39
1994 + 1995 (4)	801.3	3.96	756.7	6.10	633.3	16.10	590.7	20.33

NOTE. Represents second part of current study. Statistical level of significance of differences of CD4+ cell counts at 6, 12, 18, and 24 months between patients grouped by year of seroconversion are $P = .42$, .08, .07, and .46, respectively.
[a] Time elapsed between estimated date of seroconversion and initial measure of CD4+ cells.
[b] Time elapsed between date of initial measurement of CD4+ cells and every other count.

Table 3. Multiple linear regression model relating individual $CD4^+$ cell count slopes to prognostic factors ($n = 68$).

Prognostic factor	$b \pm$ SE	P	95% CI
Initial $CD4^+$ cell count	−0.094 ± 0.018	.000	−0.130, −0.059
Female	75.1 ± 24.0	.003	27.0, 123.1
Injection drug use	−92.9 ± 41.8	.030	−176.4, −9.4
Year of seroconversion	−1.27 ± 3.22	.694	−7.72, 5.17
Interaction 1[a]	−16.3 ± 6.2	.011	−28.7, −3.9
Interaction 2[b]	29.2 ± 10.5	.007	8.2, 50.2
Constant	15.6 ± 16.1	.337	−16.7, 47.9

NOTE. CI, confidence interval.
[a] Year of seroconversion in relation to sex.
[b] Year of seconversion in relation to injection drug use.

fection and in the year of seroconversion among SHCS participants who were free of antiretroviral treatment.

Linear analysis of the $CD4^+$ cell count within 2 years after seroconversion showed interactions between the year of seroconversion and sex and IDU. This finding differed from those of other studies [9, 18]. Our results are in the same direction as those of Sinicco et al. [13] but are not completely similar. Sinicco et al. [13] reported that the probability of the $CD4^+$ cell count falling to <500, <400, and $< 200 \times 10^6$ cells/L and of AIDS progression was higher for patients who seroconverted after December 1989. Nevertheless, in our study, the significant effect of the year of seroconversion was observed only through the interaction terms, which do not seem to have been explored in the Sinicco study. In our study, the year of seroconversion had an effect among patients followed for 2 years with a similar censoring strategy [19]. The main questions were the following: (1) did we observe the emergence of HIV strains with various levels of virulence in recent years; (2) is there any interaction between the virus strain pathogenicity and the use of injection drugs; and (3) is there any interaction between the virus strain pathogenicity and the sex of the host? Fardzadegan et al. [20] showed that women with the same virus load as men had 1.6-fold higher risk of AIDS [20]. These results, combined with ours, suggest that HIV pathogenicity might differ for males and females and by route of HIV infection.

We do not have any information on the phenotype or genotype of the virus strains, and little is known on the distribution of those strains in different populations at risk of HIV infection [21]. The phenotype defined by syncytium-inducing strains is associated with a faster progression of disease [22], but, until now, no particular genotype seemed to be associated with a faster decrease in $CD4^+$ cell counts. For example, primary HIV infection by a strain with a mutation at codon 215, which indicates acquired resistance to zidovudine, was not associated with more-severe clinical features [23, 24] or with a faster loss of $CD4^+$ cells 1 year after HIV-1 infection [24]. There is also little evidence that the viral subtype determines the rate of disease progression among US patients [25], but HIV-1 subtypes may differ in rates of progression to AIDS among female sex workers in Senegal [26]. The host's genetic status regarding the CCR-5 chemokine receptor has been associated with various rates of progression [27, 28]. In particular, HIV-1–positive patients who are heterozygous for the CCR-5 Δ32 deletion seem to have a slower early HIV-1 progression [27, 28]. We did not have this information for the SHCS participants; however, a trend toward change of the genotype over time would be surprising. This mutation alone does not explain the various rates of HIV-1 disease progression [29], which can involve many factors [30–34].

Our study did have some limitations. Even with standardized criteria of enrollment in the cohort, we cannot totally eliminate recruitment bias toward inclusion of more severely ill patients in recent years. Because the proportion of practitioners with good experience in HIV medicine increased with time, they could have referred to the university hospitals only the patients with severe clinical features at seroconversion. Thus, since the severity of acute HIV infection has been shown to be associated with faster disease progression [35], our results could be biased by a greater proportion of symptomatic seroconverters detected in the recent years. Unfortunately, valid information on the acute illness is not available in the Swiss cohort, especially for patients who seroconverterted before 1990. Moreover, the patients who received antiretroviral treatment at primary HIV infection and who were most likely to be recent seroconverters were not analyzed, so that the study could be restricted to the natural course of HIV infection.

The use of a standardized inclusion protocol and the absence of statistical differences of major baseline characteristics between centers may not have prevented some factors, such as genetic markers (i.e., the human major histocompatibility complex genes HLA groups) associated with disease progression [36], from being unequally distributed in Switzerland. The proportion of patients who received an antiretroviral treatment could have affected the results, but that proportion is expected to be higher in the recent seroconverters. Thus, we should have observed the opposite relationship between the year of seroconversion and the $CD4^+$ cell decrease. The new antiretroviral therapy guidelines proposing to treat patients as early as possible after infection could definitively mask the natural history of the $CD4^+$ cell response early in the course of infection among patients with access to health care in the future [37].

Table 4. Effect of year of human immunodeficiency virus type 1 seroconversion on individual $CD4^+$ cell count slopes with respect to each sex in combination with injection drug use (IDU).

	$b \pm$ SE	95% CI
No IDU		
Men	−1.27 ± 3.22	−7.72, 5.17
Women	−17.6 ± 5.5	−28.6, −6.6
IDU		
Men	27.9 ± 10.1	7.7, 48.1
Women	11.6 ± 11.5	−11.4, 34.6

NOTE. CI, confidence interval.

In summary, we found that the loss of $CD4^+$ cells was associated with the year of seroconversion by sex and IDU, suggesting that the pathogenetic effect of HIV could have changed since 1985 and differed by sex and route of HIV infection. Physicians should be aware of this finding when estimating drug efficacy. Moreover, if changes of HIV pathogenetic mechanisms are confirmed, they can occur on targets other than $CD4^+$ cells and need to be investigated.

Members of the Swiss HIV Cohort Study (SHCS)

The following are members of the SHCS: M. Bateguay (Co-chair of the Scientific Board); E. Bernasconi, Ph. Bürgisser, M. Egger, and P. Erb (Chairs of the Group "Laboratories"); W. Fierz and M. Flepp (Chairs of the Group "Clinics"); P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne); H. J. Furrer, P. Grob, and B. Hirschel (Chairs of the Scientific Board); and L. Kaiser, B. Ledergerber, R. Lüthy, R. Malinverni, L. Matter, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, W. Pichler, J-C. Piffaretti, M. Rickenbach, P. Sudre, J. Schupbach, A. Telenti, and P. Vernazza.

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