Geographical variation in disease progression in HIV-1 seroconverted injecting drug users in Europe?

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Background

Human immunodeficiency virus (HIV) disease progression might vary by geographical region due to differences in the spectrum of HIV-related illnesses and (access to) health care. Therefore, the effect of geographical region, next to the effect of other potential cofactors, on disease progression in 664 injecting drug users (IDU) with documented HIV seroconversion from eight cohorts in Europe was studied.

Methods

Kaplan-Meier methods and Cox proportional hazards analysis were performed to assess the effect of geographical region, other sociodemographics, drug use and repeated HIV exposure on progression from HIV seroconversion to immunosuppression, AIDS and death with AIDS. We considered the confounding effect of study-design related factors (e.g. setting of follow-up), and accounted for pre-AIDS death from natural causes by imputing when each endpoint would have occurred, had they not died without AIDS.

Results

Estimates of progression to AIDS and death with AIDS were substantially faster after taking pre-AIDS mortality into account. Median incubation time from seroconversion to the first CD4 count $\geq 200$ cells/µl was 7.7 years (95% CI: 7.1–8.3) and to AIDS 10.4 years (95% CI: 9.8–10.9). The 10-year survival was 70.3% (95% CI: 62.8–76.6). The relative hazards (RH) of AIDS for IDU from central and southern Europe compared with IDU from northern Europe was 1.9 (95% CI: 1.2–3.0) and 1.2 (95% CI: 0.6–2.3), respectively, before, and 1.5 (95% CI: 0.7–3.2) and 1.1 (95% CI: 0.6–2.3) after taking differences in study-design related factors into account. Accounting for these factors, the RH of death with AIDS was 0.9 (95% CI: 0.3–2.5) for central and 1.2 (95% CI: 0.4–3.4) for southern Europe compared with northern Europe. For the first CD4 count $\geq 200$ cells/µl these figures were 0.8 (95% CI: 0.5–1.4) and 0.8 (95% CI: 0.5–1.4). Age at seroconversion was the strongest predictor of disease progression. No statistically significant differences in disease progression were found by gender, foreign nationality, drug use and potential repeated HIV exposure.

Conclusions

We found no evidence for regional variability in HIV disease progression among European IDU. Future studies evaluating geographical differences should consider the confounding effect of study-design related factors and differential non-AIDS mortality. As age is an important determinant of disease progression, it should be considered in recommending treatment.

Keywords

Geographical variation, HIV disease progression, seroconverters, drug users, Europe

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Surveillance data show that injecting drug users (IDUs) have become the largest group of people with AIDS in Europe; IDU accounted for 40% of the 197,073 cases of AIDS reported through December 1997. Yet, the majority of studies on disease progression have been conducted in cohorts of HIV-1 infected homosexual men.

It has been postulated that immuno-activation associated with frequent and chronic infections, which IDU experience frequently as a result of their lifestyle, may accelerate HIV disease progression. Nonetheless, a number of studies found little evidence for differences in the rate of disease progression between IDU and homosexual men. However, in IDU the spectrum of AIDS-defining conditions differs from that in homosexual men, pre-AIDS mortality is much higher and the start of antiretroviral treatment seems to be delayed.

To better understand the course of HIV infection in IDU, further studies are needed to identify cofactors and markers that account for the wide variability in HIV disease progression within the group itself. Unfortunately, studies evaluating determinants of disease progression in IDU with well-estimated times of seroconversion—these studies avoid bias associated with the unknown duration of infection—are scarce because they are limited by the recent start of most cohorts, relatively small numbers of newly acquired infections and a high attrition rate. Recognizing these limitations, a collaboration was initiated that pooled data of IDU with documented HIV seroconversion from eight cohorts within Europe.

Using this unique data set, we examined the influence of sociodemographic characteristics, drug use and surrogate markers for potential repeated HIV exposure on disease progression. We focused particularly on possible geographical trends in progression from HIV seroconversion to AIDS, immunosuppression and death with AIDS, as a previous study among AIDS cases demonstrated shorter survival after the diagnosis of AIDS in southern Europe than in central and northern Europe. Geographical variation in disease progression might reflect differences in the spectrum of HIV-related illnesses and (access to) health care.

Furthermore, in a recent study we found that pre-AIDS mortality from natural causes (all pre-AIDS deaths excluding deaths from overdose, suicide and unintentional injuries) but not from non-natural causes was associated with HIV disease progression in IDU. Consequently, performing survival analysis where these deaths from natural causes are censored as withdrawn violates the requirement for random censoring. This results in an overestimation of the (AIDS-free) survival curve and leads to biased relative risks if mortality differs between categories of a cofactor. Therefore, we accounted for pre-AIDS mortality from natural causes in the present study. In addition, we considered bias caused by study-design related factors (e.g. setting of follow-up, inclusion of retrospectively identified seroconverters).

Methods

Study population

The HIV-1 positive study population comprised 664 IDU in whom the dates of the last negative and first positive HIV-1 test were known. This population of 664 IDU was the total number of IDU available and all were included in the present study. An IDU was defined as a person who, since 1979, had injected drugs before HIV seroconversion. The drugs most commonly injected in this population were either heroin or heroin together with cocaine.

The IDU originated from eight ongoing prospective studies participating in the European Seroconverter Study: the Valencian HIV Seroconversion Study (n = 246); the Edinburgh Drug Addiction Study and the Edinburgh City Hospital Cohort Study (total number of seroconverters of these two studies combined = 169); the Amsterdam Cohort Study among drug users (n = 99); the Geneva HIV Cohort Study (n = 60); the French SEROCO Study (n = 38); the Scottish National Collaborative HIV Testing Study from Glasgow (n = 31), and the Innsbruck AIDS Study (n = 21).

The original studies started between 1982 and 1988. The design and methodology of each study has been described in detail elsewhere. Briefly, participants underwent standardized medical examination, blood testing and most of them completed questionnaires every 3-6 months. Lymphocyte subsets were determined at each site by flow cytometry. Information on AIDS diagnosis and cause of death were obtained from review of medical records and/or through matching with local and national registers at each study location. Settings where participants were recruited and followed up differed across sites and sometimes within sites. These settings include research units at municipal and regional health centres, public AIDS information centres, general practice surgeries, hospital-based (HIV) clinics and methadone centres.

The study population was composed of IDU who entered the study HIV-negative and seroconverted during follow-up (prospectively identified seroconverters, n = 351), and IDU who were HIV-infected at entry into the study but had earlier blood samples available to determine the interval of seroconversion (retrospectively identified seroconverters, n = 313). For the latter, HIV-negative blood samples were mostly obtained for reasons unrelated to HIV disease progression, such as hepatitis B testing or knowledge of risk behaviour.

Definition of variables

Sociodemographic determinants examined included geographical region, gender, age at seroconversion and foreign nationality. To study the effect of geographical region, countries were classified into three groups: northern Europe (The Netherlands, UK), central Europe (Austria, France, Switzerland) and southern Europe (Spain). Age at seroconversion was categorized according to the tertiles of the study population. Foreign nationality was dichotomized as (yes/no) having the nationality of the country in which the cohort was established.

Because two cohorts did not routinely collect information on self-reported behaviour, analysis evaluating the influence of drug use and repeated HIV exposure on disease progression were limited to six out of eight cohorts. In addition, only compatible items available for at least five of these six cohorts were used in the analysis; variables on drug use were time from first injection to HIV seroconversion and continued injecting in the period between HIV-positive visits. Surrogate markers for potential repeated HIV exposure were continued borrowing of injecting equipment and having an HIV-positive steady sexual partner during HIV-positive follow-up. Categories of time since first injection were defined by cutoff points at the 33rd and 67th percentile. Due to disparate methods of collecting more precise data on frequency across cohorts, the variables continued injecting
and continued borrowing were dichotomized as (yes/no) having injected and borrowed at least once in the preceding period, respectively. For use in the analysis, responses on these items and on having an HIV-positive steady sexual partner were recoded for periods of 6 months. Then, for each IDU, these yes/no variables were compiled over the period beginning the day after the first HIV-positive visit through the third year from HIV-seroconversion, a period of time for which we assume behaviour is minimally affected by clinical manifestations. If AIDS or censoring took place before the third year from seroconversion, variables were compiled through the end of the AIDS(-free) follow-up. The scores obtained indicate the average individual 6-monthly reported frequency of continuation of injecting, borrowing and having an HIV-positive steady sexual partner over the period studied. For example, for a subject who injected at least once in two out of six biannually intervals the score for continued injecting is 0.33. Scores were recoded into tertiles of the study population for use in the analysis.

We evaluated the confounding effect of the following potential study-design related factors: setting of follow-up (research centre, hospital, other [e.g. methadone centre, general practice surgery], any combination), reason for the first study visit (regular HIV screening, HIV-related symptoms, other), length of the interval between the last negative and the first HIV positive test result (i.e. seroconversion interval: <1 years, 1–2, ≥2 years) and type of seroconverter (prospectively identified, lag time between HIV seroconversion and subsequent study entry <1 and ≥1 year).

Statistical methods

The expected date of seroconversion was imputed for each IDU by the following procedure: first, the cumulative HIV-1 seroincidence was estimated over calendar time for each cohort separately applying methods for interval-censored data; second, using the cohort-specific seroincidence distribution, the expected date of seroconversion was calculated for each subject conditional upon the date of each subject’s last HIV-negative and first HIV-positive test.5,19

Studying progression to AIDS, we accounted for pre-AIDS deaths from natural causes (i.e. all pre-AIDS deaths excluding death from overdose, suicide, unintentional injuries and unknown causes) by estimating when AIDS would have been diagnosed, had they not died. Therefore, after square-root transformation of absolute CD4 counts, we modelled the decline of CD4 counts prior to AIDS among the AIDS cases. This analysis was based on regression analysis for repeated measurements using a mixed linear model approach with an autoregressive moving average covariance structure (i.e. each CD4 count depended on the value of and the variation around the preceding CD4 count).20 The CD4 counts in the first year after seroconversion were excluded from this analysis since CD4 counts are known to drop considerably immediately after seroconversion and more slowly thereafter.21 We evaluated the effect of covariates on the intercept at AIDS and the decline before, and when the effect was found to be statistically significant, we incorporated it in the final (piecewise) linear regression equation. Then, by interpolation of the last available CD4 count before pre-AIDS death from natural causes in the obtained regression equation, the residual time to AIDS was calculated. For 7 of the 23 pre-AIDS death from natural causes for whom no CD4 count after one year from seroconversion was available, the median estimated time from pre-AIDS death to AIDS was used. The same procedure was repeated for the endpoints immunosuppression and death with AIDS.

The Kruskal-Wallis test and the χ² test were used to compare baseline characteristics by geographical region. The effect of sociodemographics, drug use and surrogate markers for repeated HIV exposure on progression from HIV seroconversion to AIDS, immunosuppression and death with AIDS were evaluated using Kaplan-Meier product-limit methods and Cox proportional hazards analysis. Significance was determined by the log-rank test and likelihood ratio test, respectively. Survival was calculated from the estimated date of seroconversion through the date of the outcome, loss to follow-up or censoring. Pre-AIDS deaths from causes other than natural were considered lost to follow-up at the date of death. For IDU for whom seroconversion was identified retrospectively, survival was calculated also from the time of seroconversion, but they were not included in the risk set until the date of entry into the study (i.e. left-truncation). Depending on the closing date of each data file merged and taking into account reporting delay of registries, censoring took place ultimately on 1 August 1995.

In this analysis, AIDS was defined by the 1987 criteria of the Centers of Disease Control.22 Immunosuppression was defined as the first CD4 count <200 cells/µl. Because not all individual cohorts have routinely determined lymphocyte counts since the start of their studies, CD4 counts were available for 526 of the 664 IDU (79.2%). To control for differences between cohorts and participants in the frequency of CD4 measurements, in this analysis we used only one CD4 measurement per 6 months with a maximum interval between two measurements of one year. If the interval between two consecutive measurements exceeded one year, subjects were additionally censored one year after the date of the first of these two measurements.

P-values < 0.05 were considered statistically significant. In Cox analysis, we checked the assumption that the hazards were proportional by examining log-minus-log survival plots and by inserting time-dependent functions of covariates. No deviations from proportionality were found.

Results

Table 1 shows characteristics of the 664 IDU stratified by geographical region. The median age at seroconversion did not differ significantly by region (median 25.1 years for the total group). In southern Europe IDU started to inject at a somewhat younger age (median 17.7 years) than IDU in other parts of Europe (P = 0.038). A smaller proportion of women was observed among IDU in southern Europe (26%) than in central (39%) and northern Europe (35%) (P = 0.012). As a consequence of the differential start of the individual cohort studies, IDU living in southern Europe were infected latest (median calendar year of HIV seroconversion 1991), followed by IDU from central Europe (1988) and northern Europe (1985) (P < 0.001).

The 664 IDU were followed for a median of 4.4 years (interquartile range [IQR] 2.1–7.5). At the end of the follow-up, 87 IDU had developed AIDS and 108 IDU had died, of whom 57 were without AIDS. Twenty-three of these 57 pre-AIDS deaths were attributable to natural causes (mainly bacterial infections and cirrhosis/liver failure). The most common single initial
AIDS defining illness was *Pneumocystis carinii* pneumonia (PCP) (29.9% of the 87 AIDS cases), followed by oesophageal candidiasis (28.7%) and HIV encephalopathy (11.5%). We observed a decrease over time of PCP as AIDS-defining illness ($P = 0.056$), which most probably will be, at least partly, the result of increased PCP prophylaxis over the course of the study period. Hence, since many more AIDS cases were observed earlier in the study period in northern Europe than in central and southern Europe because of the more recent start of the participating cohorts in the central and southern region, PCP was more common in northern Europe ($P = 0.054$). However, we found no evidence for geographical differences in the proportion AIDS cases diagnosed with PCP from 1990 onwards ($P = 0.436$). The proportion diagnosed with oesophageal candidiasis and HIV encephalopathy did not differ significantly by calendar time and geographical region. No statistically significant differences were found in the distribution of AIDS-defining conditions between men and women. The CD4 count at AIDS was estimated to be 71 cells/µl. The CD4 count at AIDS as well as the CD4 decline before did not vary significantly according to geographical region.

**Survival estimates**

Figures 1a, 1b and 1c show the Kaplan-Meier estimates of progression from HIV seroconversion to AIDS, immunosuppression and death with AIDS, respectively. In each, figures for pre-AIDS mortality unadjusted (i.e. all pre-AIDS death are censored as withdrawn at the date of death) and adjusted estimates (see statistical methods) are displayed.

For IDU who died from natural causes before AIDS, the median time from pre-AIDS death to AIDS was estimated to be 10 months (IQR: –4 month before until 18 months after pre-AIDS death), had they not died. Death with AIDS was estimated to occur at a median of 28 months (IQR 8–35) after pre-AIDS death from natural causes. Forty-seven per cent of the IDU who died from natural causes without AIDS had a CD4 count <200 cells/µl before. For the remaining IDU who died from natural causes, the first CD4 count dropping below 200 cells/µl was estimated to occur at a median of 16 months after pre-AIDS death (IQR –2–47).

As expected, accounting for pre-AIDS mortality from natural causes resulted in faster progression rates with an estimated probability of progression to AIDS (Figure 1a) at 8 years of 26.9% (95% CI: 22.0–32.8). The median incubation time from HIV seroconversion to AIDS was 10.4 years (95% CI: 9.8–¥). Accounting for pre-AIDS mortality from natural causes, the 8-year probability of a CD4 count <200 cells/µl (Figure 1b) and death with AIDS (Figure 1c) was 55.1% (95% CI: 47.8–62.7) and 16.6% (95% CI: 12.4–20.1), respectively. The adjusted median incubation time to first CD4 count <200 cells/µl was 7.7 years (95% CI: 7.1–8.3). Available follow-up was too short to estimate the median incubation time from HIV seroconversion to death with AIDS by Kaplan-Meier methods.

**Effect of geographical region and other covariates**

Univariate analysis, in which we accounted for pre-AIDS mortality from natural causes, revealed that progression to AIDS was faster in central Europe than in northern Europe.
hazard [RH] = 1.86, Table 2), but progression rates in southern Europe and northern Europe were almost similar (RH = 1.17) (log rank test $P = 0.034$). Progression to AIDS was significantly associated with older age at seroconversion ($P = 0.005$), with IDU aged 23–27 and $\geq 27$ having a risk 1.57 and 2.14 times higher, respectively, than those aged <23 years.

Progression to death with AIDS was also significantly associated with older age in univariate analysis ($P = 0.002$). The effect of geographical region did not reach significance, although again progression was faster in central Europe than in northern and southern Europe (RH = 1.79, Table 2).

In contrast to progression to AIDS and death with AIDS, progression to the first CD4 count $<200$ cells/µl was not significantly associated with age at seroconversion as categorical variable in univariate analysis ($P = 0.232$). Fitting age as a continuous variable, we found an RH of 1.31 per 10-year increment in age ($P = 0.053$). Progression to immunosuppression was comparable for the three geographical regions as shown in Table 2 ($P = 0.802$).

Progression to each of the three endpoints did not vary significantly by gender and foreign nationality in univariate analyses. Neither variables on drug use, nor on potential repeated HIV exposure were significantly associated with progression (data not shown). Progression from seroconversion to death with AIDS tended to be slightly slower in IDU who continued to inject during HIV-positive follow-up than in those who stopped injecting (borderline significance; $P = 0.059$). Furthermore, progression did not differ substantially between IDU with and without data on behaviour. Restricting the analysis to those with behaviour data, the effect of geographical region showed the same trend as presented in Table 2. The same was true for those with and without CD4 counts.

We considered the confounding effect of study-design related factors for each endpoint. Adjustment for each of these factors did not appreciably change the results obtained in univariate analysis for each of the covariates examined, except for geographical region. Firstly, it appeared that IDU whose reason for the first study visit was other than regular follow-up—most of these IDU visited the site initially because of (HIV-related) symptoms—had a faster prognosis to AIDS (RH = 2.99, 95% CI: 1.18–7.61), immunosuppression (RH = 2.65, 95% CI: 1.06–6.65) and death with AIDS (RH = 2.38, 95% CI: 0.71–7.79) compared with IDU who had their first study visit because of regular follow-up. Since all IDU who visited the sites initially for reasons other than regular follow-up (n = 12) originated from two cohorts in central Europe, inclusion of these IDU confounded our results of geographical variation in disease progression. Therefore, we excluded these 12 IDU from any further Cox analysis. In doing so, the crude RH for central Europe declined from 1.86 to 1.65 (95% CI: 0.98–3.18) for AIDS, from 1.79 to 1.59 (95% CI: 0.82–3.09) for death with AIDS and from 0.97 to 0.82 (95% CI: 0.49–1.40) for first CD4 count $<200$ cells/µl. Secondly, we found that IDU exclusively followed in a hospital had a poorer prognosis with regard to AIDS and death with AIDS than the remaining IDU. Excluding also these IDU, the crude RH of AIDS became 1.48 (95% CI: 0.68–3.18) for central and 1.13 (95% CI: 0.56–2.31) for southern Europe. The RH of death with AIDS became 0.88 (95% CI: 0.31–2.54) and 1.15 (95% CI: 0.39–3.41), respectively.

Multivariate models including geographical region and age are shown in Table 2. As setting of follow-up has been shown to be a confounder for the effect of geographical region but none of the IDU with residence in southern Europe were exclusively followed in a hospital, the effect of geographical region was quantified using a combination of these two variables. Table 2 shows that IDU exclusively followed in a hospital in central Europe, independently of age, had about a three times higher risk of AIDS and death than those not exclusively followed in a

![Figure 1](https://example.com/figure1.png)

Figure 1 Plots of crude and for pre-AIDS mortality adjusted Kaplan-Meier estimates of the probability of developing AIDS (Figure 1a), the first CD4 count $<200$ cell/µl (Figure 1b) and dying with AIDS (Figure 1c). Curves were truncated when fewer than 10 subjects remained at risk.
clinical setting in northern Europe. In northern Europe, IDU exclusively followed in a hospital also showed a somewhat faster progression to AIDS than those not so followed (RH = 1.55), although the effect was non-significant. For progression to death with AIDS, no difference within northern Europe was observed according to setting of follow-up. Older age was independently associated with faster progression to AIDS and death with AIDS. In multivariate analysis progression to first CD4 count <200 cells/μl did not differ significantly by the combined variable of geographical region and setting of follow-up, and by age at seroconversion as categorical variables. Age as continuous variable was of borderline significance (P = 0.053).

The interaction between age at seroconversion and the variable combining geographical region with setting of follow-up significantly improved the model for progression to death with AIDS; the effect of age appeared to be somewhat stronger for central Europe than for the other regions. Other sociodemographic and behavioural data did not add predictive power, nor did they confound the results presented. Finally, results from multivariate analysis concerning age were unaffected by adjustment for study site instead of adjustment for geographical region.

Discussion

Results of this study do not suggest appreciable differences in disease progression by geographical region. Results for progression to AIDS and death with AIDS were strikingly similar. The initially observed geographical variability in HIV disease progression was largely explained by differences in study-design across regions. However, significant differences by age persisted after adjusting for other factors. Furthermore, the most common AIDS-defining illnesses did not differ by geographical region, although this analysis was hampered by small numbers.

To our knowledge, among IDU, geographical differences in disease progression from HIV seroconversion onwards have not been evaluated previously. Evaluations of geographical differences in homosexual men with documented HIV seroconversion from various continents showed that progression to AIDS and death did not differ by geographical region.23–25 However, progression to immunosuppression did.24 The authors pointed out that this was likely the result of differences in measurements between laboratories.24 We did not find evidence for large geographical differences in laboratory measurements, even when we evaluated progression to first CD4 count <200 cells/μl by individual cohort (data not shown). These conflicting results might be explained by the fact that relative to the IDU in our study, the homosexual men seroconverted much earlier in time when measurement of CD4 cell counts was less standardized.

A previous study among various risk groups followed in clinical centres demonstrated a shorter survival in AIDS cases in southern Europe than in those residing in northern and central Europe.9 Because this trend was similar in the subgroup of IDU, this study is not in agreement with our results. As in the study among the AIDS cases, geographical differences decreased over time (i.e. 1979–1989); one possible explanation for this discrepancy might be that in our study the IDU from southern Europe, who all seroconverted for HIV after 1987, were followed in a calendar period in which clinical care for HIV-infected

### Table 2

Univariate and multivariate Cox proportional hazards models for progression from HIV seroconversion to AIDS, immunosuppression and death with AIDS in 664 injecting drug users (IDU) registered in the European Seroconverter. Estimates were adjusted for pre-AIDS mortality from natural causes

<table>
<thead>
<tr>
<th></th>
<th>AIDS</th>
<th>CD4 count &lt;200 cells/μl</th>
<th>Death with AIDS</th>
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<tr>
<td></td>
<td>RH^a</td>
<td>RH (95% CI)</td>
<td>RH (95% CI)</td>
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<td>Univariate analysis</td>
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<td>Geographical region</td>
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<td>1</td>
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<td>Central Europe</td>
<td>1.86 (1.16–3.00)</td>
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<td>Southern Europe</td>
<td>1.17 (0.60–2.31)</td>
<td>0.83 (0.48–1.44)</td>
<td>1.27 (0.45–3.56)</td>
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<td>Age in years at seroconversion</td>
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<tr>
<td>&lt;23</td>
<td>1.57 (0.93–2.63)</td>
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<td>2.81 (1.41–5.63)</td>
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<td>≥27</td>
<td>2.14 (1.35–3.39)</td>
<td>1.40 (0.95–2.05)</td>
<td>2.88 (1.49–5.59)</td>
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<td>Multivariate analysis^b</td>
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<td>Geographical region by setting of follow-up</td>
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<tr>
<td>hospital only</td>
<td>1.55 (0.95–2.54)</td>
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<td>Southern Europe, other</td>
<td>1.37 (0.68–2.78)</td>
<td>0.84 (0.48–1.47)</td>
<td>1.29 (0.44–3.75)</td>
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<tr>
<td>Age in years at seroconversion</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;23</td>
<td>1.55 (0.91–2.65)</td>
<td>1.22 (0.75–1.99)</td>
<td>3.00 (1.46–6.18)</td>
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<td>≥27</td>
<td>2.43 (1.50–3.93)</td>
<td>1.40 (0.95–2.08)</td>
<td>3.35 (1.67–6.72)</td>
</tr>
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</table>

^a Relative hazard.

^b 12 IDU (all from central Europe) for whom the reason for the first study visit was other than regular follow-up were excluded from multivariate analysis.
patients in all western European countries might have been optimized or was at least comparable. An alternative explanation might be that the IDU included in our study were regularly followed up, including a clinical examination, relatively long before the development of AIDS. This excludes geographical differences in referral of patients with AIDS-defining illness by health care facility, which has been suggested as explanation for the findings among the AIDS cases. Furthermore, AIDS survival might be influenced by factors that do not greatly influence the HIV incubation time.

In our study, we adjusted for pre-AIDS mortality from natural causes. As this mortality has previously been shown to underestimate the burden of disease in IDU, adjustment resulted in faster progression rates to AIDS and death with AIDS. Because CD4 count is one of the laboratory markers most closely correlated with the stage of HIV infection, imputation of the residual time to each endpoint if death had not occurred, based on the CD4 decline before each endpoint, appeared to be a useful technique. It should be noted that the adjusted progression rates given in our study reflect rates if premature death could be eliminated and can therefore be used for comparison of progression rates in other risk groups at low risk of pre-AIDS mortality (e.g. homosexual men). Rates are somewhat lower than observed for homosexual men in earlier reports, but comparable taking the younger age of IDU into account. For future planning of interventions and costs, alternative methods need to be used to estimate net disease occurrence. As most IDU who experienced pre-AIDS death from natural causes were already suffering from immunosuppression before, taking these deaths into account did not substantially change progression estimates to first CD4 count <200 cells/μl. In general, in adjusting for pre-AIDS mortality from natural causes our results on geographical differences cannot be biased by different death rates across regions. In addition, confounding by the unknown duration of infection was absent because we studied IDU with documented HIV seroconversion.

We demonstrated that study-design related factors confounded our results on geographical variability in disease progression. Firstly, IDU whose reason for the first study visit was other than regular follow-up had a poorer prognosis. This confirms results described by Biggar. Secondly, it appeared that recruitment from hospital-based settings, in which HIV seroconversions are generally determined retrospectively, might result in an overrepresentation of fast progressors to AIDS and death with AIDS. As this was not consistently found within each region, we argue that clinic-based cohorts potentially, but not necessarily, overrepresent fast progressors. Researchers should be aware of this phenomenon and consider selection bias in interpreting results.

In HIV-infected IDU and other risk groups with estimated times of HIV seroconversion, older age has consistently been found to be associated with a faster rate of disease progression. We observed a weak association between age at seroconversion and immunosuppression, the earliest endpoint in our study. This could be explained by a steeper age gradient with more advanced stages of HIV infection (i.e. the effect of age is stronger for later endpoints), as demonstrated in this and previous studies. We found no substantial effect of gender on disease progression. This is consistent with most studies.

Several in vitro studies and animal models have suggested an unfavourable effect of opiate use on HIV disease progression. Some epidemiological studies also demonstrated that drug use accelerates progression, but we and others did not find evidence for this. A recent epidemiological study found that use of mainly heroin resulted in a somewhat faster CD4 decline only at the interval of seroconversion and not later on. So, the fact that this effect was of limited duration might reconcile discordant results. Two studies from Amsterdam evaluated the impact of borrowing of injecting equipment on disease progression and found evidence of a protective effect of a high frequency of borrowing prior to study entry and HIV seroconversion on disease progression. Continued borrowing of injecting equipment during HIV-positive follow-up, a surrogate marker for repeated HIV-exposure, was not associated with a slower CD4 decline in the Amsterdam study. In agreement, we did not find evidence for an effect of continued borrowing nor for having an HIV-positive steady sexual partner during HIV-positive follow-up (another surrogate marker for potential HIV re-exposure). However, lack of evidence might be due to socially desirable answers by participants and in our study to loss of information by creating common variables.

Potential drawbacks of our study include the multicohort design with each cohort having their own study methods. Therefore, we considered bias caused by study-design related factors. In addition, individual cohorts were grouped together in geographical regions, although associations between cofactors and disease progression may not be uniform. We did so because the aim of the present study was to evaluate large geographical differences. Results other than for geographical region were unaffected when we controlled for the individual sites. Furthermore, we cannot rule out that other factors, such as lifestyle, the stage of HIV infection of the individual through whom IDU became HIV infected, completeness of AIDS/death registers, might have been of importance and might have biased the effect of the cofactors examined. As we studied cohort participants, our results cannot simply be generalized to IDU not followed in cohort studies, who might have poorer access to health care. Finally, although adjustment for calendar time of follow-up is crucial since certain events occurring at different calendar times (e.g. introduction of HIV treatment, improved diagnostics and therapy) might influence progression rates, we did not do so because calendar time effects on progression in these IDU were absent in previous evaluations.

In conclusion, there appears little evidence for geographical differences in HIV disease progression in IDU closely followed up in Europe before highly active antiretroviral treatment became generally available. Future studies evaluating geographical differences should consider the confounding effect of study-design related factors and differential non-AIDS mortality. Cofactors are not likely to play a major role in HIV pathogenesis with the exception of age at seroconversion, which is especially predictive for progression to later endpoints. Therefore, age should be considered in recommending treatment.

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