Short
report

# HIV seroconversion interval and demographic characteristics: no evidence of selection bias

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**Objectives:** To determine if the interval between the last negative and the first positive HIV test is associated with demographic characteristics of HIV seroconverters.

**Methods:** A prospective cohort of patients with HIV seroconversion enrolled in the Lyons HIV hospital database was analysed. Comparisons of demographic characteristics were performed after stratification on the duration of the interval between the last HIV negative screening test and the first HIV positive screening test, which ranged from 1 day to 24 months. Linear regression methods were used to identify the covariates associated with a negative HIV antibody test followed by a positive test.

**Results:** Age ($p=0.54$), sex ($p=0.78$), heterosexual route of infection ($p=0.78$), other route ($p=0.40$) compared with homosexual route, and estimated year of HIV infection (p value ranged from 0.84 to 0.95) were not associated with a shorter seroconversion interval after multivariate analyses. The presence of an acute HIV illness was the only predictor of a short seroconversion interval ($p=0.006$) with a reduction of 84 days of the interval when it was reported.

**Conclusions:** No selection bias for demographic characteristics of HIV seroconverters seems associated with the length of the seroconversion interval, at least for intervals ≤24 months.

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Keywords: selection bias; HIV seroconversion; study design; incidence cohort

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## Introduction

The rate of human immunodeficiency virus (HIV) disease progression can be estimated from prevalence cohorts, in which the patients are HIV infected at enrolment, or from incidence (or seroconverter) cohorts, in which the date of the last HIV negative screening test and that of the first positive test are both available. However, the maximum acceptable length of intervals between the negative and the positive HIV screening tests as an enrolment criterion differs between studies, ranging from a few weeks,[1] or to 6 months or 9 months in the Multicenter AIDS Cohort study,[2 3] to 12 months in the tricontinental seroconverter study,[4] or even to 24 months in the Italian Study of Seroconverters.[5]

The objective of this investigation was to determine if the length of time that has elapsed between the last HIV negative screening test and the first positive one (henceforth "seroconversion interval") can be associated with a selection bias affecting the baseline demographic characteristics of those HIV seroconverters included in the study. Whether this bias exists or not is important because some demographic characteristics such as age, sex, or route of HIV infection, have been reported to be predictors of survival and disease progression.[6 7]

## Methods

The Lyons HIV hospital database derives from an ongoing cohort study of all HIV infected patients followed at the Lyons university hospitals, France.[8] It was started in 1985 and is a local section of the French HIV hospital database described in detail elsewhere.[9] Briefly, after an individual has given informed consent, a data collection form is filled out, at enrolment and at least every 6 months thereafter. All HIV infected adults in the Lyons area were eligible in this cohort designed mostly to explore the quantity of care provided to these patients. Demographic, clinical, and biological data are collected by trained research nurses after a medical examination, and computerised. Regular local and national reports are produced after data validation. No change in recruitment method has occurred over the years.

**Key messages**

- Cohort studies performed among HIV seroconverters are the best way of estimating the rate of HIV disease progression, but the number of patients included with a documented seroconversion can be limited.
- A mean of enough enrolled patients to reach a good statistical power for detecting differences in terms of disease progression is to include patients with various HIV seroconversion interval durations.
- We found that whatever the duration of HIV seroconversion interval within 2 years, no major bias does exist on the principal demographic characteristics of the patients.
- However, patients with a short HIV seroconversion interval are more likely to be patients who presented an acute HIV illness at enrolment in the cohort.

*Table 1   Characteristics of seroconverters by seroconversion interval*

| | Seroconversion interval | | | | | |
|---|---|---|---|---|---|---|
| Variables | 0–6 months n=73 (%) | 6–12 months n=128 (%) | 12–18 months n=62 (%) | 18–24 months n=44 (%) | p Value | Overall sample n=307 (%) |
| Male sex | 63 (83.6)★ | 117 (91.4) | 58 (93.5) | 37 (84.1) | 0.29 | 275 (89.6) |
| Mean age in years (SD) | 34.0 (10.9) | 32.0 (8.9) | 31.9 (8.6) | 32.6 (7.7) | 0.45 | 32.5 (9.2) |
| Route of HIV infection | | | | | 0.42 | |
|   Men who have sex with men | 50 (68.5) | 102 (79.7) | 47 (75.8) | 30 (68.2) | | 229 (74.6) |
|   Heterosexual intercourse | 13 (17.8) | 19 (14.8) | 10 (16.1) | 10 (22.7) | | 52 (16.9) |
|   Other | 10 (13.7) | 7 (5.5) | 5 (8.1) | 4 (9.1) | | 26 (8.5) |
| Estimated years of seroconversion† | | | | | 0.54 | |
|   1985–89 | 13 (17.8) | 19 (14.8) | 12 (19.4) | 8 (18.2) | | 52 (16.9) |
|   1990–2 | 24 (32.9) | 37 (28.9) | 27 (43.5) | 11 (25.0) | | 99 (32.2) |
|   1993–5 | 22 (30.1) | 41 (32.0) | 14 (22.6) | 14 (31.8) | | 91 (29.6) |
|   1996–8 | 14 (19.2) | 31 (24.2) | 9 (14.5) | 11 (25.0) | | 65 (21.2) |
| Acute HIV illness reported | 17 (23.3) | 17 (13.3) | 7 (11.3) | 3 (6.8) | 0.06 | 44 (14.3) |
| First CD4 $\times 10^6$/l count after the first HIV positive screening test, mean (SD) | 489 (294) | 474 (297) | 500 (258) | 449 (275) | 0.82 | 480 (285) |
| Days between the first HIV positive screening test and the first CD4 count, mean (SD) | 539 (708) | 641 (867) | 351 (570) | 538 (910) | 0.36 | 544 (789) |
| First plasma HIV RNA level ($\log_{10}$)/µl after the first HIV positive screening test, mean, (SD) | 3.1 (1.9) | 3.4 (1.4) | 2.9 (1.4) | 3.0 (1.6) | 0.25 | 3.2 (1.6) |
| Days between the first HIV positive screening test and the first HIV RNA determination, mean (SD) | 933 (877) | 900 (918) | 837 (735) | 938 (967) | 0.92 | 900 (877) |

★% in the seroconversion interval stratum.

†Estimated as the midpoint between the last negative and the first positive HIV screening test.

At enrolment, the date of the last seronegative test if performed and the date of the first test positive for HIV antibodies are reported. HIV antibody detection is based on ELISA tests, and all patients with a positive HIV screening test are confirmed as HIV infected by western blot. The seroconversion interval is the difference, in months, between the dates of the first positive and last negative ELISA tests. For purposes of this study, we restricted the analysis to seroconversion intervals of no more than 24 months.

The data description was based on standard statistics. Comparisons between subgroups were done using the $\chi^2$ test or one way analysis of variance (ANOVA). A linear multiple regression analysis was used to identify the patient characteristics associated with a short seroconversion interval treated as the dependent variable.[10] The following covariates were included in the model: age, sex, exposure category, year of seroconversion and a report of an acute HIV infection. A two sided p value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS software (SPSS, Chicago, IL, USA).

## Results

A total of 307 seroconverters met the inclusion criteria; 15 were identified in 1988, 11 in 1989, 24 in 1990, 22 in 1991, 29 in 1992, 22 in 1993, 21 in 1994, 43 in 1995, 42 in 1996, 48 in 1997, and 29 in 1998. The last patient was included in November 1998. Their baseline characteristics are reported in table 1. After stratification on the seroconversion interval by 6 month periods (seroconversion interval ranging from 1 day to 6 months, from 6 months +1 day to 12 months, etc), the only major difference between periods was the higher proportion of seroconverters with an acute HIV illness among the 0–6 month group (table 1). The multiple linear regression model identified only the presence of an acute HIV illness as associated with a shorter HIV test interval (table 2). The CD4 count and plasma viraemia were not included in the model, because they are a consequence of HIV positivity rather than a predictor of it.

## Discussion

Seroconverter cohorts are the best means of studying HIV disease progression, but in most observational cohorts the proportion of HIV seroconverters is less than that of prevalent cases. Our results suggest that the maximum acceptable length of the seroconversion interval is associated with no major difference in demographic or laboratory characteristics, when it ranges from 6 to 24 months. However, people infected through contaminated blood and blood products could have a shorter seroconversion interval.

The improvement of the sensitivity and specificity of HIV screening tests across calendar years could be a limitation of our study. It can be advanced that the screening tests used in recent years can detect antibodies earlier than before and thus shorten the seroconversion interval. The multivariate model did not identify a more recent year of seroconversion as

*Table 2   Variables associated with the length of time between the last HIV negative screening test and the first positive one among 307 seroconverters, Lyons hospital database 1985–98, linear multiple regression analysis*

| Variables | Adjusted regression coefficient (SE) | p Value |
|---|---|---|
| Male sex (compared with women) | −12.2 (44.0) | 0.8 |
| Age (per 1 year increase) | −9.3 (15.0) | 0.5 |
| Route of infection (compared with men who have sex with men) | | |
|   Heterosexual intercourse | 9.6 (35.9) | 0.8 |
|   Other | −32.6 (39.3) | 0.4 |
| Year of seroconversion (compared with 1985–9) | | |
|   1990–2 | −6.3 (31.4) | 0.8 |
|   1993–5 | −2.9 (32.1) | 0.9 |
|   1996–8 | 2.2 (34.6) | 0.9 |
| Acute HIV illness (compared with no acute illness reported) | −84.1 (30.5) | 0.006 |

Note: the model includes all the variables in this table.

Model characteristics: R=0.17, $R^2$ 0.03, with a F=1.15 df 8,298, p=0.33.

a predictor of a shorter seroconversion interval. However, we cannot totally eliminate the possibility that a lack of statistical power, because of the low number of seroconverters in the late 1990s, resulted in differences between groups being missed. Also, the small number of acute HIV infections reported in the database is related to the study design, which was not intended for a detailed exploration of acute HIV illness among seroconverters.

Some general comments on the applicability of the results of this study are required. Firstly, if, for some patients, the follow up is short (for example, 1.5 years) but the seroconversion interval is long (for example, 2 years), the estimate of the AIDS incubation period can be biased.[11] Secondly, virological data are more likely to change with time compared with demographic variables, especially during the seroconversion interval itself[12] and we may, therefore, have missed detecting differences in baseline CD4 and RNA measurements between the seroconversion interval groups. For this reason, if virological investigations are planned for early in the course of the disease, we think that an adjustment on the seroconversion interval is necessary. Thirdly, a short seroconversion interval is probably a proxy for an acute HIV illness, which is itself a prognostic factor.[1] In our cohort, the average seroconversion interval was 10.9 months (SD 6.0) for patients with no report of acute HIV illness and 8.3 months (SD 5.4) for patients with a report of acute HIV illness (p = 0.005). However, a short seroconversion interval can also be the consequence of a decision, by the individual or his physician, to carry out repeated HIV testing after a recent potential HIV exposure.

In summary, we did not observe a selection bias in demographic or laboratory characteristics of HIV seroconverters enrolled in the Lyons hospital database associated with the duration of the seroconversion interval. The decision to lengthen the maximum acceptable HIV seroconversion interval, in order to increase the number of individuals eligible for inclusion in incidence studies, appears valid if the study variables can be considered fixed at inclusion and are unlikely to change during the seroconversion period. On the other hand, for biological data, such as HIV plasma RNA, that show important variations during the seroconversion period,[2][12] we suggest treating them as time dependent, and/or adjusting the duration of seroconversion interval in the analysis.

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 *Contributors:* PV performed statistical analyses and wrote the paper; RA contributed towards analysis, writing of the paper and critical appraisal; MD contributed to the initiation of the study and participated in statistical analysis; CC, DP, J-LT, CT, JR, JF are clinical and epidemiological referent physicians for this study and contributed to access to the data, to the result interpretation, and provided the clinical input of the paper.

1 Vanhems P, Lambert J, Cooper DA, *et al*. Acute HIV-1 illness severity and prognosis: a dose response effect. *Clin Infect Dis* 1998;**26**:323–9.
2 Lyles RH, Munoz A, Yamashita TE, *et al*. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. *J Infect Dis* 2000;**181**:872–80.
3 O'Brien TR, Hoover DR, Rosenberg PS, *et al*. Evaluation of secular trends in CD4+ lymphocyte loss among human immunodeficiency virus type 1 (HIV-1)-infected men with known date of seroconversion. *Am J Epidemiol* 1995;**142**: 636–42.
4 Veugelers PJ, Page KA, Tindall B, *et al*. Determinants of HIV disease progression among homosexual men registered in the tricontinental seroconverter study. *Am J Epidemiol* 1994;**140**:747–58.
5 Pezzotti P, Phillips AN, Dorucci M, *et al*. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. *BMJ* 1996;**313**:583–6.
6 Collaborative groups on AIDS incubation and HIV survival. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy:a collaborative re-analysis. *Lancet* 2000;**355**:1131–7.
7 Carré N, Deveau C, Belanger F, *et al*. Effect of age and exposure group on the onset of AIDS in heterosexual and homosexual HIV-infected patients. AIDS 1994;**8**:797–802.
8 Dhenain M, Vanhems P, Fabry J, *et al*. Antiretroviral treatment among HIV-1 seroconverters from Lyon, France (1985–1998). AIDS 1999;**13**:2484–6.
9 Phillips AN, Grabar S, Tassie JM, *et al*. Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. *AIDS* 1999;**13**:2075–82.
10 Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;**79**:340–9.
11 Brookmeyer R, Gail MH. The incubation period distribution. In: *AIDS epidemiology: a quantitative approach*. Oxford: Oxford University Press, 1994:82–112.
12 Kaufman G, Cunningham P, Kelleher AD, *et al*. Patterns of viral dynamics during primary human immunodeficiency virus type 1 infection. The Sydney Primary HIV Infection Study Group. *J Infect Dis* 1998;**178**:1812–5.