Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion

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Abstract

***Objectives*—To determine whether rate of development of AIDS is affected by category of exposure to HIV and whether the more rapid development found in older subjects persists for each exposure category.**

***Design*—Longitudinal study of people with known date of seroconversion to HIV.**

***Setting*—16 HIV treatment centres throughout Italy.**

***Subjects*—1199 people infected with HIV through use of injected drugs, homosexual sex, or heterosexual sex.**

***Main outcome measures*—AIDS as defined by 1987 definition of Centers for Disease Control (including and excluding neoplasms) and by 1993 European definition.**

***Results*—225 subjects (18.8%) progressed to AIDS (Centers for Disease Control 1987 definition) during median follow up of 5.8 years. Univariate analyses showed more rapid progression to AIDS for older subjects compared with younger subjects and for homosexual men compared with other exposure categories. The age effect was of similar size in each exposure category and in men and women. In a bivariate model with age and exposure categories simultaneously included as covariates, differences by exposure category disappeared for use of injected drugs and heterosexual sex compared with homosexual sex (relative hazards 1.02 (95% confidence interval 0.71 to 1.45) and 1.07 (0.70 to 1.64) respectively), while the age effect remained (relative hazard 1.55 (1.32 to 1.83) for 10 year increase in age). Analyses using the other definitions for AIDS did not appreciably change these results.**

***Conclusions*—There was no evidence of differences in rate of development of AIDS by exposure category, while there was a strong tendency for more rapid development in older subjects for all three groups. This supports the view that external cofactors do not play major role in AIDS pathogenesis but that age is of fundamental importance.**

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Introduction

Most studies of the time between seroconversion to HIV and the development of AIDS have considered only a single category of exposure; they therefore lack information about potential differences among exposure categories in the rate of development of AIDS. Inferences about this issue typically derive from comparisons of different studies, but the results can be confounded by differences in the methods of the studies considered.[1] There are seroconverter studies that have compared HIV progression by different exposure categories.[2-7] However, only a few have simultaneously compared HIV progression among the three major categories (infection by use of injected drugs, by homosexual sex (men only), and by heterosexual sex), and as yet only preliminary results are available.[1 8 9]

Results from these studies, and from others where seroconversion dates are unknown,[10-14] are inconsistent: some suggest differences between exposure categories,[1 3-6 10 12 13] while others do not.[2 7-9 11 14] It is essential that this question is resolved, since a lack of differences would argue against external cofactors having an important influence in the pathogenesis of HIV.

There is much broader agreement on the effect of age on progression of HIV infection, with older people having a poorer prognosis.[1 3 4 6-15] Nevertheless, some issues remain unresolved. It has been suggested that the effect of age is mainly limited to predicting the development of neoplasms rather than opportunistic infections.[15] It must also be determined whether the strength of the age effect differs by exposure category or by sex. An effect of similar size in different groups would provide some evidence that the age effect is not due to confounding, suggesting that age related immunological changes could be important determinants of HIV progression.

To address these issues, we analysed data from an incident cohort characterised by subjects with a relatively precise estimated date of seroconversion to HIV and belonging to different exposure categories.

Methods

STUDY POPULATION

Details of our study population have been described elsewhere.[7-9 16] In brief, this is an ongoing multicentre (16 centres) incident cohort study; the principal inclusion criteria include subjects having a documented negative test for HIV followed by a confirmed positive test within a maximum period of two years. Full clinical examinations were conducted every six months. In addition to demographic information such as age and sex, each subject's mode of transmission of the infection (that is, exposure category) was established.

To reduce possible loss to follow up of subjects, data were linked with those from the National AIDS Registry. For subjects whose last clinical visit was at least two years before June 1994, vital status was ascertained through the census bureau.

STATISTICAL ANALYSIS

The date of seroconversion for each subject was estimated as the midpoint between last negative test and first positive one. The cut off date of analysis was June 1994. Three end points were considered: the Centers for Disease Control 1987 definition of AIDS,[17] the 1993 European definition of AIDS,[18] and the 1987 Centers for Disease Control definition excluding neoplasms (that is, Kaposi's sarcoma and lymphomas). Subjects who died before reaching the end point were considered as having withdrawn. The progression to each end point was evaluated using Kaplan-Meier curves, log rank test, and Cox proportional hazards regression models.[19] The proportional hazards models that simultaneously included age at seroconversion and exposure groups (table 3) were repeated after correcting for antiretroviral and prophylactic treatment using a binary, time dependent covariate for treatment begun before the diagnosis of AIDS and a time dependent covariate for the CD4 cell count.[20]

Table 1—*Descriptive characteristics of 1199 subjects by category of exposure to HIV. (Values are medians (ranges) unless stated otherwise)*

	Exposure category		
	Use of injected drugs	Homosexual sex	Heterosexual sex
No (%) of subjects	695 (60)	298 (25)	206 (17)
% Of women	30	0	66
Time between negative and positive HIV tests (months)	8 (0.5-24)	8 (0.5-24)	7 (0.5-24)
Age (years)	25 (15-48)	33 (17-61)	26 (14-59)
Length of follow up (years)	6.0 (0.3-14.3)	5.1 (0.7-10.1)	5.2 (0.3-8.9)
No (%) of cases of AIDS*	127 (18)	67 (22)	34 (17)
No of cases of AIDS* with neoplasms as first AIDS defining disease	7	16	0
No (%) of subjects with CD4 cell count $<200 \times 10^6$ cells/l	162 (23)	84 (28)	65 (32)
% Of time receiving prophylactic or antiretroviral treatment†	55	63	75

*1993 European definition of AIDS.
†Treatment given after CD4 cell count $<200 \times 10^6$ cells/l but before AIDS. This is calculated only from visits after September 1987.

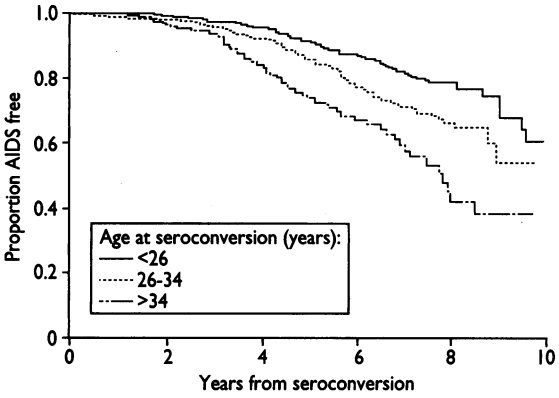

Fig 1—*Kaplan-Meier estimates of cumulative probability of AIDS (1993 European definition) by years from seroconversion to HIV in 1199 subjects stratified by age at seroconversion*

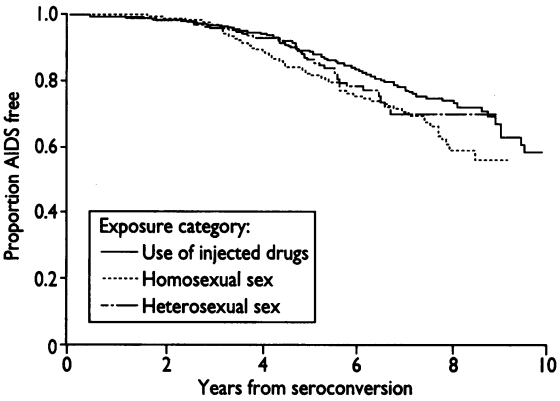

Fig 2—*Kaplan-Meier estimates of cumulative probability of AIDS (1993 European definition) by years from HIV seroconversion in 1199 subjects stratified by exposure category*

Results

The analysis included 1199 subjects who seroconverted between 1980 and 1994. Table 1 shows some descriptive characteristics of the subjects by exposure category. The time between the negative and the positive HIV tests was similar for each group, as was the follow up time. By contrast, the groups showed differences for age at seroconversion (those infected by injecting drugs or by heterosexual sex were, on average, younger than those infected by homosexual sex), type of first AIDS defining disease (those infected by homosexual sex had the highest proportion of neoplasms), and duration of antiretroviral or prophylactic treatment (after September 1987, when the first antiretroviral treatment became available, those infected by injecting drugs spent the lowest proportion of time receiving treatment after their CD4 cell count fell below 200×10^6 cells/l).

Figure 1 shows the Kaplan-Meier curves of progression to AIDS (1993 European definition) by age at seroconversion. The progression at eight years from seroconversion was 22.4% (95% confidence interval 17.3% to 27.4%) for those aged <26, 35.1% (27.9% to 41.6%) for those aged 26-34, and 58.1% (42.6% to 69.4%) for those aged ≥35. These differences were significant. The relative hazards obtained from a univariate proportional hazards model were 1.64 (1.21 to 2.22) for those aged 26-34 and 2.97 (2.10 to 4.20) for those aged ≥35 compared with the youngest group. When this analysis was repeated using the other definitions of AIDS as end points, the differences in the results were negligible (data not shown).

Figure 2 shows the Kaplan-Meier curves by exposure category. Men infected by homosexual sex showed a more rapid progression to AIDS; the relative hazards were 0.66 (0.49 to 0.88) for those infected by injecting drugs and 0.82 (0.54 to 1.23) for those infected by heterosexual sex compared with homosexual men.

We performed separate analyses by exposure category and sex and produced multivariate proportional hazards regression models for each end point in order to assess whether the univariate effect of age was due to the confounding related to the different exposure categories and vice versa (that is, if men infected by homosexual sex progressed to AIDS more rapidly than the others only because of their older age at seroconversion). The age effect was quite similar for each subgroup considered (table 2). Table 3 shows results from the proportional hazards models which simultaneously included age at seroconversion and exposure category. The adjusted hazard ratios were not significant and close to 1 for both comparisons of exposure categories. Models with covariates to correct for antiretroviral or prophylactic treatment provided similar results (data not shown).

Table 2—*Estimated univariate relative hazards (95% confidence intervals) of progression to AIDS for 10 year increase in age at seroconversion to HIV: results for 1199 subjects stratified by definition of AIDS, category of exposure to HIV, and sex*

	Exposure category			Men	Women
Definition of AIDS	Use of injected drugs	Homosexual sex	Heterosexual sex		
CDC 1987	1.87 (1.32 to 2.69)	1.42 (1.11 to 1.82)	1.54 (1.15 to 2.06)	1.51 (1.29 to 1.76)	1.93 (1.19 to 3.14)
European 1993	1.89 (1.34 to 2.66)	1.40 (1.09 to 1.79)	1.53 (1.14 to 2.05)	1.51 (1.29 to 1.76)	1.91 (1.17 to 3.10)
CDC 1987 (excluding neoplasms)	1.76 (1.24 to 2.49)	1.43 (1.09 to 1.87)	1.53 (1.14 to 2.04)	1.47 (1.25 to 1.73)	1.89 (1.16 to 3.09)

CDC = Centers for Disease Control.

Table 3—*Adjusted relative hazards (95% confidence intervals) of progression to AIDS for 10 year increase in age at seroconversion to HIV and category of exposure to HIV*

	Definition of AIDS		
	CDC 1987	European 1993	CDC 1987 (excluding neoplasms)
Increased age at seroconversion	1.55 (1.32 to 1.83)	1.55 (1.31 to 1.83)	1.54 (1.30 to 1.82)
Exposure category:			
Homosexual sex	1.00	1.00	1.00
Use of injected drugs	1.02 (0.71 to 1.45)	1.01 (0.71 to 1.44)	1.11 (0.77 to 1.61)
Heterosexual sex	1.07 (0.70 to 1.64)	1.06 (0.69 to 1.62)	1.23 (0.80 to 1.90)

CDC = Centers for Disease Control.

Discussion

ROLE OF AGE IN DISEASE PROGRESSION

We found that progression to AIDS was strongly associated with age at seroconversion for all subgroups of subjects (that is, men, women, users of injected drugs, men infected by homosexual sex, and those infected by heterosexual sex), suggesting that age was of fundamental importance in the pathogenesis of HIV. This effect seems to be mediated through an early decrease in the numbers of CD4 T lymphocytes, as previously reported in our cohort of users of injected drugs.[21] This decrease could be due to a deterioration in thymic function,[22] as suggested by studies showing that the capacity to produce new CD4 cells after chemotherapy was inversely related to the patient's age.[23] Older subjects may thus have a reduced capacity to generate new CD4 cells in response to the viral killing.[24,25] In our study, inclusion of CD4 cell counts and antiretroviral and prophylactic treatment as time dependent covariates reduced the size of the age effect but it was still significant (relative hazard 1.21 (1.01 to 1.44)).

Our results do not support those of Veugelers *et al*, who reported that the age effect was attributable only to AIDS defining neoplasms.[15] One possible explanation for this discrepancy could be that in the study by Veugelers *et al*, when the end point was any AIDS defining opportunistic infection, subjects who developed a neoplasm and then an opportunistic infection were censored in the analysis at the time of the neoplasm rather than at the time of the infection. Our results also suggest that any comparisons of disease progression among subjects who were infected with HIV by different exposures should be interpreted with caution if the effects of age are not taken into account.

ROLE OF EXPOSURE CATEGORY IN DISEASE PROGRESSION

The similar progression to AIDS by exposure categories (when adjusted for age) suggests that different methods of exposure to HIV are not of great importance in the pathogenesis of AIDS. The differences in progression by exposure category that were reported at the Multicohort Analysis Project Workshop,[1] which included earlier data from our cohort study, may have been due to the inability of the analysis to fully distinguish the effect of the different participating cohorts (each with its own diagnostic criteria, scheduled follow up, strategies for reducing drop out, etc) from that of the exposure categories, because most cohorts had subjects from a single exposure category only. Recently, a French incident cohort study that enrolled subjects infected through homosexual or heterosexual sex, found that the former subjects showed faster progression to AIDS even after adjustment for age at seroconversion or exclusion of Kaposi's sarcoma from the AIDS defining conditions.[6] The reasons for the disagreement with our study are not clear, but the French study gave no information on drop out of patients and apparently no cross check was made with other data sources.

Earlier studies suggested that use of injected drugs was a cofactor for HIV progression. Laboratory studies have reported that heroin and cocaine alter results of immunological assays and tend to stimulate HIV activity in vitro.[26-29] However, we found no important difference between users of injected drugs and those infected by homosexual or heterosexual sex, which is consistent with other comparisons between exposure categories.[30,31] The discrepancy between in vitro results and epidemiological studies could be due to various factors including the fact that in vitro studies measure acute effects of illicit drugs whereas epidemiological studies tend to enroll chronic users of drugs. Also, future studies will need to consider the potential bias related to mortality before development of AIDS (censored in this study) which might nevertheless be HIV related. The concern is that users of injected drugs might die from other causes (such as overdose or trauma) before they can progress to AIDS; if there are differential competing causes of mortality by exposure category, then the observed results could mask true differences.

LIMITATIONS OF STUDY

Since information on CD4 cell count before HIV seroconversion was not available, we cannot assess whether the effect of age on immunosuppression predates HIV infection. However, a separate study which evaluated CD4 cells in subjects who were seronegative for HIV found no age effect.[32]

Subjects infected through sexual contact were more likely to have had more regular follow up visits and to have received treatment than users of injected drugs. However, the age effect should not be highly biased because this effect was similar in each subgroup considered. Additionally, if treatment and compliance before development of AIDS differed between the exposure categories, the relative hazard for exposure categories could be biased. However, we repeated the models shown in table 3, adding time dependent covariates for treatment and CD4 cell counts, but the estimated risks by exposure category differed only negligibly from the earlier analyses. Thus, differential treatment is unlikely to account for our results.

Lastly, we did not use data measuring frequencies of sexual and injecting risk behaviours in this analysis because the multicentre structure of the study meant that such information was of low reliability.

Key messages

- Few studies have evaluated the risk of progression of HIV infection to AIDS in different exposure groups
- Many studies have found an age effect on progression to AIDS, but it is not clear if this is due to specific AIDS defining diseases such as neoplasms and if it differs by exposure groups or by sex
- Our study of 1199 subjects with known date of seroconversion to HIV showed that older subjects progressed to AIDS more rapidly in all exposure groups considered, for both men and women, and for different definitions of AIDS
- After adjustment for age at seroconversion, there was no evidence of different rates of progression among subjects belonging to different exposure categories
- Behavioural cofactors do not seem to play a major role in AIDS pathogenesis but age is of fundamental importance in disease progression

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Relation of common allelic variation at vitamin D receptor locus to bone mineral density and postmenopausal bone loss: cross sectional and longitudinal population study

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Abstract

***Objective*—To determine whether common allelic variation at the vitamin D receptor locus is related to bone mineral density and postmenopausal bone loss.**

***Design*—Cross sectional and longitudinal population study.**

***Setting*—Outpatient clinic in research centre.**

***Subjects*—599 healthy women aged 27 to 72 and 125 women with low bone mass aged 55-77 had bone mineral density measured once in the cross sectional study. 136 women aged 45-54 were followed up for 18 years in the longitudinal study.**

***Main outcome measures*—Bone mineral density measured at the lumbar spine, hip, and forearm and rate of bone loss at different times over 18 years in relation to vitamin D receptor genotype as defined by the endonucleases ApaI, BsmI, and TaqI.**

***Results*—Vitamin D receptor genotype was not related to bone mineral density at any site. The maximum difference between homozygotes was 1.3% (P = 0.33, n = 723). Women with low bone mineral density had almost the same genotype frequencies as the women with normal bone mineral densities. Vitamin D receptor genotype was not related to early postmenopausal bone loss from age 51 to 53 (mean (SD) total loss at the lower forearm −3.6% (3.6%)), late postmenopausal bone loss from age 63 to 69 (at the hip −6.2% (8.7%)), or to long term postmenopausal loss from age 51 to 69 (at the lower forearm −24.5% (11.4%)).**

***Conclusion*—Common allelic variation at the vitamin D receptor locus as defined by the endonucleases ApaI, BsmI, and TaqI is related neither to bone mineral density nor to the rate of bone loss in healthy postmenopausal Danish women.**

Introduction

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue. This results in an increase in bone fragility and susceptibility to fractures,[1] predominantly of the femoral neck, vertebrae, and lower forearm.[2]