

Influence of Age at Infection on Human Immunodeficiency Virus Disease Progression to Different Clinical Endpoints: The SEROCO Cohort (1988–1994)

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Method. The influence of age at infection on progression of human immunodeficiency virus (HIV) disease to different clinical endpoints was studied among 393 HIV-seropositive adults selected from the French SEROCO cohort; follow-up lasted from January 1988 to November 1994. Selected patients had a known date of infection and were enrolled shortly after seroconversion. Age-associated risk ratios (RR) were estimated using the Cox model (age fitted as a continuous variable and RR expressed for each 10-year increment after adjustment for symptomatic primary infection and sexual preference).

Results. Age had a weak influence on progression from the date of infection to the first category B event (crude RR = 1.15; adjusted RR = 1.09; 95% confidence interval [CI] : 0.89–1.36) but a marked influence on progression from the first category B to the first category C event (crude RR = 1.95; adjusted RR = 1.97; 95% CI : 1.37–2.79). Similar results were obtained after adjustment for the CD4 + cell count at enrolment. A qualitative CD4 + cell defect could explain the influence of age, but this remains to be confirmed.

Conclusion. Age at infection should be included in the definition of CD4 + cell count thresholds for clinical management and treatment initiation. Risk factors for progression should be assessed according to the different clinical endpoints.

Keywords: HIV infections, acquired immunodeficiency syndrome, age factors, cohort studies, disease progression, disease-free survival, CD4-positive T-lymphocytes

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The clinical progression of human immunodeficiency virus (HIV) infection can be categorized in several clinical stages.¹ After the sometimes severe but brief initial clinical reaction to HIV infection, the disease course comprises an early stage, in which patients may be totally asymptomatic; a middle stage, in which patients can suffer from minor manifestations (category B events in the 1993 Centers for Disease Control and Prevention [CDC] classification²); and a late stage which encompasses major manifestations (category C events that define clinical acquired immunodeficiency syndrome [AIDS]). In most studies of risk factors for progression, the endpoint is the onset of AIDS. Epidemiological studies have suggested a shorter AIDS incubation period in patients with symptomatic primary infection (SPI)^{3,4} and among homosexual patients (relative to heterosexuals⁵ and haemophiliacs⁶). To date, age at infection is the most widely recognized risk factor for progression to AIDS.

Its influence was initially described in patients infected through blood transfusion: patients over 60 had a risk of progression to AIDS twice that of younger patients.⁷ In haemophiliacs infected through blood products, the risk of progression to AIDS was found to increase 45–60% per 10-year age increment.^{6,8} In homosexual men, the influence of age varies according to the study, with an increase in risk estimated at between 10 and 40% every 10-year increment,^{6,9,10} but not always in a statistically significant manner. Among the sexually infected patients in the French SEROCO cohort, the 10-year rise in the risk of progression to AIDS has been estimated at 40%.⁵

The pathophysiological phenomena underlying the influence of age are poorly known. Some authors explain it through the physiological decline in immune function,^{11–14} which has been attributed to a quantitative¹¹ or qualitative⁸ deficiency in CD4+ lymphocytes. One study has suggested that the influence of age on biological progression only emerges at a certain degree of immunodeficiency:¹⁵ increasing age was associated with a more rapid decline in the CD4+ cell count only when it fell below 500/ μ l. However, this delayed influence of age has never been investigated in terms of progression to the different clinical stages of the disease. Although the CD4+ cell count reflects the clinical progression of HIV disease,¹¹ it is not always reliable.¹⁶ We therefore studied the influence of age on the risk of clinical progression from the date of infection to minor manifestations (category B), and then to major manifestations (category C) of HIV disease.

PATIENTS AND METHODS

Study Population

Patients were selected from the French multicentre SEROCO cohort.^{5,17} In all, 1467 volunteers who were HIV 1-seropositive (enzyme-linked immunosorbent assay confirmed by a conclusive Western blot) and at least 18 years of age have been included in this cohort since January 1988. Enrolment must take place no more than one year after the diagnosis of HIV seropositivity in AIDS-free patients, unless the date of infection is known to within 6 months. Patients are seen every 6 months, or every 3 months in case of clinical or biological deterioration. To study the course of HIV disease after infection, we selected patients whose date of infection was situated in an interval of no more than 2 years between the last negative and the first positive serological test. They were all enrolled rapidly after the diagnosis of HIV infection (median 2.9 months, range [0–31] months). The first clinical manifestation of progression was a category C event in 39 cases; these

patients were excluded from this analysis as progression between category B and category C could not be studied. The analysis was thus based on 393 patients.

METHODS

The date of infection was determined hierarchically from the seroconversion interval in the following way. In 36 cases the date of infection was estimated as 30 days before the date of an inconclusive Western blot. In 77 cases, it was estimated as the date of onset of clinical signs highly evocative of symptomatic primary infection (lymphocytic meningitis, isolated acute mononucleosis-like syndrome, neuropsychiatric signs, or a syndrome combining fever, arthralgia and myalgia). In 17 cases, given the absence of other risk factors, the date of infection was that of a single potentially infective event. Finally, in the remaining 263 cases, the date of infection was estimated as the midpoint of the seroconversion interval.

The cutoff date for this analysis was 1 November 1994.

The influence of age at the time of infection was first studied in terms of overall progression, i.e. from the date of infection to the onset of a first category C event. The study of the influence of age in the early stage of HIV disease was based on disease progression from the date of infection to the first category B event. We then studied the influence of age on progression from the first category B event to the first category C event. These analyses were based on event-free Kaplan-Meier survival curves for four age groups (17–26, 27–36, 37–46 and ≥ 47 years). The curves were compared by using the nonparametric log rank test.

Relative risks (RR) of progression to an event according to age at the time of infection were estimated through the Cox Model.¹⁸ These RR were estimated by fitting the model with age as a continuous variable and after adjustment for sexual preference (as stated by the subject at enrolment) and symptomatic primary infection.

Fitting age as a continuous variable by using the Cox model requires log-linearity of the associated RR. This hypothesis could not be rejected graphically, or by the comparison of nested models, or by using Akaike's criterion.^{19,20}

The proportional hazards hypothesis was checked for each variable and in each model by using the time-interaction test.²¹ Only symptomatic primary infection (SPI) failed to fit with this hypothesis when we studied progression from the date of infection to category C events. The adjustment for SPI was thus made by stratification.²¹

TABLE 1 Characteristics of the 393 HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

Age (years)	17–26 n (%)	27–36 n (%)	37–46 n (%)	≥47 n (%)	P
N	169	156	48	20	
Sexual preference (homo/bisexual)	94 (56)	117 (75)	40 (83)	11 (55)	<0.001
Symptomatic primary infection	44 (26)	41 (26)	14 (29)	8 (40)	0.59
Median follow-up (months)	53	56	57	52	0.66

The nonparametric Kruskal Wallis test was used to compare the distribution of a quantitative variable among several classes of a qualitative variable.

Percentages were compared by using the χ^2 test or, when necessary, Fisher's exact test (extended version).

The analyses were performed on SAS software (SAS Institute, Cary, North Carolina, USA), using the NPARIWAY, FREQ, LIFETEST and PHREG procedures.

RESULTS

The 393 patients selected for this study were 17–61 years old at the time of infection (median 28 years). The distribution of baseline characteristics in the four age groups is shown in Table 1.

In all, 262 male patients (67%) stated having homosexual or bisexual intercourse. They were older (median 29 years) than the heterosexual patients (median 26 years) ($P = 0.0007$).

A symptomatic primary infection (excluding isolated diarrhoea, fever or sore throat) occurred in 107 patients (27%). The frequency of SPI did not differ significantly among the four age groups.

The date of infection was known to within a median of 5.0 months (90th percentile: 17 months), and this precision did not differ with age.

The patients were monitored for a mean of 53 months after infection (range 2–102 months; median 54 months); in total, the follow-up corresponded to 1750 person-years and did not differ among the four age groups (Table 1, $P = 0.66$).

At the cutoff date, 116 patients had developed a category B event and 35 a category C event.

Category C event-free survival curves starting at the date of infection showed that the risk of progression increased with age (Figure 1, $P = 0.003$). No significant association between age and progression to a category

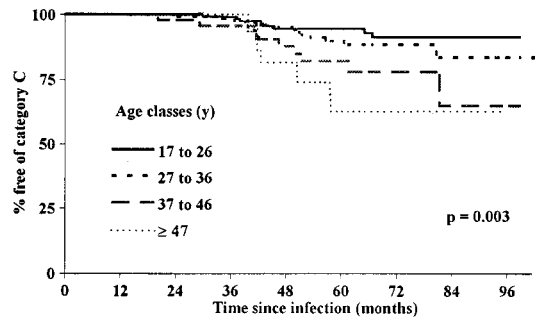


FIGURE 1 Category C event-free survival curves according to age at infection in the 393 HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

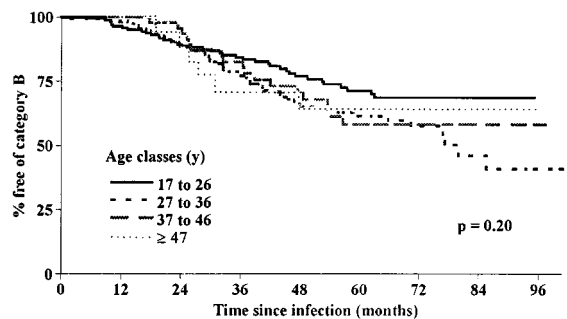


FIGURE 2 Category B event-free survival curves according to age at infection in the 393 HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

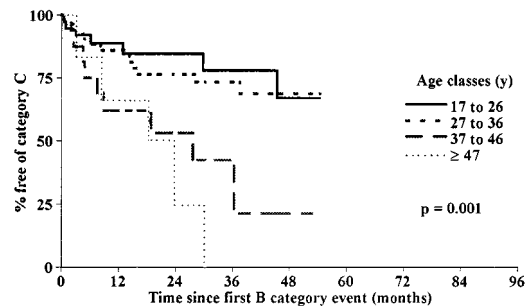


FIGURE 3 Category B to category C progression-free survival curves according to age at infection in 116 HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

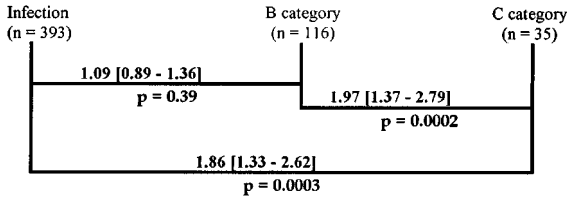


FIGURE 4 Age at infection-associated RR a/decade^a (95% confidence interval) of progression between different stages of HIV disease among patients selected from the French SEROCO cohort (1988–1994)

^a Relative risk for each 10-year increment and after adjustment for sexual preference and stratification for symptomatic primary HIV infection.

B event was noted (Figure 2, $P = 0.20$), but progression from category B to category C events was significantly linked to age at the time of infection (Figure 3, $P = 0.001$).

The influence of age on disease progression was quantified by using the Cox model, after taking into account SPI and sexual preference (Figure 4). Ten-year increments in age at the time of infection were associated with more rapid progression from the date of infection to category C events (crude RR per decade: RR c/decade = 1.88; adjusted RR per decade (RR a/decade) = 1.86; 95% CI : 1.33–2.62; $P = 0.0003$). The influence of age on progression to category B events was weak (RR c/decade = 1.15; RR a/decade = 1.09; 95% CI : 0.89–1.36; $P = 0.39$) but was far more pronounced on progression from category B to category C events (RR c/decade = 1.95; RR a/decade = 1.97; 95% CI : 1.37–2.79; $P = 0.0002$).

Similar results were obtained when Kaposi’s sarcoma (an early manifestation generally affecting homosexuals) was excluded from the definition of category C events.

The CD4+ cell counts were assessed several times during the course of the infection (Table 2). At enrolment the median count depended on age ($P = 0.04$), decreasing with increasing age. A similar relation was found at the onset of category B events, but the difference was not statistically significant ($P = 0.20$). In contrast, at the onset of category C events (Kaposi’s sarcoma excluded) the median count was lower among the youngest patients, though not significantly ($P = 0.26$). The more rapid progression in older patients was not explained by the initial quantitative deficiency in CD4+ cells, as adjustment for the CD4+ cell count at inclusion did not modify the influence of age in the different clinical stages. Similarly, after adjustment for the CD4+ cell count at the time of the first category B event, age

TABLE 2 Median CD4+ cell count/μl at inclusion and before diagnosis of the first category B and the first category C event according to age at infection among HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

Age groups	17–26 CD4+ (n) ^b	27–36 CD4+ (n)	37–46 CD4+ (n)	≥47 CD4+ (n)	P
Inclusion	611 (166)	546 (153)	434 (48)	525 (20)	0.04 ^a
Category B ^c	460 (34)	372 (51)	325 (16)	277 (6)	0.20 ^a
Category C ^c	30 (7)	76 (11)	104 (10)	65 (5)	0.26 ^a
(Kaposi’s sarcoma excluded)			83 ^a		

^a The 37–46 and ≥47 age classes are grouped because of the small sample size.

^b Number of cases in whom the CD4+ cell count was known.

^c Median CD4+ cell count within the previous 6 months.

remained associated with progression from category B to category C.

The type of first category B event or first category C event (infectious disease versus others) was not significantly associated with age at infection (Table 3, $P = 0.84$ and 0.65 , respectively).

DISCUSSION

This study revealed a different influence of age at the time of infection on the risk of progression of HIV infection according to the clinical endpoint. While the influence of age was confirmed on the overall risk of progression, its influence on the risk of progression from the date of infection to a category B event was weak (RR a/decade = 1.09; $P = 0.39$); it was far more marked on progression from a category B event to a category C event (RR a/decade = 1.97; $P = 0.0002$). These RR were estimated after adjustment for potential cofactors of disease progression (sexual preference and symptomatic primary infection).

To our knowledge, the weak influence of age on the risk of progression to category B events has never been described. A potential bias due to noninclusion of rapid progressors²² cannot explain this result. Indeed, an analysis restricted to the 264 patients enrolled within the year following infection yielded similar results, i.e. a weak influence of age on progression to category B events (RR a/decade = 1.05; $P = 0.70$) and a marked

TABLE 3 Percentage of infectious diseases (ID) among category B and C events according to age at infection among HIV-seropositive patients selected from the French SEROCO cohort (1988–1994)

Age groups	17–26	27–36	37–46	≥47	P
All category B events	39	55	17	5	
% ID ^a	74%	78%	71%	100%	
			78%*		0.84*
All category C events	8	13	9	5	
% ID ^b	50%	62%	78%	60%	
			71%*		0.65*

* The 37–46 and ≥47 age classes are grouped because of the small sample size.

^a Oral hairy leukoplakia (n = 39), thrush (n = 38), multidermatomal herpes zoster (n = 12). NB: other category B events = weight loss (n = 10), thrombocytopenia (n = 1), diarrhoea (n = 7), fever (n = 6), peripheral neuropathy (n = 3).

^b Cytomegalovirus infection (n = 2), *Mycobacterium avium* infection (n = 2), *Pneumocystis carinii* pneumonia (n = 6), oesophageal candidiasis (n = 3), cryptococcosis (n = 1), chronic mucocutaneous or disseminated herpes simplex virus infection (n = 1), cerebral toxoplasmosis (n = 3), tuberculosis (n = 2).

NB: other category C events = HIV wasting syndrome (n = 3), dementia (n = 1), Kaposi's sarcoma (n = 9), non-Hodgkin's lymphoma (n = 1), cerebral lymphoma (n = 1).

influence on progression from category B to category C events (RR a/decade = 2.28; $P = 0.003$).

The slower progression to category C events in the youngest age group was not explained by more frequent prescription of antiretroviral therapy or prophylaxis of opportunistic infections, as the contrary was observed. In such an observational study, these treatments should be considered as markers of disease progression.¹¹

The 39 patients excluded from the analysis because they progressed directly to category C events did not differ from the patients who developed a category B event before a category C event, in terms of age, sexual preference, SPI and time to onset of category C events. A larger proportion of these 39 patients were seen irregularly (31% versus 17%) and there was a larger proportion of women (13% versus 3%), though not significantly. Category B events may have been underdiagnosed in these 39 patients. Indeed, category B events (1993 CDC definition²) specific to women (recurrent vaginal candidiasis and *in situ* cervical carcinoma) were not routinely recorded until 1994. Furthermore, the irregular follow-up of some patients may have delayed

the diagnosis of category B events. Inclusion of these patients in the analysis by assuming that they developed a category B event at the time of their category C event did not change the observed age associated RR (data not shown).

Longini *et al.*¹¹ studied the influence of age on HIV disease progression to a biological endpoint (CD4+ cell count) rather than to a clinical event. They showed that increasing age was associated with a more rapid decline in the CD4+ cell count only when it fell below 500/μl. Our results support their findings, as the median CD4+ cell count at the onset of category B events was 387/μl. It thus seems that age only has a discernible influence on progression after a certain stage of HIV disease progression (clinical or biological).

The interaction with latent coinfections has been proposed to explain the influence of age on disease progression.⁸ However, there was no evidence in our study that infectious diseases were any more frequent among older patients. The physiological decline in immune function with age^{8,11–14} is reflected by lower CD4+ cell counts at inclusion in older patients in this study, as described by others.²³ This initial quantitative deficiency does not seem initially sufficient to explain the influence of age on disease progression. Indeed, progression to category B events was weakly associated with age, as was the fall in CD4+ cell count to 500/μl in the study by Longini *et al.*¹¹ and adjustment for CD4+ cell count at inclusion did not modify the results. The age-related reduction in the efficiency of the immune system would only become apparent when clinical or biological¹¹ disease progression reaches a certain threshold (category B and CD4+ cell count <500/μl respectively). In our study, older patients tended to have higher CD4+ cell counts than younger patients at the onset of category C events, pointing to a qualitative deficiency that remains to be investigated.

In conclusion, this study suggests that CD4+ cell count thresholds for clinical management and treatment initiation should be adjusted for age at the time of infection. The variable influence of age according to the clinical stage of HIV infection also shows the importance of assessing risk factors according to different endpoints.

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